Central Administration of Pharmaceutical Care
General Administration for Drug Utilization and Pharmacy Practice

Egyptian National Drug Formulary

Targeted Anti-Cancer Drugs

Code: EDA.DUPP. Formulary.007
Version No: 1.0
Issue Date: 2025

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Preface

The *Egyptian National Drug Formulary* is published by the **Egyptian Drug Authority (EDA)**. It has been developed by the **General Administration of Drug Utilization and Pharmacy Practice**, under the supervision of the **Central Administration of Pharmaceutical Care**, and reviewed by the **Committee of Pharmacy Practice Guides and National Drug Lists** at the EDA.

The *Egyptian National Drug Formulary* aims to provide pharmacists and other healthcare professionals with accessible, evidence-based, and reliable information on medications available in the Egyptian drug database, supporting sound clinical decision-making and promoting the rational use of medicines across healthcare settings.

This formulary serves as a reference guide that should be applied in conjunction with professional clinical judgment. Every effort has been made to ensure the accuracy and completeness of the information at the time of publication. However, as medical knowledge and best practices continue to evolve, users are encouraged to apply their professional judgment when using this formulary.

Egyptian National Drug Formulary Manual

(Targeted Anti-cancer Drugs)

The Egyptian National Drug Formulary (Targeted Anti-cancer Drugs) contains a list of medicines registered in the Egyptian drug database, included in the essential medicines list, or widely used on the Egyptian pharmaceutical market. It is designed as drug monographs classified pharmacologically and arranged alphabetically. There is a pharmacologically classified drug index at the beginning of the document and another alphabetically classified index at the end.

The Targeted Anti-Cancer Drugs chapter of the Egyptian National Drug Formulary presents detailed practical information for healthcare providers about medicines.

Each monograph includes:

1. Generic name
2. Dosage forms/strengths available in Egypt from the EDA database.
3. Route of administration
4. Pharmacological category and ATC code
5. Indications: Labeled indications
6. Dosage regimens for adults and pediatrics
7. Dosage adjustments if needed
8. Contraindications
9. Adverse drug reaction
10. Monitoring parameters
11. Drug interactions: That imply avoidance or considering modifications.
12. Pregnancy and lactation
13. Administration: Detailed administration information for all routes [parenteral (preparation, compatibility with diluents, infusion rate, precautions during administration), oral (food correlation)].

14. Emetogenicity: Incidence of emesis in the absence of prophylaxis.
15. Warnings/Precautions
16. Storage and light sensitivity
    - For reconstituted vials, apply the mentioned storage conditions only if prepared in aseptic techniques and ISO-controlled conditions according to USP 797 standards; otherwise, discard immediately if not used.
    - USP develops standards for compounding medications to help ensure patient benefit and reduce risks such as contamination, infection, or incorrect dosing.
17. Patient counselling keys
18. Sequence of administration:
19. Considerations for the administration sequence of parenteral antineoplastic drugs that are administered on the same day:
    - Cycle-specific antineoplastic agents in infusion are recommended to be administered before cycle-nonspecific agents. This is supposed to maximize the effect in cells with high cell division rates, as neoplastic cells.
    - Administer the vesicant antineoplastic drug first, as vascular integrity decreases with time. It is therefore advantageous to infuse the vesicant antineoplastic agent when the vein is more stable and less irritated.
    - Consider the less toxic agent first.
20. Pharmaco-genomics: Gene considerations, if any.

Refer to the manufacturer's PIL (Patient Information Leaflet) and SPC (Summary of Product Characteristics) if there are other specific considerations.

Targeted Anti-Cancer Drugs Formulary

This document includes medications that contribute to the management of malignant tumors. Therapeutic classes include: protein kinase inhibitors (BCR-ABL tyrosine kinase inhibitors, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase (CDK) inhibitors, EGFR tyrosine kinase inhibitors, HER_2 tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) kinase inhibitors, other protein kinase inhibitors), monoclonal antibodies (CD20 inhibitors, EGFR inhibitors, HER_2 inhibitors, pd-1/pd-l1 inhibitors, VEGF/VEGFR inhibitors), proteasome inhibitors, and monoclonal antibody bone-modifying agent.

Acknowledgments

The General Administration of Drug Utilization and Pharmacy Practice expresses its deepest appreciation to **Dr. Ali Elghamrawy, Chairman of the Egyptian Drug Authority (EDA),** for his remarkable leadership and relentless dedication to advancing pharmaceutical services in Egypt.

We want to express our gratitude to **Dr. Yasin Ragaey Afify, Assistant Chairman for Media, Community Engagement, and Investment Support, and Supervisor of Pharmaceutical Care Central Administration**, for his support and efforts. Without his guidance and encouragement, this project would not have been possible.

We are extremely grateful to **Dr. Shereen Abdelgawad, Former Head of Pharmaceutical Care Central Administration,** for her contributions to the completion of this work. Dr. Abdelgawad has been instrumental in ensuring all goals and objectives were achieved. We are deeply thankful for her support.

The development of the Egyptian National Drug Formulary is fostered by the exceptional expertise and insightful contributions of the **Members of the Oncology Pharmacy Committee - EDA.** Their rigorous scientific review, advice, and recommendations have been pivotal in ensuring that this work adheres to the highest standards of quality and effectiveness. We extend our sincere gratitude for their remarkable contributions to this important endeavor.

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Abbreviations List

ACE	Angiotensin-Converting Enzyme
ALL	Acute Lymphoblastic Leukemia
ALT	Aspartate Aminotransferase
anti-HBc	Hepatitis B core antibody
AP	Accelerated Phase
ARB	Angiotensin Receptor Blocker
ASM	Aggressive Systemic Mastocytosis
AST	Alanine Aminotransferase
ATE	Arterial Thromboembolic Events
BC	Blast Crisis
BCR	Breakpoint Cluster Region (BCR)
BTK	Bruton's Tyrosine Kinase
CBC	Complete Blood Count
CDK	Cyclin-Dependent Kinase
CD20	Clusters of Differentiation 20
CEL	Chronic Eosinophilic Leukemia
CHF	Congestive Heart Failure
cHL	Classical Hodgkin Lymphoma
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukaemia
COPDAM	Cyclophosphamide, Oncovin (vincristine), Prednisolone, Adriamycin (doxorubicin), Methotrexate
CP	Chronic Phase
CRC	Colorectal Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CYM	CYtarabine (Aracytine, Ara-C), Methotrexate
CYVE	CYtarabine (Aracytine, Ara-C), VEposide
dMMR	Mismatch Repair Deficient
DFSP	Dermatofibrosarcoma Protuberans
DLBCL	Diffuse Large B-Cell Lymphoma
DMARDs	Disease-Modifying Antirheumatic Drugs
DTC	Differentiated Thyroid Carcinoma
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
GI	Gastrointestinal

GIST	Gastrointestinal Stromal Tumours
GPA	Granulomatosis with Polyangiitis
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HER2	Human Epidermal Growth Factor Receptor 2
HES	Hypereosinophilic Syndrome
HLH	Hemophagocytic Lymphohistiocytosis
ILD	Interstitial lung disease
IS	International Scale
JC virus	John Cunningham virus
LDH	Elevated Lactate Dehydrogenase
MDS/MPD	Myelodysplastic/Myeloproliferative Diseases
MMR	Major Molecular Response
MPA	Microscopic Polyangiitis
MPM	Malignant Pleural Mesothelioma
MR	Molecular Response
MSI-H	Microsatellite instability-high
mTOR	Mammalian Target of Rapamycin
MVF	Multiple Vertebral Fractures
NHL	Non-Hodgkin's Lymphoma
ONJ	Osteonecrosis of the jaw
PAH	Pulmonary Arterial Hypertension
PDGFR	Platelet-Derived Growth Factor Receptor
PD-1/PD-L1	Programmed cell death protein 1/death ligand 1
P-gp	Permeability glycoprotein
Ph+	Philadelphia chromosome positive
PIL	Patient Information Leaflet
PJP/PCP	Pneumocystis Jirovecii Pneumonia, formerly known as Pneumocystis Carinii Pneumonia
PML	Progressive Multifocal Leukoencephalopathy
PRES	Posterior Reversible Encephalopathy Syndrome
PV	Pemphigus Vulgaris
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RA	Rheumatoid Arthritis
RCC	Renal Cell Carcinoma

RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SCCHN	Squamous Cell Cancer of the Head and Neck
SEGA	Subependymal Giant Cell Astrocytoma
TNF	Tumor Necrosis Factor
TSC	Tuberous Sclerosis Complex
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolic Events

PROTEIN KINASE INHIBITORS

BCR-ABL tyrosine kinase inhibitors

Dasatinib

Generic Name	Dasatinib
Dosage Form/Strengths	Tablet: 50 mg, 70mg, 140mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, BCR-ABL Tyrosine Kinase Inhibitor. ATC code: L01EA02.
Indications	**N.B.** Refer to the literature and specific protocols for all indications. **In adult patients, for the treatment of** • Newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase. • Chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy, including imatinib. • Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL). **In pediatric patients (1 year of age and above) for the treatment of** • Ph+ CML in chronic phase. • Newly diagnosed Ph+ ALL in combination with chemotherapy.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing**

	Initial dose	Escalate the dose to
Chronic phase CML	100 mg once daily	140 mg daily
Accelerated, blast phase (advanced phase) CML or Ph+ ALL	140 mg once daily	180 mg daily

N.B. Dose escalation is not recommended for patients who undergo hematologic or cytogenetic response.

Pediatric dosing

Chronic phase CML and ALL: starting dose based on body weight.

Body Weight (kg)	Daily Dose (mg)	Dose after escalation for Ph+ CML
10 to less than 20	40 mg	50 mg
20 to less than 30	60 mg	70 mg
30 to less than 45	70 mg	90 mg
At least 45	100 mg	120 mg

Not recommended for use with less than 10 kg.

N.B. Dose escalation is not recommended for pediatric patients with Ph+ ALL

Duration of treatment (adults and pediatrics)

- Pediatric patients with Ph+ ALL: start before day 15 of induction of chemotherapy and continue for a maximum duration of 2 years.

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	• Other cases: Continue until disease progression or until no longer tolerated by the patient.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** No dosage adjustment is necessary. **Hepatic Impairment** No dosage adjustment is necessary. Use with caution. **Myelosuppression** ➢ **Adults with chronic phase CML (starting dose 100 mg once daily)** If ANC < 0.5 x 10^9/L and/or platelets < 50 x 10^9/L • Withhold treatment until ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. • Resume treatment at the original starting dose. • If platelets < 25 x 10^9/L and/or recurrence of ANC < 0.5 x 10^9/L for > 7 days, repeat step 1 and resume treatment at a reduced dose of 80 mg once daily for the second episode. For the third episode, further reduce the dose to 50 mg once daily (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy, including imatinib). ➢ **Adults with accelerated and blast phase CML and Ph+ ALL (starting dose 140 mg once daily)** If ANC < 0.5 x 10^9/L and/or platelets < 10 x 10^9/L • Check if cytopenia is related to leukemia (marrow aspirate or biopsy). • If cytopaenia is unrelated to leukemia, withhold treatment until ANC ≥ 1.0 x 10^9/L and platelets ≥ 20 x 10^9/L and resume at the original starting dose. • If recurrence of cytopenia, repeat step 1 and resume treatment at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily • daily (third episode). • If cytopaenia is related to leukemia, consider dose escalation to 180 mg once daily. ➢ **Dose adjustments for neutropenia and thrombocytopenia in pediatric patients with Ph+ CML** • If cytopenia persists for more than 3 weeks, check if cytopenia is related to leukemia (marrow aspirate or biopsy). • If cytopenia is not related to leukemia, withhold therapy until ANC ≥1.0 × 10^9 /L and platelets ≥75 × 10^9 /L and resume at the original starting dose or a reduced dose. • If cytopenia recurs, repeat marrow aspirate/biopsy and resume dasatinib at a reduced dose.

Original starting daily dose	One-Level dose reduction	Two-Level dose reduction
40 mg	20 mg	--
60 mg	40 mg	20 mg
70 mg	60 mg	50 mg
100 mg	80 mg	70 mg

Non-hematologic adverse reactions

➢ **Adults**

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	• Grade 1: No dose modification is required. • Grade 2: Withhold dasatinib until the adverse reaction has resolved or returned to baseline. Resume at the same dose level if the first occurrence or at a reduced dose level if the recurrent adverse effect. • Grade 3 or 4: withhold until resolved. Then, resume at a reduced dose level depending on the initial severity of the adverse effect. • 100 mg >> 80 mg >> 50 mg. 140 mg >> 100 mg >> 50 mg. ➢ **Paediatric patients** **CML:** Follow the dose reduction recommendation for hematologic adverse effects. **In Ph+ ALL:** If needed, one level of dose reduction should be followed, according to the dose reduction recommendations for hematologic adverse reactions that are described above. **Pleural effusion** Withhold until the patient is asymptomatic or returned to baseline. After the first episode, resume at the same dose level. Following a subsequent episode or severe adverse effect, resume at one dose level reduction. **Dose reduction for concomitant use of strong CYP3A4 inhibitors** If Dasatinib must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to: o 40 mg daily for patients taking Dasatinib 140 mg tablet daily. o 20 mg daily for patients taking Dasatinib 100 mg tablet daily. o 20 mg daily for patients taking Dasatinib 70 mg tablet daily. o Withhold for patients taking Dasatinib 40 -60 mg tablet daily. - If dasatinib is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt dasatinib until the inhibitor is discontinued. - Allow a washout period of approximately 1 week after the inhibitor is stopped before the dasatinib dose is increased.
Contra-indications	Hypersensitivity to the active substance or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema. **Dermatologic**: Pruritus (12%), skin rash (11% to 21%). **Endocrine and metabolic**: Fluid retention (19% to 48%; cardiac related: 9%), hypocalcemia (grades 3/4: ≤12%), hypokalemia (grades 3/4: 2% to 15%), hypophosphatemia (grades 3/4: 7% to 18%). **Gastrointestinal**: Abdominal pain (7% to 16%), diarrhea (17% to 31%; grades 3/4: ≤5%), nausea (8% to 24%; grades 3/4: 1% to 3%), vomiting (5% to 16%; grades 3/4: 1%). **Hematologic and oncologic**: Anemia (grades 3/4: 13% to 74%), febrile neutropenia (4% to 12%; grades 3/4: 4% to 12%), hemorrhage (8% to 26%; grades 3/4: 1% to 9%), neutropenia (grades 3/4: 29% to 79%), thrombocytopenia (grades 3/4: 22% to 85%). **Hypersensitivity**: Facial edema. **Infection**: Infection (9% to 14%; serious infection: 5%).

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	Local: Localized edema (3% to 22%; superficial). **Nervous system**: Fatigue (8% to 26%), headache (12% to 33%), pain (11%). **Neuromuscular and skeletal**: Arthralgia (5% to 13%), limb pain (19%), musculoskeletal pain (8% to 22%), myalgia (7% to 13%). **Respiratory**: Dyspnea (3% to 24%), pleural effusion (10% to 28%; **serious**: 5% to 11%). **Miscellaneous**: Fever (6% to 18%). **1% to 10%** **Cardiovascular**: Cardiac conduction disturbance (7%; including cardiac arrhythmias [tachycardia, ventricular arrhythmia, ventricular tachycardia], palpitations), cardiac disorder (≤4%; including cardiomyopathy, heart failure, left ventricular dysfunction, ischemic heart disease [4%], reduced ejection fraction), chest pain, edema (1% to 4%), flushing, hypertension, pericardial effusion (0% to 4%), prolonged QT interval on ECG (≤1%). **Dermatologic**: Acne vulgaris, alopecia, dermatitis, eczema, hyperhidrosis, urticaria, xeroderma. **Endocrine and metabolic**: Hyperuricemia, weight gain, and weight loss. **Gastrointestinal**: Abdominal distention, change in appetite, colitis (including neutropenic colitis), constipation (10%), dysgeusia, dyspepsia, enterocolitis, gastritis, gastrointestinal hemorrhage (2% to 9%), stomatitis. **Hematologic and oncologic**: Bruise. **Hepatic**: Increased serum alanine aminotransferase (grades 3/4: 0% to 5%), increased serum aspartate aminotransferase (grades 3/4: 0% to 4%), increased serum bilirubin (grades 3/4: <1% to 6%). **Infection**: Herpes virus infection, sepsis. **Nervous system:** Asthenia, chills, depression, dizziness, drowsiness, insomnia, intracranial hemorrhage (≤3%), myasthenia, neuropathy, peripheral neuropathy. **Neuromuscular and skeletal**: Abnormal bone growth (children: 5%; including epiphyses delayed fusion, growth suppression, osteopenia), muscle spasm (5%), stiffness. **Ophthalmic**: Blurred vision, decreased visual acuity, dry eye syndrome, and visual disturbance. **Otic**: Tinnitus. **Renal**: Increased serum creatinine (grades 3/4: 1% to 8%). **Respiratory**: Cough, pneumonia, pneumonitis, pulmonary edema (≤4%), pulmonary hypertension (0% to 5%), pulmonary infiltrates, upper respiratory tract infection. **Miscellaneous**: Soft tissue injury (oral).

Monitoring Parameters	• CBC
	  ○ In adult patients with advanced phase CML or Ph+ ALL: Monitor weekly for the first 2 months, and then monthly thereafter, or as clinically indicated.
	  ○ In adult and pediatric patients with chronic phase CML: Monitor every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated.
	  ○ In pediatric patients with Ph+ ALL: Monitor before the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, CBCs should be performed every 2 days until recovery.
	• Electrolytes (calcium, magnesium) before and during treatment.

Dasatinib

	• Echocardiography before therapy in patients with cardiac disease or at risk of cardiac or pulmonary disease. • Chest x-ray if symptoms of pleural effusion develop. • Monitor bone growth and development in pediatric patients. • Liver function tests at baseline and monthly or as clinically indicated during treatment. • Monitor for bleeding and fluid retention symptoms.
Drug Interactions	***Risk X: Avoid the combination*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Domperidone, Etrasimod, Fexinidazole, Filgotinib, Grapefruit Juice, Histamine H2 Receptor Antagonists, Inhibitors of the Proton Pump (PPIs and PCABs), Lefamulin, Levoketoconazole, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Piperaquine, Poliovirus Vaccine (Live/Trivalent/Oral), Posaconazole, Ritlecitinib, Ruxolitinib (Topical), Saquinavir, Sertindole, St John's Wort, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Thioridazine, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine, Zoster Vaccine (Live/Attenuated). ***Risk D: Consider therapy modification*** Acetaminophen, Antacids, Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), CYP3A4 Inducers (Strong), CYP3A4 Inhibitors (Strong), Deferiprone, Denosumab, Encorafenib, Fusidic Acid (Systemic), Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Propacetamol, QT-prolonging Agents (Highest Risk), QT-prolonging Strong CYP3A4 Inhibitors (Highest Risk), QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk), Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Non-Live/Inactivated/Non-Replicating). **Notes** • **H2 antagonists or proton pump inhibitors** may decrease the level of dasatinib. Consider the use of antacids in place of H2 antagonists or proton pump inhibitors. Administer the antacid at least 2 hours before or 2 hours after the dose of dasatinib. • **Avoid coadministration with strong CYP3A4 Inducers or inhibitors**. Change of dosing of dasatinib may be needed when coadministered with dasatinib.
Pregnancy and Lactation	**Pregnancy:** Dasatinib causes congenital malformations. Effective contraception should be used during treatment and for 30 days after the last dose. **Fertility**: Based on animal data, dasatinib may result in damage to female and male reproductive tissues. **Lactation**: No human data. Breastfeeding is not recommended during treatment and for 2 weeks after the last dose due to the potential risk of adverse effects.
Administration	**Hazardous agent:** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: Oral**

Dasatinib

	• Administer with or without meals, either in the morning or the evening. • Swallow whole; do not break, cut, crush, or chew tablets. • Dasatinib should not be taken with grapefruit or grapefruit juice. • Crushing and dispersing a tablet in juice showed decreased exposure to dasatinib (36% lower than using intact tablets- limited data). • Missed dose: Advise patients that if they miss a dose, they should take the next scheduled dose at its regular time. The patient should not take two doses at the same time. N.B. Refer to the manufacturer's PIL if there are specific considerations.
Emetogenicity	Minimal to low emetic risk: (<30% frequency of emesis).
Warnings/ Precautions	**Myelosuppression** • Treatment with dasatinib is associated with severe thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced-phase CML or Ph+ ALL than in chronic-phase CML. • Perform complete blood counts regularly. Myelosuppression was generally reversible and usually managed by withholding temporarily or dose reduction. **Bleeding Related Events** • Severe hemorrhage, including fatalities, has been reported rarely and generally required treatment interruptions and transfusions. • Most bleeding events were associated with severe thrombocytopenia. • Caution if patients are required to take medications that inhibit platelet function or anticoagulants. **Fluid Retention** • Patients who develop symptoms suggestive of pleural effusion, such as dyspnea or dry cough, should be evaluated by chest X-ray. • Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids. Grade 3 or 4 pleural effusion may require thoracocentesis and oxygen therapy. **Hepatotoxicity** • Elevations in bilirubin, AST, ALT, and alkaline phosphatase have occurred. • Monitor regularly. Reduce dose, withhold, or permanently discontinue dasatinib based on severity. **QT Prolongation** • Caution in patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking medicines that lead to QT prolongation (e.g., antiarrhythmics), and cumulative high-dose anthracycline therapy. Correct hypokalemia or hypomagnesemia before administration. **Cardiovascular disorders** • The following cardiac adverse reactions occurred: congestive heart failure, pericardial effusion, arrhythmias, QT prolongation, and myocardial infarction, most commonly arrhythmia and palpitation. • Monitor patients for signs or symptoms such as chest pain, shortness of breath, and diaphoresis and treat appropriately.

Dasatinib

	Pulmonary Arterial Hypertension • Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) in adult and pediatric patients, which may occur any time after initiation, including after more than 1 year of treatment. • Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. Evaluate symptoms for common etiologies, including pleural effusion, pulmonary oedema, anemia, or lung infiltration. • PAH may be reversible on discontinuation of therapy. **Severe Dermatologic Reactions** • Discontinue permanently in patients who experience a severe mucocutaneous reaction (including Stevens-Johnson syndrome and erythema multiforme) during treatment if no other etiology can be identified. **Effects on Growth and Development in Pediatric Patients** In pediatric patients with chronic phase CML after at least 2 years of treatment, adverse reactions are associated with bone growth and development. **Strong CYP3A4 Inducers** Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If it cannot be avoided, consider a dose increase for dasatinib, then monitor the patient carefully for toxicity.
Storage and Light Sensitivity	Store between 15°C and 30°C. **N.B.** Refer to the manufacturer's PIL if there are specific considerations.
Patient Counselling Keys	• Blood cell count may be changed. The patient should avoid causes of infection and bleeding and report any related symptoms immediately. • The patient contacts the healthcare provider immediately if any of the following have developed: Fluid retention (swelling, weight gain, dry cough), cardiovascular toxicity (chest pain, shortness of breath, palpitations), pulmonary arterial hypertension (dyspnea, fatigue, hypoxia), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine). • The patient should tell the healthcare provider before starting if they have any of these problems: liver or heart disorders, or lactose intolerance. • The patient can tell the doctor about any symptoms of GIT disturbance. Antacids should be taken at least two hours before or after dasatinib. • The patient should tell the doctor before taking any drugs, as the dose may be changed, and avoid grapefruit during treatment. • Close monitoring of growth in children is needed during prolonged treatment.
Pharmaco-genomics	**Testing required** **BCR-ABL1** (CML): Testing is required for a diagnosis of Ph+ CML. **Outcome**: Efficacy – **Evidence of Testing Benefit**: Strong.

Imatinib

Generic Name	Imatinib
Dosage Form/Strength	Tablets: 100 mg and 400 mg Capsules: 100 mg and 400 mg
Route of Administration	**Oral**
Pharmacologic Category	Antineoplastic Agent, BCR-ABL Tyrosine Kinase Inhibitor **ATC Code:** L01EA01
Indications	N.B. Refer to the literature and specific protocols for all indications. • Adult and pediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive chronic myeloid leukaemia (Ph+ CML). • Adult and pediatric patients with Ph+ CML in chronic phase (CP) after failure of interferon-alpha therapy, or in accelerated phase (AP) or blast crisis (BC). • Adult patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia Ph+ ALL as monotherapy. • Adult and pediatric patients with newly diagnosed acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy. • Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements. • Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement. • Treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST). • Adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117) positive GIST. • Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown. • Treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

Imatinib

Dosage Regimen

Disease	Dose
Adults with Ph+ CML chronic phase	400 mg/day (may be increased up to 800 mg/day) continued until disease progression.
Adults with Ph+ CML AP or BC	600-800 mg/day continued until disease progression.
Pediatrics with Ph+ CML CP	340-570 mg/m^2/day (not to exceed 800 mg).
Adults with Ph+ ALL	The 600 mg/day duration may vary according to the program.
Pediatrics with Ph+ ALL	340 mg/m^2 /day (not to exceed 600 mg) in combination with chemotherapy.
Adults with MDS/MPD	400 mg/day until disease progression.
Adults with ASM	100-400 mg/day.
Adults with HES/CEL	100-400 mg/day continued as long as the patient continues to benefit.
Adults with DFSP	800 mg/day.
Adults with metastatic and/or unresectable GIST	400 mg/day continued until disease progression.

Pediatrics: Dosing for children should be based on body surface area (mg/m^2). There is no experience with children under 1 year of age.

Dosage Adjustment

N.B. Refer to the protocol used for specific dose modifications.

Renal Impairment

No dose adjustment required.

Renal dysfunction or on dialysis patients: Caution. Initial dose: the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy.

Hepatic Impairment

Mild to moderate hepatic impairment: 400 mg/day

If bilirubin > 3 x ULN or ALT/AST > 5 x ULN

- Withhold treatment until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN.
- Restart at 300 mg (reduced from 400 mg), 400 mg (reduced from 600 mg), 600 mg (reduced from 800 mg), or 260 mg/m^2/day (in children, reduced from 340).

Dose adjustment with adverse reactions

- **Severe non-hematological adverse reaction** (such as severe hepatotoxicity or severe fluid retention): Withhold until the event has resolved. Thereafter, treatment can be resumed as appropriate according to the initial severity of the event.
- **Haematological adverse reactions:** Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as follows

HES/CEL	ANC < 1.0 x 10^9 /l	**1.** Stop imatinib until ANC ≥ 1.5 x

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(starting dose 100 mg)	**and/or** platelets < 50 x 10^9 /l	10^9 /l and platelets ≥ 75 x 10^9 /l. **2.** Resume treatment with imatinib at the previous dose (i.e., before the adverse reaction developed).
Chronic phase CML, MDS/MPD, and GIST (starting dose 400 mg) **HES/CEL** (at a dose of 400 mg)	ANC < 1.0 x 10^9 /l **and/or** platelets < 50 x 10^9 /l	**1.** Stop imatinib until ANC ≥ 1.5 x 10^9 /l and platelets ≥ 75 x 10^9 /l. **2.** Resume treatment with imatinib at the previous dose (i.e., before the adverse reaction developed). **3.** If recurrent ANC < 1.0 x 10^9 /l and/or platelets < 50 x 10^9 /l, repeat step 1 and resume imatinib at a reduced dose of 300 mg.
Pediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 0.5 x 10^9 /l **and/or** Platelets < 10 x 10^9 /l (after at least 1 month of treatment)	**1**. Check cytopenia (by bone marrow aspirate or biopsy). **2**. If cytopenia is unrelated to leukemia, reduce the dose of imatinib to 400 mg. **3.** If cytopenia persists for 2 weeks, reduce further to 300 mg. **4.** If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop imatinib until ANC ≥ 1 x 10^9 /l and platelets ≥ 20 x 10^9 /l, then resume treatment at 300 mg.
Accelerated phase CML and blast crisis, and Ph+ ALL (starting dose 600 mg)	ANC < 0.5 x 10^9/l **and/or** Platelets < 10 x 10^9/l (after at least 1 month of treatment)	**1.** Check cytopenia (by bone marrow aspirate or biopsy). **2.** If cytopenia is unrelated to leukemia, reduce the dose of imatinib to 400 mg. **3.** If cytopenia persists for 2 weeks, reduce further to 300 mg. **4.** If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop imatinib until ANC ≥ 1 x 10^9 /l and platelets ≥ 20 x 10^9 /l, then resume treatment at 300 mg.
Paediatric accelerated phase CML and blast crisis (starting dose 340 mg/m^2)	ANC < 0.5 x 10^9/l **and/or** Platelets < 10 x 10^9/l (after at least 1 month of treatment)	**1.** Check cytopenia (by bone marrow aspirate or biopsy). **2.** If cytopenia is unrelated to leukemia, reduce the dose of imatinib to 260 mg/m^2. **3.** If cytopenia persists for 2 weeks, reduce further to 200 mg/m^2. **4.** If cytopenia persists for 4 weeks and is still unrelated to leukemia,

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			stop imatinib until ANC ≥ 1 x 10^9 /l and platelets ≥ 20 x 10^9 /l, then resume treatment at 200 mg/m^2.
	DFSP (at a dose of 800 mg)	ANC < 1.0 x 10^9 /l **and/or** Platelets < 50 x 10^9/l	**1.** Stop imatinib until ANC ≥ 1.5 x 10^9 /l and platelets ≥ 75 x 10^9 /l. **2.** Resume treatment with imatinib at 600 mg. **3.** In the event of recurrence of ANC < 1.0 x 10^9 /l and/or platelets < 50 x 10^9 /l, repeat step 1 and resume imatinib at a reduced dose of 400 mg.
Contra-indications	Hypersensitivity to imatinib or any component of the formulation.		
Adverse Drug Reactions	**>10%** **Cardiovascular:** Chest pain (7% to 11%), edema (11% to 86%; severe edema: 2% to 11%), and peripheral edema (20% to 41%). **Dermatologic:** Alopecia (7% to 15%), dermatitis (29% to 39%), diaphoresis (9% to 13%), exfoliation of skin (≤50%), night sweats (13% to 17%), pruritus (7% to 26%), and skin rash (≤50%). **Endocrine and metabolic:** Fluid retention (62% to 76%; can be severe), hypoalbuminemia (12% to 21%), hypokalemia (6% to 13%), increased lactate dehydrogenase (43% to 60%), and weight gain (5% to 32%). **Gastrointestinal:** Abdominal distension (7% to 19%), abdominal pain (3% to 57%; including abdominal cramps), anorexia (7% to 36%), constipation (8% to 16%), diarrhea (43% to 59%; grades 3/4: ≤5%), dysgeusia (7% to 13%), dyspepsia (≤27%), flatulence (10% to 25%), heartburn (≤11%), nausea (41% to 73%; grades 3/4: ≤5%), upper abdominal pain (14%), and vomiting (23% to 58%; grades 3/4: ≤4%). **Hematologic and oncologic:** Anemia (32% to 35%; grades 3/4: 1% to 42%), granulocytopenia (≤16%), hemorrhage (3% to 53%; grades 3/4: 2% to 19%), hypoproteinemia (24% to 32%), leukopenia (5% to 20%; grades 3/4: <1%), neutropenia (≤16%; grades 3/4: 3% to 48%), and thrombocytopenia (grades 3/4: ≤33%). **Hepatic:** Hepatotoxicity (6% to 12%), increased serum alanine aminotransferase (17% to 34%), increased serum alkaline phosphatase (11% to 17%), increased serum aspartate aminotransferase (12% to 38%), and increased serum bilirubin (11% to 13%). **Hypersensitivity:** Facial edema (7% to 14%). **Infection: I**nfection (14% to 28%), and influenza (≤14%). **Nervous system:** Anxiety (8% to 12%), asthenia (≤75%), chills (≤11%), depression (3% to 15%), dizziness (5% to 19%), fatigue (≤75%), headache (8% to 37%), insomnia (9% to 15%), lethargy (≤75%), malaise (≤75%), pain (20% to 46%), paresthesia (5% to 12%), and rigors (≤12%). **Neuromuscular and skeletal:** Arthralgia (9% to 40%), back pain (17%), limb pain (16%), muscle cramps (28% to 62%), muscle spasm (16% to 49%), musculoskeletal		

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	pain (adults: 38% to 49%; children: 21%), myalgia (9% to 32%), and ostealgia (11%). **Ophthalmic:** Blurred vision (5% to 11%), eyelid edema (19%), increased lacrimation (10% to 18%), and periorbital edema (15% to 74%). **Renal:** Increased serum creatinine (10% to 44%) and nephrotoxicity (14%; including genitourinary). **Respiratory:** Cough (13% to 27%), dyspnea (6% to 21%), nasopharyngitis (1% to 31%), pharyngitis (≤15%), pharyngolaryngeal pain (18%), pneumonia (4% to 13%), sinusitis (4% to 11%), and upper respiratory tract infection (3% to 21%). **Miscellaneous:** Fever (6% to 41%). **1% to 10%** **Cardiovascular:** Hypertension (4%), palpitations (5%), and pericardial effusion (≤6%). **Dermatologic:** Skin photosensitivity (4% to 7%), xeroderma (6% to 7%). **Endocrine and metabolic:** hypocalcemia (6%), hypophosphatemia (grade 3/4: 10%), and weight loss (10%). **Gastrointestinal**: Decreased appetite (10%), gastroenteritis (10%), gastroesophageal reflux disease, gastrointestinal hemorrhage (2% to 8%; including gastric antral vascular ectasia), increased serum amylase, increased serum lipase (grades 3/4: 4%), stomatitis (≤10%), and xerostomia. **Hematologic and oncologic:** lymphocytopenia (6% to 10%). **Hepatic:** Ascites (≤6%). **Nervous system**: Intracranial hemorrhage (≤9%). **Ophthalmic:** Conjunctivitis (5% to 8%). **Respiratory:** Epistaxis, oropharyngeal pain (6%), pleural effusion (≤6%), and pulmonary edema (≤6%).
Monitoring Parameters	• CBC with differential weekly during the 1st month, twice a week during the 2nd month, and periodically thereafter (for example, every 2-3 months). • Liver function (before initiation and monthly thereafter or as clinically indicated). • Renal function test baseline and as clinically needed. • Monitor weight regularly (fluid retention). • Test for HBV infection before initiating treatment. • Growth monitoring in children. • Thyroid function test (in thyroidectomy patients). • Monitor carefully for signs and symptoms of CHF in patients with a history or predisposing risk factors.
Drug Interactions	***Risk X: Avoid the combination*** Abrocitinib, Aprepitant, Asunaprevi, Adenovirus (Types 4, 7) Vaccine, BCG (Intravesical), Bosutinib, Brivudine, Baricitinib, Budesonide (Topical), Cladribine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cholera Vaccine, Deucravacitinib, Dipyrone, Domperidone, Doxorubicin (Conventional), Dengue Tetravalent Vaccine (Live), Eletriptan, Elacestrant, Etrasimod, Ebola Zaire Vaccine (Live), Fexinidazole, FilgotinibIvabradine, Flibanserin, Fosaprepitant, Fusidic Acid (Systemic), Grapefruit Juice, Infigratinib, Influenza Virus Vaccine (Live/Attenuated), Ivabradine, Lemborexant, Lomitapide, Lonafarnib, Methysergide, Measles, Mumps, Rubella, and Varicella Virus Vaccine, Mumps Virus Vaccine, Natalizumab,

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Nisoldipine, Nirogacestat, Nadofaragene Firadenovec, Orelabrutinib, Pimozide, Poliovirus Vaccine, Pacritinib, Pimecrolimus, Repotrectinib, Ritlecitinib, Rotavirus Vaccine, Ruxolitinib (Topical), Sertindole, Simeprevir, Smallpox Vaccine Live, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Varicella Virus Vaccine, Yellow Fever Vaccine, Zoster Vaccine (Live/Attenuated)

Risk D: Consider therapy modification

Acalabrutinib, Alfentanil, Alprazolam, Astemizole, Anthrax Vaccine Adsorbed, Apalutamide, Avanafil, Avapritinib, Brigatinib, Bromocriptine, Budesonide (Systemic), Capivasertib, Carbamazepine, Cilostazol, Cisapride, Cobimetinib, COVID-19 Vaccine (Adenovirus Vector) , CYP3A4 Inducers (Strong), Dapoxetine, Daridorexant, Deferiprone, Deflazacort, Denosumab, Dexamethasone (Systemic), Diphtheria, Tetanus Toxoids, Acellular Pertussis, Hepatitis B (Recombinant), Poliovirus (Inactivated) Vaccine, Encorafenib, Entrectinib, Enzalutamide, Eplerenone, Fentanyl, Fosphenytoin, Gepirone, Guanfacine, Haemophilus b Conjugate Vaccine, Hepatitis A and Hepatitis B Recombinant Vaccine, Human Papillomavirus Vaccine, Ibrutinib, Ivacaftor, Ibuprofen, Influenza Virus Vaccine, Ivosidenib, Japanese Encephalitis Virus Vaccine, Leflunomide, Lumacaftor, Ivacaftor, Lumateperone, Lurasidone, Lurbinectedin, Mavacamten, Methadone, Midazolam, Mitapivat, Mitotane, Mobocertinib, Naloxego, lvoclosporin, Olaparib, Omaveloxolone, Palovarotene, Pemigatinib, Pexidartinib, Phenobarbital, Phenytoin, Poliovirus Vaccine (Inactivated), Polymethylmethacrylate, Pralsetinib, Primidone, Q Fever Vaccine, Rabies Vaccine, Ranolazine, Respiratory Syncytial Virus Vaccine, Rifampin, Rimegepant, Ropeginterferon Alfa-2b, Selpercatinib, Selumetinib, Sipuleucel-T, Sirolimus (Conventional), Sirolimus (Protein Bound), Smallpox, Monkeypox Vaccine (Live), Sonidegib, Suvorexant, Tazemetostat, Tetanus Toxoid (Adsorbed), Tezacaftor, Ivacaftor, Tick-Borne Encephalitis Vaccine, Tolvaptan, Travelers' Diarrhea and Cholera Vaccine, Triazolam, Typhoid and Hepatitis A Vaccine, Ubrogepant, Vardenafil, Venetoclax, Voclosporin, Warfarin, Zanubrutinib, Zoster Vaccine (Recombinant).

Notes

- Imatinib is an inhibitor of CYP3A4 and CYP2D6, which may increase blood concentration of other drugs (e.g., cyclosporine, tacrolimus, sirolimus, ergotamine, fentanyl, bortezomib, docetaxel, quinidine).
- CYP3A4 inducers may decrease imatinib blood concentration (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's Wort).
- CYP3A4 inhibitors may increase imatinib blood concentration (e.g., protease inhibitors such as ritonavir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin).
- Patients who require anticoagulation should receive low-molecular-weight or standard heparin and not warfarin.

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Pregnancy and Lactation	**Pregnancy:** Limited human data. Post-marketing reports of spontaneous abortions and infant congenital abnormalities. Women of childbearing potential should use effective contraception during treatment and for at least 15 days after stopping treatment. **Fertility**: Effects on reproductive parameters were observed. **Lactation**: Limited human data. Found in human milk. Lactation is not recommended during treatment and for at least 15 days after stopping treatment.
Administration	**Hazardous agent**: Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Oral Administration** • Administer with a meal and a large glass of water to minimize the risk of gastrointestinal irritation. • Do not crush tablets; avoid skin or mucous membrane contact with crushed tablets; if contact occurs, wash thoroughly. • Tablets may be dispersed in water or apple juice; stir until the tablet disintegrates completely and administer the suspension immediately. • Doses ≤600 mg may be given once daily; the 800 mg dose should be administered as 400 mg twice daily. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Emetogenicity	• Imatinib >400 mg/day: Moderate to high emetic risk: (≥30% frequency of emesis). • Imatinib ≤400 mg/day: Minimal to low emetic risk: (<30% frequency of emesis).
Warnings/ Precautions	**Myelosuppression** • Treatment is associated with anemia, neutropenia, and thrombocytopenia. • Manage with dose reduction, dose interruption, or discontinuation of treatment. Monitor CBC regularly. **Cardiac disorders** • Severe congestive heart failure and left ventricular dysfunction have been reported. Cardiac disease and comorbidities, e.g., renal disease, are risk factors. Monitor and evaluate patients for any signs of cardiac disorders. • Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of imatinib in patients with conditions associated with high eosinophil levels (e.g., HES, MDS/MPD, and ASM). • Symptoms are reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding imatinib. **Fluid Retention** • Severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites) may occur. Weight should be monitored regularly. • An unexpected rapid weight gain should be carefully investigated and, if necessary, managed by drug interruption and diuretics. • History of cardiac disease and being elderly are risk factors. **Hepatotoxicity** Severe hepatotoxicity, including fatalities, may occur. Monitor regularly. If developed, interruption of treatment and/or dose adjustment may be needed.

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	HBV reactivation Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred. Carrier patients should be closely monitored for signs of active HBV infection during therapy and for several months after termination of therapy. **Gastrointestinal Disorders** • There have been rare reports of gastrointestinal perforation (including fatalities). • Gastrointestinal and intra-tumoural haemorrhages were reported with unresectable and/or metastatic GIST cases. Monitoring and management should be applied. **Hypereosinophilic Cardiac Toxicity** • In patients with hyper eosinophilic syndrome and cardiac involvement, cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy. • The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding treatment. **Dermatologic Toxicities** Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported. **Renal Toxicity** A decline in renal function may occur. Monitor at baseline and during therapy. **Phototoxicity** Exposure to direct sunlight should be avoided or minimized due to the risk of phototoxicity. Patients should be instructed to use measures such as protective clothing and sunscreen with a high sun protection factor (SPF). **Hypothyroidism** During treatment with imatinib, clinical cases of hypothyroidism have been reported in thyroidectomy patients taking levothyroxine replacement therapy. TSH levels should be closely monitored in such patients. **Growth retardation** May occur in children receiving imatinib. Close monitoring of growth in children during treatment is recommended. **Ability to drive and use machines** Caution should be recommended when driving a car or operating machinery due to possible undesirable effects such as dizziness, blurred vision, or somnolence.
Storage and Light Sensitivity	• Store between 15°C and 30°C. • Protect from moisture. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**

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Patient Counselling Keys	• Blood cell count may be changed. The patient should avoid causes of infection and bleeding and report any related symptoms immediately. • Patient should contact healthcare provider immediately if any of the following have developed: fluid retention (swelling, weight gain, dry cough), cardiovascular toxicity (chest pain, shortness of breath, palpitations), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine). • The patient should tell the doctor before taking any drugs (or supplements), as the dose may be changed, and avoid grapefruit during treatment. • If patients have GIT disorders, they can talk with the doctor. There may be ways to lower these side effects. • Close monitoring of growth in children is needed during prolonged treatment.
Pharmaco-genomics	**Gene Testing Required (Strength of Evidence: High)** • **BCR-ABL1 - Imatinib** (Chronic Myeloid Leukemia): testing is required for a diagnosis of Ph+ CML. **Outcome**: Efficacy – **Evidence of Testing Benefit**: Strong • **KIT - Imatinib** (Gastrointestinal Stromal Tumors): testing is required for a diagnosis of *KIT* (CD117)–positive GIST. **Outcome:** Efficacy **– Evidence of Testing Benefit:** Strong **Gene Testing Recommended (Strength of Evidence: Moderate)** • PDGFB - Imatinib (Dermatofibrosarcoma Protuberans DFSP): Routine molecular testing is not needed in all patients; however, it should be used if the diagnosis is in doubt or to predict response to imatinib **Outcome**: Efficacy – **Evidence of Testing Benefit**: Moderate • PDGFR - Imatinib (Myelodysplastic Syndrome/Myeloproliferative Neoplasm) **Outcome**: Efficacy – **Evidence of Testing Benefit**: Moderate • PDGFRA - Imatinib (Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia) **Outcome**: Efficacy – **Evidence of Testing Benefit**: Moderate

Nilotinib

Generic Name	Nilotinib
Dosage Form/Strength	Capsules: 150mg, 200mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, BCR-ABL Tyrosine Kinase Inhibitor. ATC: L01EA03
Indications	**N.B.** Refer to the literature and specific protocols for all indications used. **Chronic myeloid leukemia, Philadelphia chromosome positive (Ph+ CML)** In Adult and pediatric patients (2 years and over) for • Newly diagnosed (Ph+ CML) in chronic phase (CP). • Chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior tyrosine-kinase inhibitor therapy (imatinib).
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Philadelphia chromosome-positive CML** **- Adult dosing** • **Newly diagnosed chronic phase CML**: Oral: 300 mg twice daily. **Duration**: Minimum 3 years, may be discontinued if a molecular response of at least MR4.0 is maintained for one year before discontinuation and an MR4.5 (BCR-ABL/ABL ≤0.0032% IS) is achieved for the last assessment taken immediately before discontinuation of therapy. With no history of accelerated phase or blast crisis, and no history of relapses after prior attempts at treatment-free remission discontinuation. • **Resistant or intolerant to prior therapy, chronic or accelerated phase CML**: Oral: 400 mg twice daily. **Duration**: Minimum 3 years, may be discontinued if a molecular response of at least MR4.5 is maintained for one year before discontinuation. With no history of accelerated phase or blast crisis, and no history of relapses after prior attempts at treatment-free remission discontinuation. **- Pediatric dosing (more than 1 year of age)** **Oral**: 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal impairment** No dose modifications needed. Not studied but not renally excreted. **Hepatic impairment** Dose adjustment is not necessary. Caution. **Cardiac disorders** Caution. Patients with uncontrolled or significant cardiac disease were excluded from studies. **Dosage adjustments for neutropenia and thrombocytopenia** ANC less than 1.0 x 10^9 /L and/or platelet counts less than 50 x 10^9 /L: 1. Withhold nilotinib, and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC greater than 1.0 x 10^9 /L and/or platelets greater than 50 x 10^9 /L for adults or greater than 1.5 x 10^9 /L and/or

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	platelets greater than 75 x 10^9/L for pediatrics. 3. If blood counts remain low for greater than 2 weeks, reduce the dose to 400 mg once daily for adults or to 230 mg/m^2 once daily for pediatrics. If clinically appropriate, re-escalation of the dose to the starting dose may be considered. 4. If the event recurs after dose reduction, consider discontinuing treatment. **Dosage modifications for other non-hematologic toxicities** **Dosage Modification for QT Interval Prolongation** IF ECGs with a QTc greater than 480 msec: 1. Withhold nilotinib. Correct serum potassium and magnesium if below the lower limit. 2. Resume within 2 weeks at prior dose if QTcF returns to less than 450 msec and to within 20 msec of baseline. 3. If QTcF is between 450 msec and 480 msec after 2 weeks, reduce the dose to 400 mg once daily in adults and 230 mg/m^2 once daily in pediatric patients. 4. Discontinue if QTcF returns to greater than 480 msec after resuming with the reduced dose. 5. An ECG should be repeated approximately 7 days after any dose adjustment. **Elevated serum lipase for Grade 3-4**: • In adults, the dose should be reduced to 400 mg once daily or interrupted. • While in pediatrics, nilotinib should be withheld until the event returns to less than or equal to Grade 1, then resumes at a reduced dose (once daily). If the prior dose was 230 mg/m^2 once daily, treatment should be discontinued. **Elevated bilirubin and hepatic transaminases to Grade 3 or more (adults) or for Grade 2 bilirubin elevations or Grade 3 hepatic transaminase elevations (pediatrics):** • In adults, the dose should be reduced to 400 mg once daily or interrupted. • While in pediatrics, nilotinib should be withheld until the event returns to less than or equal to Grade 1, then resumes at a reduced dose (once daily). If the prior dose was 230 mg/m^2 once daily, and recovery to Grade 1 takes longer than 28 days, treatment should be discontinued.
Contra-indications	Hypersensitivity to the active substance or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Hypertension (11%), occlusive arterial disease (9% to 15%; including limb stenosis), peripheral edema (9% to 15%), prolonged QT interval on ECG (children and adolescents: >30 msec from baseline: 28%; adults: >60 msec from baseline: 4%; adults: >500 msec: <1%). **Dermatologic**: Alopecia (11% to 13%), night sweats (12% to 27%), pruritus (20% to 32%), skin rash (children and adolescents: >20%; adults: 29% to 38%), xeroderma (12%). **Endocrine and metabolic**: Hyperglycemia (50%), hypophosphatemia (grades 3/4: 8% to 17%), increased HDL cholesterol (≤28%), increased LDL cholesterol (≤28%), increased VLDL. **Gastrointestinal**: Abdominal pain (15% %), constipation (19% to 26%),

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decreased appetite (15% to 17%; including anorexia), diarrhea (children and adolescents: >20%; adults: 19% to 28%; grades 3/4: 1% to 3%), increased serum lipase (28%), nausea (children and adolescents: >20%; adults: 22% to 37%; grades 3/4: ≤2%), upper abdominal pain (12% to 18%), vomiting (children and adolescents: >20%; adults: 13% to 29%; grades 3/4: <1%).

Hematologic and oncologic: Anemia (8%; grades 3/4: 4% to 27%; decreased hemoglobin: children and adolescents: 38%), decreased absolute lymphocyte count (children and adolescents: 36%), decreased white blood cell count (children and adolescents: 54%), neutropenia (children and adolescents: grades 3/4: >5%; adults: 15%; grades 3/4: 12% to 42%, grade 3: 16%, grade 4: 15% to 26%; decrease in absolute neutrophil count: children and adolescents: 44%), thrombocytopenia (adults: 18%; grades 3/4: 10% to 42%, grade 3: 11% to 12%, grade 4: 18% to 32%; decreased platelet count: children and adolescents: 44%).

Hepatic: Hyperbilirubinemia (children and adolescents: >20%; adults: ≥10%), increased serum alanine aminotransferase (children and adolescents: >20%; adults: 72%), increased serum aspartate aminotransferase (children and adolescents: >20%; adults: 47%).

Infection: Influenza (13%).

Nervous system: Asthenia (15%), dizziness (12%), fatigue (23% to 32%), headache (>20%), insomnia (7% to 12%).

Neuromuscular and skeletal: Arthralgia (16% to 26%), back pain (15% to 19%), limb pain (children and adolescents: >20%; adults: 15% to 20%), muscle spasm (12% to 15%), musculoskeletal pain (11% to 12%), myalgia (16% to 19%), ostealgia (14% to 15%).

Respiratory: Cough (17% to 27%), dyspnea (9% to 15%), nasopharyngitis (children and adolescents: >20%; adults: 15% to 27%), oropharyngeal pain (7% to 12%), upper respiratory tract infection (children and adolescents: >20%; adults: 10% to 17%).

Miscellaneous: Fever (children and adolescents: >20%; adults: 14% to 28%).

1% to 10%

Cardiovascular: Angina pectoris, cardiac arrhythmia (including atrial fibrillation, atrioventricular block, bradycardia, cardiac flutter, extrasystoles, tachycardia), chest discomfort, chest pain, flushing, ischemic heart disease (5% to 9%), palpitations, pericardial effusion (≤2%), peripheral arterial disease (3% to 4%).

Dermatologic: Acne vulgaris, cutaneous papilloma, dermatitis (including acneiform eruption, allergic dermatitis, exfoliative dermatitis), eczema, erythema of skin, folliculitis, hyperhidrosis, urticaria.

Endocrine and metabolic: Decreased serum albumin (grades 3/4: 3% to 4%), diabetes mellitus, fluid retention (grades 3/4: 3% to 4%), hypercalcemia, hyperkalemia (grades 3/4: 2% to 6%), hyperphosphatemia, hypertriglyceridemia, hypocalcemia (grades 3/4: ≤5%), hypokalemia (grades 3/4: ≤9%), hypomagnesemia, hyponatremia (grades 3/4: 1% to 7%), weight gain, weight loss.

Gastrointestinal: Abdominal distention, abdominal distress, dysgeusia, dyspepsia (4% to 10%), flatulence, gastroenteritis (7%), gastrointestinal hemorrhage (3% to 5%), increased serum amylase, pancreatitis.

Genitourinary: Pollakiuria.

Hematologic and oncologic: Bruise, change in serum protein (decreased globulins), eosinophilia, febrile neutropenia, hemophthalmos, hemorrhage (grades

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	3/4: 1% to 2%), leukopenia, lymphocytopenia, pancytopenia. **Hepatic**: Abnormal liver function, ascites (≤2%), increased gamma-glutamyl transferase, increased serum alkaline phosphatase (grades 3/4: ≤1%). **Nervous system**: Anxiety, cerebral ischemia (1% to 3%), depression, hypoesthesia, malaise, myasthenia, noncardiac chest pain, pain, paresthesia, peripheral neuropathy, vertigo, voice disorder. **Neuromuscular and skeletal**: Increased creatine phosphokinase in blood specimen, linear skeletal growth rate below expectation (children and adolescents: 5%; including decreased plasma growth hormone level, growth suppression), musculoskeletal chest pain, neck pain. **Ophthalmic**: Conjunctivitis, dry eye syndrome, eye pruritus, eyelid edema (1%). **Renal**: Flank pain. **Respiratory**: Dyspnea on exertion, epistaxis, pleural effusion (≤2%).
Monitoring Parameters	• BCR-ABL transcript levels (quantitative diagnostic test validated to measure molecular response (MR) levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS)). • CBC with differential monitored every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. • Lipid profiles (before initiating therapy, at month 3 and 6 after initiation, and at least yearly during chronic therapy). • Blood glucose levels: before initiation and during treatment. • ECG (before therapy, 7 days thereafter, and as clinically indicated). • Serum electrolytes (before initiation, and regularly during treatment, to be corrected). • Serum lipase levels (monthly or as clinically indicated). • Hepatic functions (monthly or as clinically indicated). **Monitoring after discontinuation**: CBC with differential and BCR-ABL transcript levels: Monthly for one year, then every 6 weeks for the 2nd year, and every 3 months thereafter.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Aprepitant, Baricitinib, BCG Products, Bosutinib, Brivudine, Budesonide (Topical), Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, CYP3A4 Inducers (Strong), Dengue Tetravalent Vaccine (Live), Deucravacitinib, Domperidone, Doxorubicin, Elacestrant, Eletriptan, Encorafenib, Entrectinib, Etrasimod, Fexinidazole, Filgotinib, Flibanserin, Fosaprepitant, Grapefruit Juice, Inhibitors of the Proton Pump (PPIs and PCABs), Ivabradine, Ivosidenib, Lefamulin, Lemborexant, Levoketoconazole, Lomitapide, Methysergide, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Nirogacestat, Nisoldipine, Orelabrutinib, Pimecrolimus, Pimozide, Piperaquine, Poliovirus Vaccine (Live/Trivalent/Oral), Posaconazole, QT-prolonging Agents (Highest Risk), QT-prolonging Strong, CYP3A4 Inhibitors (Highest Risk), Repotrectinib, Sertindole, Simeprevir, Talimogene Laherparepvec, Tertomotide, Thioridazine, Tofacitinib, Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine, Zoster Vaccine (Live/Attenuated). ***Risk D: Consider therapy modification***

Nilotinib

	Acalabrutinib, Alfentanil, Alprazolam, Antacids, Avanafil, Avapritinib, Brigatinib, Bromocriptine, Budesonide (Systemic), Capivasertib, Cilostazol, Cobimetinib, Coccidioides immitis Skin Test, Colchicine, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), CYP3A4 Inhibitors (Strong), Dapoxetine, Daridorexant, Deferiprone, Deflazacort, Denosumab, Elexacaftor, Tezacaftor, and Ivacaftor, Eliglustat, Eplerenone, Fentanyl, Gepirone, Guanfacine, Histamine H2 Receptor Antagonists, Ibrutinib, Influenza Virus Vaccines, Ivacaftor, Lumateperone, Lurasidone, Lurbinectedin, Mavacamten, Midazolam, Mitapivat, Naloxegol, Olaparib, Omaveloxolone, Palovarotene, Pemigatinib, Pexidartinib, Polymethylmethacrylate, Pralsetinib, QT-prolonging Strong, CYP3A4 Inhibitors (Moderate Risk), Rabies Vaccine, Ranolazine, Ribociclib, Rimegepant, Ropeginterferon Alfa-2b, Selumetinib, Sipuleucel-T, Sirolimus (Conventional), Sirolimus (Protein Bound), Sonidegib, Suvorexant, Tazemetostat, Tezacaftor and Ivacaftor, Tolvaptan, Triazolam, Ubrogepant Vaccines (Non-Live/Inactivated/Non-Replicating), Vardenafil, Venetoclax, Voclosporin, Zanubrutinib.
Pregnancy and Lactation	**Pregnancy**: Limited human data. Reproductive toxicity in animal studies. Women of childbearing potential have to use highly effective contraception during treatment with nilotinib and for two weeks after ending treatment. **Lactation**: No human data. Nilotinib is present in milk. Women should not breastfeed during treatment and for 14 days after the last dose due to the potential of serious adverse reactions in a breastfed child.
Administration	**Hazardous agent:** Only developmental and/ or reproductive hazard. Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Oral Administration** • To be taken orally on an empty stomach. No food should be consumed for 2 hours before and for at least 1 hour after the dose. • The hard capsules should be swallowed whole with water. • For patients who are unable to swallow capsules, the contents of a capsule may be dispersed in 1 teaspoon of puréed apple. The mixture should be taken immediately (within 15 minutes) and should not be stored for future use. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Emetogenicity	Minimal to low emetic risk: (<30% frequency of emesis).
Warnings/ Precautions	**Myelosuppression** Thrombocytopenia, neutropenia, and anemia can occur. Monitor CBC during therapy and manage with treatment interruption or dose reduction. **QT prolongation** • Significant prolongation of the QT interval (sometimes fatal) may occur. • Risk factors include congenital long QT prolongation, uncontrolled or significant cardiac disease, or taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation. Hypokalemia and hypomagnesemia may further enhance this effect. • ECG should be monitored as baseline and as clinically indicated. Serum electrolytes should be monitored before and periodically during therapy. • Uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients

Nilotinib

with imatinib-resistant or intolerant CML in chronic phase or accelerated phase with a past medical history of cardiac disease or significant cardiac risk factors. Ventricular repolarization abnormalities may have been contributory factors. No cases of sudden death were reported in the Phase III study in newly diagnosed patients with CML in chronic phase.

Cardiovascular events

- Grade 3-4 cardiovascular events developed in newly diagnosed CML patients included peripheral arterial occlusive disease, ischemic heart disease, and ischemic cerebrovascular events.
- Monitor and manage during therapy. Appropriate therapy should be prescribed to manage cardiovascular risk factors.

Fluid retention

- Severe forms of drug-related fluid retention, such as pleural effusion, pulmonary oedema, and pericardial effusion, were uncommonly (0.1 to 1%) observed in newly diagnosed CML patients.
- Unexpected, rapid, or severe weight gain should be carefully investigated and treated accordingly.

Hepatotoxicity

- Reactivation of hepatitis B in chronic carrier patients has occurred. Some cases resulted in acute hepatic failure or fulminant hepatitis, leading to liver transplantation or a fatal outcome.
- Patients should be tested for HBV infection before initiating treatment. Carriers of HBV should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following discontinuation of therapy.

Pancreatitis

- Elevation in serum lipase has been observed. Caution is recommended in patients with a previous history of pancreatitis.
- Monitor serum lipase; if elevations are accompanied by abdominal symptoms, nilotinib therapy should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis.

Electrolyte Abnormalities

- Nilotinib can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities before initiating nilotinib and monitor periodically during therapy.

Effects on Growth and Development in Pediatrics

Growth retardation has been reported in pediatric patients treated with nilotinib. Monitor growth and development in pediatric patients.

Eligibility for discontinuation of treatment

- Patients must have typical BCR-ABL transcripts. A test with a detection limit below MR4.5 must be used to determine eligibility for discontinuation.

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	• Consider discontinuation in patients with newly diagnosed Ph+ CML-CP who have:
	  ○ been treated with nilotinib for at least 3 years
	  ○ maintained a molecular response of at least MR4.0 (corresponding to = BCR-ABL/ABL ≤ 0.01% IS) for one year before discontinuation of therapy
	  ○ achieved an MR4.5 for the last assessment taken immediately before discontinuation of therapy.
	  ○ been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2).
	  ○ no history of accelerated phase or blast crisis.
	  ○ no history of prior attempts at treatment-free remission discontinuation that resulted in relapse.
	• Consider discontinuation in patients with Ph+ CML-CP who are resistant or intolerant to imatinib who have:
	  ○ been treated with nilotinib for a minimum of 3 years.
	  ○ been treated with imatinib only before treatment with nilotinib.
	  ○ achieved a molecular response of MR4.5 (corresponding to = BCR-ABL/ABL ≤ 0.0032% IS).
	  ○ sustained an MR4.5 for a minimum of one year immediately before discontinuation of therapy.
	  ○ been confirmed to express the typical BCR-ABL transcripts (e13a2/b2a2 or e14a2/b3a2).
	  ○ no history of accelerated phase or blast crisis.
	  ○ no history of prior attempts at treatment-free remission discontinuation that resulted in relapse.
	• Patients must be frequently monitored to detect possible loss of remission.
	• Newly diagnosed patients who lose MMR must reinitiate treatment within 4 weeks at the dose level before discontinuation of therapy.
	• Patients resistant or intolerant to prior treatment that included imatinib with confirmed loss of MR4.0 (2 consecutive measures separated by at least 4 weeks showing loss of MR4.0) or loss of MMR must reinitiate treatment within 4 weeks at the dose level before discontinuation of therapy.
	• Patients who reinitiate therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR4.0 is re-established and every 12 weeks thereafter.

Storage and Light Sensitivity	Store between 15°C and 30°C. Protect from moisture. N.B. Refer to the manufacturer PIL if there are specific considerations.
Patient Counselling Keys	• Blood cell count may be changed. The patient should avoid causes of infection and bleeding and report any related symptoms immediately. • Patient should contact healthcare provider immediately if any of the following have developed: fluid retention (swelling, weight gain, dry cough), cardiovascular toxicity (chest pain, shortness of breath, palpitations), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine), or pancreatitis (sudden stomach area pain with accompanying nausea and vomiting).

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	• Patient should tell the doctor before taking any drugs (or supplements), as the dose may be changed, and avoid grapefruit during treatment. • Close monitoring of growth in children is needed during prolonged treatment.
Pharmaco-genomics	**Testing required** • **BCR-ABL1 (**CML**)** **Outcome:** Efficacy **– Evidence of Testing Benefit:** Strong • **BCR-ABL1 (**B-cell Acute Lymphoblastic Leukemia/Lymphoma, Philadelphia Chromosome-Positive**)** (not approved indication**).** **Outcome**: Efficacy – **Evidence of Testing Benefit**: strong. **Gene testing may be considered** • **UGT1A1** **Outcome**: Hyperbilirubinemia — **Overall Evidence Quality:** Poor.

Bruton's tyrosine kinase (BTK) inhibitors

Ibrutinib

Generic Name	Ibrutinib
Dosage Form/Strength	Capsules: 140 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Tyrosine Kinase Inhibitor. ATC Code: L01EL01.
Indications	**N.B.** Refer to the literature and specific protocols for all indications. • **Relapsed or refractory mantle cell lymphoma (MCL)** in adults (as a single agent). • **Chronic lymphocytic leukemia** (CLL) with 17p deletion in adults**.** • **Waldenström macroglobulinemia (WM)** in adults.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. • **Mantle Cell Lymphoma:** 560 mg once daily. • **CLL/SLL and WM**: 420 mg once daily. Duration: Continue until disease progression or unacceptable toxicity • **cGVHD** o Patients 12 years and older: 420 mg once daily. o Patients 1 to less than 12 years of age: 240 mg/m^2 once daily (up to a dose of 420 mg). **N.B.** When administering ibrutinib in combination with anti-CD20 therapy (e.g., rituximab or obinutuzumab), it is recommended to administer ibrutinib before anti-CD20 therapy when given on the same day.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment: Adult** • **Mild or moderate renal impairment** (greater than 30 mL/min creatinine clearance): No dose adjustment is needed. Monitor renal functions periodically and maintain hydration. • **Severe renal impairment** (<30 mL/min creatinine clearance): No data. Administer only if the benefit outweighs the risk, and monitor patients closely for signs of toxicity. **Hepatic Impairment: Adult** • **Mild impairment**: Reduce dose to 140- 280 mg once daily. Monitor more frequently for toxicities. • **Moderate impairment**: Reduce dose to 70-140 mg once daily. Monitor more frequently for toxicities. • **Severe impairment**: Use is not recommended.

Ibrutinib

Dose adjustments for toxicities

	Toxicity occurrence	MCL after recovery	CLL and WM, in patients 12 Years or older, after recovery
• **Grade 2 cardiac failure**	First	Restart at 420 mg daily	Restart at 280 mg daily
	Second	Restart at 280 mg daily	Restart at 140 mg daily
	Third	Discontinue	Discontinue
• **Grade 3 cardiac arrhythmias**	First	Restart at 420 mg daily	Restart at 280 mg daily
	Second	Discontinue	Discontinue
• **Grade 3 or 4 cardiac failure** • **Grade 4 cardiac arrhythmias**	First	Discontinue	Discontinue
• **Other Grade 3 or 4 non-hematological toxicities** • **Grade 3 or 4 neutropenia with infection or fever** • **Grade 4 hematological toxicities**	First	Restart at 560 mg daily	Restart at 280- 420 mg daily
	Second	Restart at 420 mg daily	Restart at 140-280 mg daily
	Third	Restart at 280 mg daily, then discontinue if it recurs.	Restart at 140 or discontinue

Severe cardiac disease patients

No data. Not included in trials.

- **Concomitant use with moderate CYP3A4 inhibitors:** 280 mg once daily.
- **Concomitant use with strong CYP3A4 inhibitors:** 140 mg once daily or withheld for up to 7 days.

Contra-indications

Hypersensitivity to the active substance or any of the excipients.

Adverse Drug Reactions

>10%

Cardiovascular: Hypertension (11% to 16%; cumulative rate increased over time), peripheral edema (12% to 22%), sinus tachycardia (11%).

Dermatologic: Pruritus (13%), skin infection (15% to 18%), skin rash (12% to 25%).

Endocrine and metabolic: Hypokalemia (12% to 15%).

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	Gastrointestinal: Abdominal pain (13% to 23%), constipation (12% to 22%), decreased appetite (16%), diarrhea (28% to 59%; grades ≥3: 2% to 10%), dyspepsia (11% to 12%), gastroesophageal reflux disease (12%), nausea (19% to 26%; grades ≥3: 1% to 4%), stomatitis (14% to 29%; grades ≥3: 1% to 9%), vomiting (13% to 19%; grades ≥3: 2%). **Genitourinary**: Urinary tract infection (10% to 12%). **Hematologic and oncologic**: Anemia (≥20%; grades 3/4: 3%), bruise (11% to 51%; grades ≥3: 1% to 2%), hemorrhage (17% to 28%; including major hemorrhage, gastrointestinal hemorrhage, hematuria, postprocedural hemorrhage), hypogammaglobulinemia (11%), lymphocytosis (66%), neutropenia (≥30%; grades 3/4: 2% to 23%), petechia (13% to 16%), thrombocytopenia (≥20%; grades 3/4: 1% to 8%). **Hepatic**: Increased serum alanine aminotransferase (11%). **Infection**: Infection (including bacterial infection, fungal infection, viral infection [reactivation of HBV]), sepsis (10% to 11%). **Nervous system**: Asthenia (14%), chills (12%), dizziness (11% to 20%), falling (17%), fatigue (18% to 57%), headache (12% to 21%). **Neuromuscular and skeletal**: Arthralgia (16% to 24%), muscle spasm (11% to 29%), musculoskeletal pain (14% to 36%), osteonecrosis (11%). **Ophthalmic**: Blurred vision (≤13%), decreased visual acuity (≤11%), dry eye syndrome (17%), increased lacrimation (13%). **Respiratory**: Cough (13% to 22%), dyspnea (10% to 12%), oropharyngeal pain (14%), pneumonia (12% to 23%), sinusitis (11% to 22%), upper respiratory tract infection (16% to 47%). **Miscellaneous**: Fever (12% to 30%). **1% to 10%** **Cardiovascular**: Atrial fibrillation (≤8%), atrial flutter (≤8%), heart failure (2%), ventricular tachyarrhythmia (1%). **Endocrine and metabolic**: Weight loss (10%). **Hematologic and oncologic**: Second primary malignant neoplasm (10%; grades ≥3: 2%; including carcinoma [non-skin] and skin carcinoma [nonmelanoma]). **Nervous system**: Cerebrovascular disease (1%; including cerebral ischemia, cerebrovascular accident, intracranial hemorrhage, ischemic stroke, subdural hematoma, transient ischemic attacks).
Monitoring Parameters	• CBC monthly. • Renal and hepatic function baseline and periodically as clinically indicated. • Monitor blood pressure regularly. • Evaluate cardiac history/function at baseline; monitor ECG and for cardiac arrhythmias as clinically indicated.
Drug Interactions	***Risk X: Avoid the combination*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, CYP3A4 Inducers (Strong), Dengue Tetravalent Vaccine (Live), Deucravacitinib, Etrasimod, Fexinidazole, Filgotinib, Grapefruit Juice, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), St John's Wort, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine,

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	Upadacitinib, Vaccines (Live), Yellow Fever Vaccine, Zoster Vaccine (Live/ Attenuated). ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), CYP3A4 Inhibitors (Moderate), Deferiprone, Denosumab, Fusidic Acid (Systemic), Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Posaconazole, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Non-Live/Inactivated/Non-Replicating), Voriconazole.
Pregnancy and Lactation	**Pregnancy**: No human data. Studies in animals have shown reproductive toxicity. Ibrutinib should not be used during pregnancy. Effective contraception should be used during treatment and for 1 month after the last dose. **Lactation**: No human data. Breastfeeding should be discontinued during treatment with Ibrutinib and for 1 week after the last dose due to the potential of serious adverse reactions.
Administration	**Oral administration** Administer with a glass of water at approximately the same time each day. Swallow capsules whole. Do not open, break, or chew capsules. Maintain adequate hydration during treatment. **Missed dose**: Administer as soon as the missed dose is remembered on the same day; return to normal scheduling the following day. Do not take extra doses to make up for the missed dose. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk (<30% frequency of emesis).
Warnings/ Precautions	**Cytopenia** Cytopenias of grade 3 or 4 (neutropenia, thrombocytopenia, and anemia) were reported in patients treated with Ibrutinib. Monitor complete blood counts monthly. **Hemorrhage** • Bleeding events have been reported, either minor or major, some are fatal. Cases include cerebral bleeding, gastrointestinal bleeding, and hematuria. • Monitor for bleeding and manage. • Risk of significant bleeding increases with coadministration with anticoagulant or antiplatelet medicines. Warfarin or other vitamin K antagonists should not be administered concomitantly with Ibrutinib. • Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the risk of bleeding and the type of surgery. • Supplements such as fish oil and vitamin E preparations should be avoided. **Leukostasis** • Monitor closely. High circulating lymphocytes (>400,000/mcL) are a risk. Consider temporarily withholding Ibrutinib. • Administer supportive care, including hydration and/or cytoreduction as indicated.

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Infections

- Ibrutinib treatment has resulted in bacterial, viral, and fungal infections, some are fatal.
- Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis Jirovecii pneumonia (PJP) have occurred in patients treated with Ibrutinib.
- Consider prophylaxis in high-risk patients for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Splenic rupture

- Cases of splenic rupture have been reported following discontinuation of Ibrutinib treatment.
- Patients who develop left upper abdominal or shoulder tip pain should be evaluated, and a diagnosis of splenic rupture should be considered.
- Disease status and spleen size should be carefully monitored (e.g., clinical examination, ultrasound) when Ibrutinib treatment is stopped.

Cardiac arrhythmias and cardiac failure

- Fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with Ibrutinib. Monitor for symptoms of arrhythmias and cardiac failure and manage. Some cases of cardiac failure resolved or improved after withdrawal or dose reduction.
- Risk factors include acute infections, hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia.
- Alternative treatment may be considered for patients with cardiac risk factors.
- If a ventricular tachyarrhythmia develops, temporary discontinuation is needed. consider risk/benefit before restarting therapy.

Hypertension

Monitor regularly. Initiate or adjust antihypertensives if needed.

Cerebrovascular accidents

- Cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke, including fatalities, have been reported in patients treated with Ibrutinib.
- Regular monitoring is needed. The onset is after several months, starting from 1 month.

Interstitial Lung Disease (ILD)

- Monitor for pulmonary signs of ILD.
- If symptoms appear, interrupt Ibrutinib and manage ILD.
- Consider the risk/benefit of continuation of therapy if symptoms persist.

Drug-drug interactions

- CYP3A4 Inducers: Avoid coadministration with strong CYP3A4 inducers, as lack of efficacy may occur.
- CYP3A4 inhibitors: Co-administration may raise the risk of toxicity. Avoid co-administration with strong CYP3A4 inhibitors.

Hemophagocytic lymphohistiocytosis (HLH)

- HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. HLH is characterized by fever, hepatosplenomegaly, hypertriglyceridemia, high serum ferritin, and cytopenias.

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	• Early diagnosis of HLH should be considered if symptoms develop. **Second primary malignancies** Other malignancies have occurred in patients, including skin cancers and other carcinomas. **Hepatic events** • Patients treated with Ibrutinib have experienced cases of hepatotoxicity, reactivation of hepatitis B, and cases of potentially chronic hepatitis E, and have experienced hepatic failure, including fatality. • Monitor liver functions regularly.
Storage and Light Sensitivity	Store between 15°C and 30°C in the original container. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient Counselling Keys	• Blood cell count may be changed. The patient should avoid causes of infection and bleeding and report any related symptoms immediately. • The patient should tell the doctor before taking any drugs, as the dose may be changed, and avoid grapefruit during treatment. • The atient should contact healthcare provider immediately if any of the following have developed: Cardiovascular Toxicity (hyperstension, chest pain, shortness of breath, palpitations, swelling of the feet, ankles, or legs), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine), A severe brain infection (confusion, memory problems, depression, trouble speaking or thinking, change in eyesight). • Diarrhea is a common side effect. The patient should drink plenty of fluids to help avoid dehydration and tell the doctor if diarrhea does not go away.

Cyclin-dependent kinase (CDK) inhibitors

Abemaciclib

Generic Name	Abemaciclib
Dosage Form/Strength	Tablet: 50 mg, 100 mg, 150 mg, 200 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Cyclin-Dependent Kinase Inhibitor. ATC Code: L01EF03.
Indications	**N.B.** Refer to the literature and specific protocols for all indications. **Advanced or metastatic Breast cancer** Locally advanced or metastatic HR-positive, HER2-negative breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy, or with fulvestrant after progression on endocrine therapy, or as monotherapy in women with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. **Early Breast cancer at high risk** Adjuvant treatment of HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence (in combination with endocrine therapy [an aromatase inhibitor or tamoxifen) in adults at high risk of recurrence.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing** • **In combination therapy (with fulvestrant, tamoxifen, or an aromatase inhibitor)** **Oral:** 150 mg twice daily. • **Monotherapy (Progressive disease following endocrine therapy and prior chemotherapy)** **Oral:** 200 mg twice daily **Duration of treatment** • **Advanced or metastatic breast cancer** Continue as long as the patient has clinical benefit from therapy or until unacceptable toxicity occurs. • **Early breast cancer** Continue for two years, or until disease recurrence or unacceptable toxicity. **Pediatrics** The safety and efficacy of abemaciclib in children and adolescents aged less than 18 years have not been established. No data are available.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** • Mild or moderate renal impairment: No dose adjustment is necessary. • Severe renal impairment: No data. Caution. Close monitoring for toxicity. **Hepatic Impairment**

Abemaciclib

- Mild or moderate impairment: No dosage adjustment necessary.
- Severe impairment (Child-Pugh class C): Reduce the abemaciclib frequency to once daily.

➢ **Dose modifications due to adverse effects**

- The dose should be decreased by 50 mg each time a dose lowering is needed. i.e., 150 mg twice daily decreased to 100 mg twice daily…
- Discontinue for patients unable to tolerate 50 mg twice daily.

Hematologic Toxicities

- CTCAE Grade 1 or 2: No dose modification is required.
- CTCAE Grade 3: Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
- CTCAE Grade 3 recurrent or 4: Suspend dose until toxicity resolves to ≤Grade 2. Resume at the next lower dose.

  N.B. ANC: Grade 1: ANC < 1,500 / mm^3; Grade 2: ANC 1,000 - < 1,500 / mm^3; Grade 3: ANC 500 - < 1,000 / mm^3; Grade 4: ANC < 500 / mm^3.

Hepatotoxicity during treatment (CTCAE Grade for ALT and AST)

- Grade 1 (≤3 times ULN), Grade 2 (3 to 5 times ULN) without an increase in total bilirubin >2 times ULN: No dosage modification is required.
- Persistent or recurrent grade 2, or grade 3 (>5 to 20 times ULN) without increase in total bilirubin >2 times ULN: Withhold abemaciclib until toxicity resolves to baseline or grade 1, then resume at the next lower dose.
- AST and/or ALT >3 times ULN with total bilirubin >2 times ULN (in the absence of cholestasis): Discontinue abemaciclib.
- Grade 4 (>20 times ULN): Discontinue abemaciclib.

Diarrhea

- Grade 1: No dose modification is required.
- Grade 2: If toxicity does not resolve within 24 hours to ≤ Grade 1, suspend dose until resolution: No dose reduction is required.
- Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures: Suspend dose until toxicity resolves to ≤ Grade 1. Resume at the next lower dose.
- Grade 3 or 4 or requires hospitalization: Suspend dose until toxicity resolves to ≤ Grade 1. Resume at the next lower dose.

Interstitial Lung Disease/Pneumonitis (CTCAE Grade)

- Grade 1 or 2: No dose modification is required.
- Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1: Withhold dose until toxicity resolves to baseline or ≤Grade 1. Resume at the next lower dose
- Grade 3 or 4: Discontinue abemaciclib.

Venous Thromboembolic Events (VTEs)

Early Breast Cancer

Any Grade: Withhold dose and treat as clinically indicated. Resume when the patient is clinically stable.

Advanced or Metastatic Breast Cancer

- Grade 1 or 2: No dose modification is required.

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	• Grade 3 or 4: Withhold dose and treat as clinically indicated. Resume when the patient is clinically stable. **Other Toxicities** • Grade 1 or 2: No dose modification is required. • Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1: Withhold dose until toxicity resolves to baseline or ≤ Grade 1. Resume at the next lower dose. • Grade 3 or 4: Withhold dose until toxicity resolves to baseline or ≤Grade 1. Resume at the next lower dose. **CYP3A4 inhibitors** • Co-administration of CYP3A4 inhibitors together with abemaciclib should be avoided. If avoidance is not possible, the dose of abemaciclib should be reduced to 100 mg twice daily (or 50 mg twice if already have been reduced due to adverse effects), followed by careful monitoring of toxicity. • If the CYP3A4 inhibitor is discontinued, the abemaciclib dose should be increased to the dose used before the initiation of the CYP3A4 inhibitor (after 3 to 5 half-lives of the CYP3A4 inhibitor). • Coadministration with moderate or weak CYP3A4 inhibitors: No dose adjustment is necessary. However, close monitoring for signs of toxicity is needed.
Contra-indications	Hypersensitivity to the active substance or any of the excipients.
Adverse Drug Reactions	**>10%** **Dermatologic**: Alopecia (12%). **Endocrine and metabolic**: Weight loss (14%). **Gastrointestinal**: Abdominal pain (39%), constipation (17%), decreased appetite (45%), diarrhea (90%; grade 3: 20%), dysgeusia (12%), nausea (64% grade 3: 5%), stomatitis (14%), vomiting (35%; grade 3: 2%), xerostomia (14%). **Hematologic and oncologic**: Anemia (69%), decreased neutrophils (88%; grade 3: 22%; grade 4: 5%), decreased platelet count (41%; grade 3: 2%), decreased white blood cell count (91%; grade 3: 28%), lymphocytopenia (42%; grade 3: 13%; grade 4: <1%). **Hepatic**: Increased serum alanine aminotransferase (ALT) (31%), increased serum aspartate aminotransferase (AST) (30%). **Infection**: Infection (31%). **Nervous system**: Dizziness (11%), fatigue (65%), headache (20%). **Neuromuscular and skeletal**: Arthralgia (15%). **Renal**: Increased serum creatinine (99%). **Respiratory**: Cough (19%). **Miscellaneous**: Fever (11%). **1% to 10%** **Endocrine and metabolic**: Dehydration (10%). **Frequency not defined** **Cardiovascular**: Arterial thrombosis. **Respiratory**: Interstitial pulmonary disease, pneumonitis.

Abemaciclib

Monitoring Parameters	• CBC with differential every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. **N.B.** Before treatment initiation, absolute neutrophil counts (ANC) ≥ 1500/ mm^3, platelets ≥ 100000 / mm^3, and hemoglobin ≥ 8 g/dL are recommended. • Monitor ALT, AST, and serum bilirubin before initiation, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. • Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis. • Monitor for signs/symptoms of diarrhea/dehydration, venous thrombosis, and pulmonary embolism.
Drug Interactions	***Risk X: Avoid the combination*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, CYP3A4 Inducers (Moderate), CYP3A4 Inducers (Strong), Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Grapefruit Juice, Ketoconazole (Systemic), Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), CYP3A4 Inhibitors (Strong), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** No human data. Abemaciclib was teratogenic in animal studies. effective contraception should be used during treatment and for at least three weeks following the last dosage. **Fertility**: Abemaciclib may impair fertility in males based on animal data. **Lactation**: No human data. Breastfeeding is not recommended during treatment and for at least three weeks after the last dose.
Administration	**Administration: Oral** • May be administered with or without food. Swallow whole, do not crush, chew, or split tablets. • Administer at approximately the same times each day. • Missed dose: Next dose should be taken at its scheduled time without an additional dose. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk: (<30% frequency of emesis).
Warnings/ Precautions	**Diarrhea** • Diarrhea is the most common adverse reaction. • At the first sign of loose stools, patients should increase their oral fluid intake

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	and start taking antidiarrheal drugs (e.g., loperamide). **Neutropenia** • Neutropenia is associated with abemaciclib, including febrile neutropenia and severe neutropenic sepsis. • Monitoring and dose modification are recommended for patients who develop Grade 3 or 4 neutropenia. • Patients should be monitored for signs and symptoms of infection and treated as medically appropriate. **Hepatotoxicity** Abemaciclib has been associated with ALT and AST elevations. Monitoring, dosage modifications, or discontinuation may be needed in severe cases. **ILD/pneumonitis** • Patients on abemaciclib have reported cases of ILD/pneumonitis. Patients must be treated as medically appropriate and kept under observation for respiratory symptoms suggestive of ILD or pneumonia. • The dosage of abemaciclib may need to be adjusted depending on the severity of ILD or pneumonia. abemaciclib should be permanently discontinued in patients with Grade 3 or 4 ILD/pneumonitis. **Venous Thromboembolism** • Abemaciclib is associated with venous thromboembolic events (VTEs). Dose modifications may be required according to the grade of VTE. • Monitor patients for signs and symptoms of thrombosis and pulmonary embolism and treat as medically appropriate. **Arterial Thromboembolic Events** • A potential increased risk for serious arterial thromboembolic events (ATEs), including ischemic stroke and myocardial infarction. • The benefits and risks of continuing abemaciclib in patients who experience a serious ATE should be considered. **CYP3A4 inducers** Concomitant use of strong CYP3A4 inducers (e.g, carbamazepine, phenytoin) to avoid decreased efficacy of abemaciclib.
Storage and Light Sensitivity	Store between 15°C and 30°C. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient Counselling Keys	• Diarrhea is frequently seen with this medication, which may be severe in some cases. The patient should start antidiarrheal therapy (loperamide) and tell the doctor once they experience diarrhea. If diarrhea does not resolve with antidiarrheal therapy within 24 hours, treatment should be withheld as instructed by the doctor. • The patient should contact the healthcare provider immediately if any of the following have developed: Venous thromboembolism (chest pain, shortness of breath, palpitations, swelling in an extremity), pneumonitis (dyspnea, hypoxia, cough), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine), or infections. • The patient should tell the doctor before taking any drugs, as the dose may be changed, and avoid grapefruit during treatment.

Ribociclib

Generic Name	Ribociclib
Dosage Form/Strength	Tablets: 200 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Cyclin-Dependent Kinase Inhibitor ATC: L01EF02

Indications	**N.B.** Refer to the literature and specific protocols for all indications used.
	
	Treatment of Breast cancer HR-positive, HER2-negative
	• Advanced or metastatic breast cancer in combination with:
	  ○ An aromatase inhibitor as initial endocrine-based therapy; or
	  ○ Fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy.
	
	N.B. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing** • **Advanced or Metastatic Breast Cancer** **Oral**: 600 mg once daily for 21 consecutive days followed by 7 days off treatment (28-day cycle). **Duration**: Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. **Pediatrics** The safety and efficacy in pediatric patients have not been established.

Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications.
	
	Dose modifications: Dose can be decreased by 200 mg steps when needed.
	
	Renal impairment
	• **Mild or moderate renal impairment:** No dose adjustment is necessary.
	• **Severe renal impairment:** Initial dose: 200mg.
	
	Hepatic impairment
	• **Mild hepatic impairment:** No dose adjustment is necessary.
	• **Moderate and severe hepatic impairment**
	  ○ Advanced or metastatic disease: Initial dose: 400mg.
	  ○ Early breast cancer: No need to initiate dose change.
	• **If Grade ≥ 2 abnormalities:** Monitor more frequently, and as clinically indicated.
	
	Neutropenia

Ribociclib

- **Grade 1 or 2** (ANC 1000/mm^3)
  No dose modifications.
- **Grade 3** (ANC 500 -<1000/mm^3)
  - Interrupt until recovery to grade ≤2. Then resume at the same dose level.
  - In case of febrile neutropenia or recurrence, the resumed dose should be reduced by 1 dose level.
- **Grade 4** (ANC<500/mm^3)
  Interrupt until recovery to grade ≤2. Then resume at a reduced dose level.

Hepatobiliary toxicity

AST and/or ALT elevations from baseline, WITHOUT an increase in total bilirubin above 2 x ULN

- **Grade 1 (> ULN – 3 x ULN)**
  No dose adjustment is required.
- **Grade 2 (> 3 to 5 x ULN)**
  Baseline at < Grade 2: Interrupt dose until recovery to ≤ baseline grade, then resume at same dose level. If Grade 2 recurs, resume at the next lower dose level.
  Baseline at Grade 2: No dose interruption.
- **Grade 3 (> 5 to 20 x ULN)**
  Interrupt dose until recovery to ≤ baseline grade, then resume at next lower dose level. If Grade 3 recurs, discontinue.
- **Grade 4 (> 20 x ULN)**
  Discontinue ribociclib.

AST and/or ALT elevation combined WITH total bilirubin increase, in the absence of cholestasis

If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue ribociclib.

QT prolongation

- **QTcF prolongation > 480 ms and ≤ 500 ms**
  - Interrupt treatment and wait until QTcF resolves to < 480 ms. Then resume at the same dose in early breast cancer or at a reduced dose level in advanced or metastatic breast cancer.
  - If QTcF > 480 ms recurs, interrupt treatment and wait until QTcF resolves to < 480 ms, then resume at the next lower dose level.
- **QTcF prolongation > 500 ms**
  Interrupt treatment and wait until QTcF resolves to < 480 ms, then resume at the next lower dose level. If QTcF > 500 ms recurs, discontinue ribociclib.
- **Permanently discontinue:** if QTcF interval prolongation is either > 500 ms or > 60 ms change from baseline AND associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, syncope, or signs/symptoms of serious arrhythmia.

Cutaneous Adverse Reactions Including SCARs (severe cutaneous adverse reactions)

- **Grade 1, 2:** No dose adjustment is required.
- **Grade 3** (severe rash not responsive to medical management; > 30% BSA with

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	active skin toxicity, signs of systemic involvement present; SJS): Interrupt until the etiology of the reaction has been determined. If the etiology is a SCAR, permanently discontinue. If the etiology is not a SCAR, interrupt the dose until recovery to Grade ≤ 1, then resume at the same dose level. If the cutaneous adverse reaction still recurs at Grade 3, resume at the next lower dose level. • **Grade 4** (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences; TEN): Permanently discontinue. **Interstitial Lung Disease/Pneumonitis** • **Grade 1 (asymptomatic):** No dose interruption or adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. • **Grade 2 (symptomatic):** Interrupt treatment until recovery to Grade ≤ 1, then consider resuming at the next lower dose level. If Grade 2 recurs, discontinue. • **Grade 3 (severe symptomatic) or 4 (life-threatening):** Discontinue ribociclib. **Other toxicities** • **Grade 1 or 2:** No dose interruption or adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. • **Grade 3:** Interrupt treatment until recovery to grade ≤1, then resume at the same dose level. If grade 3 recurs, resume at the next lower dose level. • **Grade 4:** Discontinue ribociclib. **Use with Strong CYP3A4 Inhibitors (if avoidance is not possible)** • **Early breast cancer**: Reduce dose to 200 mg once daily with close monitoring. • **Advanced or metastatic breast cancer**: Reduce dose to 400 mg once daily with close monitoring.
Contra-indications	Hypersensitivity to the active substance or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (7% to 15%). **Dermatologic:** Alopecia (15% to 33%), pruritus (7% to 20%), skin rash (9% to 23%). **Endocrine and metabolic**: Decreased serum albumin (12%), decreased serum glucose (10% to 23%), decreased serum phosphate (13% to 18%). **Gastrointestinal**: Abdominal pain (11% to 17%), constipation (13% to 25%), decreased appetite (5% to 19%), diarrhea (15% to 35%; grade 3: ≤1%), nausea (23% to 52%; grade 3: ≤2%), stomatitis (6% to 12%; grade 3: <1%), vomiting (8% to 29%; grade 3: 1% to 4%). **Hematologic and oncologic**: Decreased hemoglobin (47% to 84%; grades 3/4: ≤4%), leukopenia (93% to 95%; grades 3/4: 26% to 36%), lymphocytopenia (51% to 97%; grades 3/4: 14% to 19%), neutropenia (63% to 75%). **Hepatic**: Increased gamma-glutamyl transferase (42% to 52%), increased serum alanine aminotransferase (33% to 46%), increased serum aspartate aminotransferase (37% to 50%). **Infection**: Infection (36% to 42%; including gastroenteritis, respiratory tract infection, sepsis [≤1%], urinary tract infection [11%]).

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	Nervous system: Asthenia (17%), dizziness (9% to 13%), fatigue (22% to 37%), headache (22% to 23%), insomnia (12%). **Neuromuscular and skeletal**: Arthralgia (34%), back pain (20%). **Renal**: Increased serum creatinine (8% to 65%). **Respiratory**: Cough (13% to 22%), dyspnea (7% to 15%). **Miscellaneous**: Fever (11% to 17%). **1% to 10%** **Cardiovascular**: Prolonged QT interval on ECG (≤6%), syncope (≤1%). **Dermatologic**: Erythema of skin (4%), vitiligo (3%), xeroderma (8% to 9%). **Endocrine and metabolic**: Hypocalcemia (2% to 5%), hypokalemia (5%). **Gastrointestinal**: Dysgeusia (7%), dyspepsia (5%), xerostomia (5%). **Hematologic and oncologic**: Febrile neutropenia (≤2%), thrombocytopenia (9%). **Hepatic**: Hepatic injury (≤2%), increased serum bilirubin (1%). **Nervous system**: Vertigo (5%). **Neuromuscular and skeletal**: Limb pain (10%). **Ophthalmic**: Dry eye syndrome (4% to 5%), increased lacrimation (4%). **Respiratory**: Interstitial lung disease (≤2%), oropharyngeal pain (6% to 7%), pneumonia (≤2%), pneumonitis (≤2%).
Monitoring Parameters	• **CBC** before initiation every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. • **Liver function test** before initiation every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. • **ECG** before initiation of treatment in all patients. Repeat ECGs at approximately Day 14 of the first cycle, and as clinically indicated. • **Serum electrolytes** (including potassium, calcium, phosphorus, and magnesium) should be performed before initiation of treatment, at the beginning of the first 6 cycles, and then as clinically indicated.
Drug Interactions	***Risk X: Avoid the combination*** Abrocitinib, Aprepitant, BCG Products, Baricitinib, Bosutinib, Brivudine, Budesonide (Topical), Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, CYP3A4 Inducers (Strong), Dengue Tetravalent Vaccine (Live), Deucravacitinib, Domperidone, Doxorubicin, Elacestrant, Eletriptan, Encorafenib, Entrectinib, Etrasimod, Fexinidazole, Filgotinib, Flibanserin, Fosaprepitant, Ivabradine, Lefamulin, Lemborexant, Levoketoconazole, Lomitapide, Methysergide, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Nirogacestat, Nisoldipine, Orelabrutinib, Pimecrolimus, Pimozide, Piperaquine, Poliovirus Vaccine (Live/Trivalent/Oral), Posaconazole, QT-prolonging Agents (Highest Risk), QT-prolonging Strong CYP3A4 Inhibitors (Highest Risk), Repotrectinib, Ritlecitinib, Sertindole, Simeprevir, St John's Wort, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Thioridazine, Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine, Zoster Vaccine (Live/Attenuated). ***Risk D: Consider therapy modification*** Acalabrutinib, Alfentanil, Alprazolam, Avanafil, Avapritinib, Brigatinib, Bromocriptine, Budesonide (Systemic), Capivasertib, Cariprazine, Cilostazol, Cobimetinib, Coccidioides immitis Skin Test, Colchicine, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), CYP3A4 Inhibitors (Strong),

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	Dapoxetine, Daridorexant, Deferiprone, Deflazacort, Denosumab, Eliglustat, Eplerenone, Fentanyl, Fusidic Acid (Systemic), Gepirone, Guanfacine, Ibrutinib, Influenza Virus Vaccines, Ivacaftor, Leflunomide, Lumateperone, Lurasidone, Lurbinectedin, Mavacamten, Midazolam, Mitapivat, Naloxegol, Nilotinib, Olaparib, Omaveloxolone, Palovarotene, Pemigatinib, Pexidartinib, Polymethylmethacrylate, QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk), Rabies Vaccine, Ranolazine, Rimegepant, Ropeginterferon Alfa-2b, Selumetinib, Sipuleucel-T, Sirolimus (Conventional), Sirolimus (Protein Bound), Sonidegib, Suvorexant, Tamoxifen, Tazemetostat, Tezacaftor and Ivacaftor, Tolvaptan, Triazolam, Ubrogepant, Vaccines (Non-Live/Inactivated/Non-Replicating), Vardenafil, Venetoclax, Voclosporin, Zanubrutinib.
Pregnancy and Lactation	**Pregnancy:** No adequate human data. Based on animal studies, ribociclib can cause fetal harm. Childbearing potential women should use effective contraception during therapy and for at least 21 days after stopping treatment. **Fertility**: Based on animal studies, ribociclib may impair fertility in males of reproductive potential. **Lactation:** No human data. Patients receiving ribociclib should not breast-feed for at least 21 days after the last dose.
Administration	**Oral Administration** • Taken with or without food. • Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. • Tablet should be swallowed whole (do not chew, crush, or split). **Missed dose**: If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk**:** (<30% frequency of emesis)
Warnings/ Precautions	**Neutropenia** • Monitor CBC periodically. Based on the severity of the neutropenia, ribociclib may require dose interruption, reduction, or discontinuation. **QTc prolongation** • Ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients: with long QT syndrome, with electrolyte abnormalities, and with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias. • Any abnormality in electrolytes should be corrected before initiating and during treatment. • ECG should be assessed before initiating treatment. Treatment should be initiated only in patients with QTcF values less than 450 milliseconds. • If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced. **Interstitial lung disease/pneumonitis** • Monitor for pulmonary symptoms, including hypoxia, cough, and dyspnea. • Based on the severity of the ILD or pneumonitis, which may be fatal, ribociclib

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	may require dose interruption, reduction, or discontinuation. **Severe Cutaneous Adverse Reactions (SCARs)** • Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur. • Permanently discontinue therapy in patients with SCARs or other life-threatening cutaneous reactions. **Hepatotoxicity** Increases in serum transaminase and bilirubin levels have been observed. **Blood creatinine increases** Blood creatinine may increase. Evaluate for renal impairment. **CYP3A4 substrates** Ribociclib is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose. Thus, ribociclib may interact with medicinal products that are metabolized via CYP3A4, which may lead to increased serum concentrations of CYP3A4 substrates.
Storage and Light Sensitivity	Store between 15 °C and 30 °C. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient Counselling Keys	• The patient should contact healthcare provider immediately if any of the following have developed: Cardiac disorders (irregular heartbeat, dizziness), pneumonitis (dyspnea, hypoxia, chest pain, cough), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine), dermatological toxicity (severe rash or rash that keeps getting worse, skin pain or burning, blisters on the skin or mouth, skin peeling, with or without fever) or infections. • The patient should tell the doctor before taking any drugs, as the dose may be changed, and avoid grapefruit during treatment.

EGFR tyrosine kinase inhibitors

Erlotinib

Generic Name	Erlotinib
Dosage Form/Strength	Tablet: 100 mg, 150 mg
Route of Administration	Oral
Pharmacologic Category	Epidermal Growth Factor Receptor (EGFR) Inhibitor; Tyrosine Kinase Inhibitor, Antineoplastic Agent ATC: L01EB02

Indications	**N.B.** Refer to the literature and specific protocols for all indications.
	• **Non-Small Cell Lung Cancer (NSCLC)**
	  ○ The treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) activating mutations (exon 19 deletions or exon 21 substitution mutations) as first-line, maintenance, or after failure of at least one prior chemotherapy regimen.
	  ○ In patients with tumours without EGFR activating mutations, erlotinib is indicated when other treatment options are not considered suitable.
	• **Pancreatic cancer**
	  Treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine.

Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing** • **Non-small cell lung cancer** **Oral**: 150 mg Treatment should continue until disease progression or unacceptable toxicity occurs • **Pancreatic cancer** **Oral**: 100 mg Treatment should continue until disease progression or unacceptable toxicity occurs. After 4-8 weeks, further treatment should be reassessed if a rash has not developed. **Pediatrics** Use of erlotinib in pediatric patients is not recommended.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** • **Mild to moderate:** No dose adjustment is necessary. • **Severe renal impairment**: use is not recommended. **Hepatic Impairment**

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	• **Mild to moderate:** No dose adjustment is necessary. Dose reduction or interruption is needed if severe adverse effects occur. • **Severe hepatic impairment (AST and ALT > 5 x ULN)**: Not studied. Use is not recommended
Contra-indications	Hypersensitivity to erlotinib or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Chest pain (18%). **Dermatologic**: Paronychia (14%), pruritus (13% to 16%), skin rash (60% to 85%; including acne vulgaris, bullous dermatitis [≤1%], dermal ulcer, desquamation, eczema, exfoliative dermatitis [≤1%], folliculitis, furuncle, hyperpigmentation, palmar-plantar erythrodysesthesia, skin fissure), xeroderma (12% to 21%). **Gastrointestinal**: Anorexia (52%), decreased appetite (≥30%), diarrhea (20% to 62%; grades 3/4: ≤6%), mucosal swelling (18%), nausea (33%; grade 3: 3%), stomatitis (17%; grade 3: <1%), vomiting (≥20%). **Infection**: Infection (24%). **Nervous system**: Asthenia (≥30%), fatigue (52%). **Neuromuscular and skeletal**: Arthralgia (13%), back pain (19%), musculoskeletal pain (11%). **Ophthalmic**: Conjunctivitis (12% to 18%), eye disease (≤18%; including abnormal eyelash growth, decreased lacrimation, dry eye syndrome [12%], keratitis). **Respiratory**: Cough (48%), dyspnea (41% to 45%). **1% to 10%** **Hepatic**: Abnormal hepatic function tests (including increased serum alanine aminotransferase [grades ≥2: 3% to 4%], increased serum aspartate aminotransferase, increased serum bilirubin [grades ≥2: 5%]).
Monitoring Parameters	• Serum electrolytes, including potassium • Renal functions • Hepatic functions • INR regularly in patients taking warfarin or other coumarin-derivative anticoagulants. • Monitored carefully for symptoms of ILD or ocular toxicity.
Drug Interactions	***Risk X: Avoid the combination*** Fexinidazole, Inhibitors of the Proton Pump (PPIs and PCABs). ***Risk D: Consider therapy modification*** Antacids, Atogepant, Ciprofloxacin (Systemic), CYP1A2 Inducers (Moderate), CYP3A4 Inducers (Strong), CYP3A4 Inhibitors (Strong), Fluvoxamine, Fosphenytoin-Phenytoin, Fusidic Acid (Systemic), Grapefruit Juice, Histamine H2 Receptor Antagonists, Hormonal Contraceptives, Rifabutin, Rifapentine, St John's Wort, Tobacco (Smoked), Ubrogepant. **Notes** **Concomitant use with other agents** **CYP3A4 inhibitors**: Avoid concomitant use. If not possible, reduce erlotinib dose. **CYP3A4 inducers:** Avoid concomitant use. If not possible, increase erlotinib dose. **Cigarette smoking and CYP1A2 inducers:** Avoid concomitant use. If not possible, increase erlotinib dose.

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	Drugs that increase gastric pH decrease erlotinib plasma concentrations. ○ **Proton pump inhibitors**: Avoid concomitant use if possible. ○ **H-2 receptor antagonists:** Take erlotinib 10 hours after H-2 receptor antagonist dosing. ○ **Antacids:** Separate dosing by several hours.
Pregnancy and Lactation	**Pregnancy**: No adequate data. Increased fetal lethality in animal studies. Females of reproductive potential should use effective contraception during therapy and for one month after the last dose. **Lactation:** Not studied. Breastfeeding is not recommended during treatment and for at least 2 weeks after the last dose**.**
Administration	**Hazardous agent:** Only developmental and/ or reproductive hazard**.** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Oral Administration** Administer on an empty stomach, at least one hour before or two hours after the ingestion of food. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk: (<30% frequency of emesis.
Warnings/ Precautions	**Smokers** Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers are reduced, which is clinically significant. **Interstitial Lung Disease** • Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly. Risk factors include concomitant or prior chemotherapy, prior radiotherapy, or lung disease. Symptoms started from a few days to several months after initiating erlotinib therapy. • Withhold for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough, and fever. Discontinue if ILD is diagnosed. **Diarrhea, dehydration, Electrolyte imbalance, and renal failure** • Diarrhea (including very rare fatal cases) has occurred in approximately 50% of patients. Moderate or severe diarrhea should be treated with, e.g., loperamide. • In some cases, dose reduction (by 50 mg) may be necessary. In more severe or persistent cases of diarrhea, or cases leading to dehydration or elderly, erlotinib should be interrupted with IV rehydration as appropriate. • Hypokalemia and renal failure have been rarely reported. **Hepatotoxicity** • Serious cases of drug-induced liver injury (DILI) have been reported. Risk factors may include pre-existing liver disease or concomitant hepatotoxic medications. • Erlotinib should be interrupted if severe changes in liver function occur. Use is not recommended in patients with severe hepatic dysfunction. **Gastrointestinal perforation** • Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, taxane-based chemotherapy, or who have a prior history of peptic ulceration or

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	diverticular disease are at increased risk. • Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation. **Bullous and exfoliative skin disorders** • Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions. • Patients with bullous and exfoliative skin disorders should be tested for skin infection and treated according to local management guidelines. **Ocular disorders** • Caution in patients with a history of keratitis or severe dry eye. • Refer promptly to an ophthalmology specialist if the patient develops signs and symptoms suggestive of keratitis, such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, or red eye. **Interactions with other medicinal products** Potent inducers of CYP3A4 may reduce the efficacy of erlotinib, while potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided. **Microangiopathic hemolytic anemia with Thrombocytopenia** The risk is increased in patients with pancreatic cancer. **Hemorrhage in Patients Taking Warfarin** Severe and fatal hemorrhage associated with International Normalized Ratio (INR) elevations can occur when erlotinib and warfarin are administered concurrently. Monitor prothrombin time and INR regularly.
Storage and Light Sensitivity	Store between 15°C and 30°C. Protect from moisture. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient Counselling Keys	• The patient should contact healthcare provider immediately if any of the following have developed: Lung disease (dyspnea, hypoxia, cough), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine), ocular disorders (lacrimation, light sensitivity, blurred vision, eye pain), gastrointestinal perforations (severe abdominal pain), severe skin reactions (red, blistered, or peeling skin or skin irritation) or cerebrovascular accidents. • The patient should tell the doctor before taking any drugs, as the dose may be changed, and avoid grapefruit during treatment. • Skin reactions can occur or worsen on sun-exposed areas. As prophylaxis patient may use alcohol-free emollient cream and sunscreen or avoid sun exposure. • Diarrhea can usually be managed with loperamide. The patient should contact the healthcare provider for severe or persistent diarrhea. • Hair and nail disorders, including hirsutism and brittle and loose nails, may occur. • Advise patients to stop smoking and to contact their health care provider for any changes in smoking habits, as the dose may need to be changed.

Erlotinib

Pharmaco-genomics	**Gene Testing required** EGFR - Erlotinib ± Ramucirumab or Bevacizumab (Non-Small Cell Lung Cancer) Outcome: Efficacy – Evidence of Testing Benefit: Strong

Gefitinib

Generic Name	Gefitinib
Dosage Form/Strength	Tablets: 250 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Epidermal Growth Factor Receptor (EGFR) Inhibitor; Tyrosine Kinase Inhibitor. ATC Code: L01EB01.
Indications	**N.B.** Refer to the literature and specific protocols for all indications. Monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (exon 19 deletions or exon 21 (L858R) substitution mutations).
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols **Adult dosing** **Oral**: 250 mg tablet once a day, until disease progression or unacceptable toxicity. **Pediatrics** The safety and effectiveness in pediatric patients have not been established.
Dosage Adjustment	N.B. Refer to the protocol used for specific dose modifications. **Renal Impairment** • CrCl >20 ml/min: No dosage adjustment likely to be necessary. • CrCl ≤ 20 ml/min: Limited data. Caution should be taken. **Hepatic Impairment** • Mild Impairment: No dose reduction is necessary. • Moderate or severe impairment: High systemic exposure. Monitor for adverse reactions. May need to reduce the gefitinib dose by 50% according to the literature. **Dose Adjustment for Toxicity** • **Hepatic toxicity during treatment** o Worsening of liver function: Withhold for up to 14 days; may resume when fully resolved or improved to grade 1. o Severe hepatic toxicity (Grade 2 or higher): Permanently discontinue. • **Dermatologic toxicity** o Skin reactions (grade 3 or higher): Withhold gefitinib for up to 14 days; may resume when fully resolved or improved to grade 1. o Severe bullous, blistering, or exfoliating dermatological conditions: Permanent discontinuation may be needed. • **Gastrointestinal toxicity** o Diarrhea (grade 3 or higher): Withhold gefitinib for up to 14 days; may resume when fully resolved or improved to grade 1. o Gastrointestinal perforation: Permanently discontinue gefitinib. • **Ocular toxicity**

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	○ Signs/symptoms of severe or worsening disorders, including keratitis: Withhold gefitinib for up to 14 days; may resume when fully resolved or improved to grade 1. ○ Persistent ulcerative keratitis: Permanently discontinue gefitinib. • **Pulmonary toxicity** ○ Acute onset or worsening symptoms (dyspnea, cough, fever): Withhold for up to 14 days; may resume when fully resolved or improved to grade 1. ○ Confirmed Interstitial lung disease: Permanently discontinue gefitinib.
Contra-indications	Hypersensitivity to the active substance or any of the excipients.
Adverse Drug Reactions	**>10%** **Dermatologic**: Dermatologic reaction (47%). **Gastrointestinal**: Decreased appetite (17%), diarrhea (29%; severe diarrhea: 3%), nausea (18%), vomiting (14%). **Genitourinary**: Proteinuria (35%). **Hepatic**: Increased serum alanine aminotransferase (11% to 38%), increased serum aspartate aminotransferase (8% to 40%). **Neuromuscular and skeletal**: Asthenia (17%). **1% to 10%** **Dermatologic**: Alopecia (5%), nail disease (5%), urticaria (≤1%). **Endocrine and metabolic**: Dehydration (2%). **Gastrointestinal**: Stomatitis (7%), xerostomia (2%). **Hematologic and oncologic**: Hemorrhage (4%; including epistaxis, hematuria). **Hepatic**: Increased serum bilirubin (3%). **Hypersensitivity**: Angioedema (≤1%), hypersensitivity reaction (≤1%). **Ophthalmic**: Blepharitis (≤6%), conjunctivitis (≤6%), dry eye syndrome (≤6%). **Renal**: Increased serum creatinine (2%). **Respiratory**: Acute respiratory distress syndrome (≤1%), interstitial pulmonary disease (≤1%), pneumonitis (≤1%), pulmonary fibrosis (≤1%), pulmonary infiltrates (≤1%). **Miscellaneous**: Fever (9%).
Monitoring Parameters	• Liver function test. • INR or prothrombin time in patients taking warfarin and gefitinib concomitantly. • Monitor for signs/symptoms of dermatologic toxicity, diarrhea, GI perforation, ocular toxicity, and pulmonary toxicity (promptly assess worsening respiratory symptoms, such as dyspnea, cough, and fever).
Drug Interactions	***Risk X: Avoid the combination:*** Fexinidazole, Fusidic Acid (Systemic). ***Risk D: Consider therapy modification:*** Antacids, CYP3A4 Inducers (Strong), H2 Receptor Antagonists, Proton Pump Inhibitors. **Notes** • CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, or barbiturates) may increase the metabolism of gefitinib and decrease gefitinib plasma concentrations and efficacy. Increase dose to 500 mg daily in patients receiving a strong CYP3A4 inducer. • Monitor adverse reactions if concomitant use with CYP3A4 inhibitors or with a

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	potent CYP2D6 inhibitor.
Pregnancy and Lactation	**Pregnancy**: No human data. Reproductive toxicity in animals. Gefitinib should not be used during pregnancy unless clearly necessary. Females of reproductive potential should use effective contraception during treatment and for at least two weeks after discontinuation. **Fertility:** Gefitinib may result in reduced fertility in females of reproductive potential. **Lactation:** No human data. Women should discontinue breastfeeding during treatment due to the potential for serious adverse reactions in nursing infants.
Administration	**Administration: Oral** • Administer with or without food. • For patients unable to swallow the tablet whole, disperse the tablet in half a glass of drinking water and stir for up to 20 minutes; immediately drink the liquid or administer through a naso-gastric tube or gastrostomy tube. • **Missed dose:** If a patient missed a dose, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take two doses at the same time. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk (<30% frequency of emesis).
Warnings/ Precautions	**Interstitial Lung Disease** • Rare cases of interstitial lung disease (ILD) (some are fatal), or other symptoms including acute respiratory distress syndrome, lung infiltration, pneumonitis, or pulmonary fibrosis, have been reported. • Any patient exhibiting worsening respiratory symptoms (cough, fever, dyspnea) should be evaluated immediately, and treatment should be withheld. If confirmed, interstitial lung disease treatment should be discontinued. • In cases of congestive heart failure with symptoms, stop using Gefitinib. **Dermatological toxicities** • Roughly half of the patients experienced skin reactions. • There have been reports of bullous skin conditions such as dermatitis bullosa, Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis. • Treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions. **Hepatotoxicity** • Increases in ALT, AST, and bilirubin, and grade 3 or higher toxicity have been observed. Fatal hepatotoxicity has occurred rarely. Periodic liver function testing is recommended. • Treatment should be interrupted or discontinued according to the severity of hepatotoxicity. **Gastrointestinal effects** • Diarrhea develops in one-third of patients. Grade 3 or 4 diarrhea may occur.

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	• Withhold for severe or persistent diarrhea. Discontinue if GI perforation develops. **Eye disorders** • There have been reports of ocular disorders such as blepharitis, conjunctivitis, keratitis, and corneal erosion. • Evaluate symptoms as soon as possible, including lacrimation, blurred vision, pain in the eyes, red eyes, sensitivity to light, or vision changes. Therapy may be withheld or discontinued according to severity. **Hemorrhage in patients taking warfarin** Monitor changes in prothrombin time or INR.
Storage and Light Sensitivity	• Store between 15°C and 30°C. • Protect from light and moisture. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient Counselling Keys	• The patient should contact healthcare provider immediately if any of the following have developed: Lung disease (dyspnea, hypoxia, cough), Hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine), Ocular disorders (lacrimation, light sensitivity, blurred vision, eye pain), Gastrointestinal perforations (severe abdominal pain), or Severe skin reactions (red, blistered, or peeling skin or skin irritation). • This medication often causes diarrhea. Dehydration can result from diarrhea. The patient should consult the doctor for severe or persistent diarrhea. • The patient should tell the doctor before taking any drugs, including those for acidity and allergy.
Sequence of Administration	**Gene Testing Required** **EGFR - Gefitinib (Non-Small Cell Lung Cancer)** **Outcome:** Efficacy –**Evidence Quality:** Strong • Patients diagnosed with metastatic, non-squamous non-small cell lung cancer (NSCLC) should undergo epidermal growth factor receptor (*EGFR*) testing at diagnosis to determine appropriate initial treatment.

HER2 tyrosine kinase inhibitors

Lapatinib

Generic Name	Lapatinib
Dosage Form/Strength	Tablets: 250 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Anti-HER2; Epidermal Growth Factor Receptor (EGFR) Inhibitor, Tyrosine Kinase Inhibitor. ATC Code: L01EH01.
Indications	**N.B.** Refer to the literature and specific protocols for all indications. **Metastatic or advanced breast cancer whose tumors overexpress HER2** • In combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, including anthracyclines, taxanes, and trastuzumab. • In combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy. • In combination with an aromatase inhibitor for postmenopausal women with hormone receptor-positive metastatic disease, for whom hormonal therapy is indicated and not currently intended for chemotherapy.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing** • **Lapatinib/capecitabine combination** o **Oral**: 1250 mg (i.e., five tablets) once daily continuously on an empty stomach. o The recommended dose of capecitabine is 2000 mg/m^2/day taken in 2 doses 12 hours apart on days 1-14 in a 21-day cycle. • **Lapatinib/trastuzumab combination** o **Oral**: 1000 mg (i.e., four tablets) once daily continuously on an empty stomach. o The recommended dose of trastuzumab is an IV loading dose of 4 mg/kg, followed by IV 2 mg/kg weekly. • **Lapatinib/aromatase inhibitor combination** o **Oral**: 1500 mg (i.e., six tablets) once daily continuously on an empty stomach. o When coadministered with letrozole, the recommended dose of letrozole is 2.5 mg once daily. **Pediatrics** The safety and efficacy in children below 18 years of age have not yet been established. No data are available.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal impairment** • Mild to moderate renal impairment: No dosage adjustment is necessary. • Severe impairment: Caution. No experience. **Hepatic Impairment** • Mild impairment: No dose adjustment necessary.

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- Moderate to severe: Insufficient data. Caution, due to higher lapatinib exposure.
- Severe hepatotoxicity during therapy: Lapatinib should be discontinued immediately and not rechallenged.

Dose Adjustment for Toxicities during therapy (according to NCI CTCAE grading)

Cardiac toxicity

- Grade 1 or 2: No adjustment is needed.
- Grade 3 or greater decreased left ventricular ejection fraction (LVEF) or if their LVEF drops below the institution's lower limit of normal (LLN):

1. Lapatinib therapy should be interrupted for at least two weeks.
2. When the patient is asymptomatic and LVEF returns to normal, Lapatinib treatment can be resumed at a reduced dose:

	Initial dose	Lower dose (after toxicity resolves)
In combination with trastuzumab	1000 mg/day	750 mg/day
In combination with Capecitabine	1250 mg/day	1000 mg/day
In combination with Letrozole	1500 mg/day	1250 mg/day

Interstitial lung disease/pneumonitis

- Grade 1 or 2: No adjustment is needed.
- Grade 3 pulmonary symptoms or greater: Therapy should be discontinued.

Diarrhea

- Grade 1 or 2 without complicating features: No adjustment is needed.
- Patients with grade 3 or grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea or vomiting greater than or equal to NCI CTCAE grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding or dehydration): Lapatinib therapy should be interrupted.
- When diarrhea resolves to grade 1 or less: reintroduce at a lower dose as previous table.
- Grade 4: Permanently discontinue.

Other toxicities

- Grade 2 or greater: Discontinue or interrupt therapy.
- Dosing can be restarted when the toxicity improves to grade 1 or less, at the same doses. If the toxicity recurs, lapatinib should be restarted at a lower dose as previous table.

Contra-indications

Hypersensitivity to the active substance or to any of the excipients.

Adverse Drug Reactions

>10%

Dermatologic: Alopecia (with letrozole: 13%), nail disease (with letrozole: 11%), palmar-plantar erythrodysesthesia (with capecitabine: 53%), pruritus (with letrozole: 12%), skin rash (with capecitabine: 28%; with letrozole: 44%), xeroderma (10% to 13%).

Gastrointestinal: Anorexia (with letrozole: 11%), diarrhea (64% to 65%; grades

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	3/4: ≤13%), dyspepsia (with capecitabine: 11%), nausea (with capecitabine: 44%; with letrozole: 31%; grade 3: ≤2%), stomatitis (with capecitabine: 14% to 15%), vomiting (17% to 26%; grades 3/4: ≤2%). **Hematologic and oncologic**: Decreased hemoglobin (with capecitabine: 56%; grade 3: <1%), decreased neutrophils (with capecitabine: 22%; grades 3/4: ≤3%), decreased platelet count (with capecitabine: 18%; grade 3: <1%). **Hepatic**: Increased serum alanine aminotransferase (37% to 46%), increased serum aspartate aminotransferase (49% to 53%), increased serum bilirubin (with letrozole: 22%; with capecitabine: 45%). **Nervous system**: Asthenia (with letrozole: 12%), fatigue (with letrozole: 20%), headache (with letrozole: 14%). **Neuromuscular and skeletal**: Back pain (with capecitabine: 11%), limb pain (with capecitabine: 12%). **Respiratory**: Dyspnea (with capecitabine: 12%), epistaxis (with letrozole: 11%). **1% to 10%** **Cardiovascular**: Decreased left ventricular ejection fraction (with letrozole: 4%, grades 3/4: <1%; with capecitabine: grade 2: 2%, grade 3: <1%). **Nervous system**: Insomnia (with capecitabine: 10%).
Monitoring Parameters	• CBC with differential. • Liver function test (including transaminases, bilirubin, and alkaline phosphatase) before initiation and monthly thereafter, and as clinically indicated. • Electrolytes, including potassium and magnesium. • Left ventricular ejection fraction before initiation and during treatment. • ECG monitoring if at risk for QTc prolongation before initiation and during treatment. • Monitor for fluid retention and signs/symptoms of pneumonitis, diarrhea (instruct patients to report any changes in bowel habits immediately), and dermatologic toxicity.
Drug Interactions	***Risk X: Avoid combination:*** Bilastine, Dexamethasone (Systemic), Doxorubicin (Conventional), Fexinidazole, Grapefruit Juice, Pazopanib, Pimozide, Repotrectinib, Sirolimus (Protein Bound), St. John's Wort, Topotecan, Vincristine. ***Risk D: Consider therapy modification:*** Afatinib, Alpelisib, Berotralstat, Cladribine, Colchicine, CYP3A4 Inducers (Strong), CYP3A4 Inhibitors (Strong), Digoxin, Fusidic Acid (Systemic), Lefamulin, Lemborexant, Lomitapide, Pralsetinib, Relugolix, Rimegepant, Sirolimus (Conventional), Ubrogepant, Venetoclax.
Pregnancy and Lactation	**Pregnancy**: No human data. Fetal toxicity based on animal studies. Lapatinib should not be used during pregnancy unless clearly necessary. Effective contraceptives should be used during and for at least a week after the last dose. **Lactation:** No human data**.** Breastfeeding must be discontinued in women who are receiving therapy with Lapatinib and for at least a week after the last dose.
Administration	**Oral Administration** • Administer on an empty stomach, 1 hour before or 1 hour after a meal.

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	• Administer the full dose once a day (tablets administered all at once); dividing the dose throughout the day is not recommended. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk (<30% frequency of emesis).
Warnings/ Precautions	**Cardiac toxicity** • Lapatinib has been associated with reports of decreases in LVEF. • Caution in patients with risk factors (including coadministration with potentially cardiotoxic medicinal products). • It is advised to perform baseline and recurring LVEF assessments. **QT prolongation** • Lapatinib has been shown to prolong the QT interval. • Caution and periodic monitoring of electrolytes and electrocardiograms before and during treatment in patients with risk factors. • Risk factors include congenital long QT syndrome, patients taking antiarrhythmic medicines or cumulative high-dose anthracycline therapy, conditions that increase the exposure of lapatinib, such as co-administration of strong CYP3A4 inhibitors or electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia. **Pulmonary toxicity** • There have been reports of pneumonitis and interstitial lung disease in treated patients with lapatinib either in combination or monotherapy. Monitor for symptoms of pulmonary toxicity (dyspnoea, cough, fever). Pulmonary toxicity may be severe and lead to respiratory failure. • Lapatinib should be discontinued in patients who experience grade 3 or greater pulmonary symptoms. **Hepatotoxicity** • Hepatotoxicity may occur, sometimes severe, rarely fatal. There have been reports of total bilirubin >2 times ULN and ALT or AST increases >3 times ULN. The onset of symptoms can be a few days to many months later. • Lapatinib should be discontinued if changes in liver function are severe. Patients should not be retreated. • Severe preexisting hepatic impairment implies dose reduction. **Diarrhea** • Diarrhea is common (usually lasting 4 to 5 days, with an onset within 6 days); it can be severe or even fatal. • Diarrhea can be potentially life-threatening if accompanied by dehydration, renal insufficiency, neutropenia, and/or electrolyte imbalances. Fatal cases have been reported. • Early intervention is key to managing diarrhea; patients should report any changes in their bowel patterns right away. • Prompt treatment of diarrhea with antidiarrheal agents (such as loperamide). Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, use of antibiotics, such as fluoroquinolones (especially if diarrhea is persistent beyond 24 hours, there is fever, or Grade 3 or 4

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	neutropenia), and interruption or discontinuation of lapatinib. **Serious Cutaneous Reactions** • Serious cutaneous reactions have been reported with Lapatinib. • If life-threatening reactions, such as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g., progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment. **Concomitant treatment with inhibitors or inducers of CYP3A4** • Concomitant treatment with inducers of CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin) should be avoided due to the risk of decreased exposure to Lapatinib. • Concomitant treatment with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, voriconazole) should be avoided due to the risk of increased exposure to Lapatinib. • Grapefruit juice should be avoided during treatment with Lapatinib.
Storage and Light Sensitivity	Store between 15°C and 30°C. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient Counselling Keys	• This medication often causes diarrhea. The patient can discuss options with the doctor as soon as possible if they experience diarrhea. • The patient should contact healthcare provider immediately if any of the following have developed: Cardiac disorders (shortness of breath, palpitations, fatigue), lung disease (dyspnea, hypoxia, cough), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, dark-colored urine), diarrhea (any change in bowel patterns or severe diarrhea) or severe skin reactions (red, blistered, peeling skin, skin lesions, sores in your mouth, throat, nose, or eyes). • The patient should tell the doctor before taking any drugs, as the dose may be changed, and avoid grapefruit during treatment.
Pharmaco-genomics	**Testing required** • HER2 - Lapatinib (Breast Cancer) • HER2 - Lapatinib + Trastuzumab (Colorectal Cancer) **Outcome**: Efficacy – **Evidence of Testing Benefit**: Moderate.

Mammalian target of rapamycin (mTOR) kinase inhibitors

Everolimus

Generic Name	Everolimus
Dosage Form/Strengths	Tablets: 0.25 mg, 0.75 mg, 5 mg, 10 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Immunosuppressant Agent; mTOR Kinase Inhibitor ATC: L01EG02, L04AH02
Indications	**N.B.** Refer to the literature and specific protocols for all indications. **Low concentrations (0.25 mg, 0.75 mg)** • **Kidney and heart transplantation** Prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant (in combination with ciclosporin and corticosteroids). • **Liver transplantation** Prophylaxis of organ rejection in adult patients receiving a hepatic transplant (in combination with tacrolimus (reduced doses) and corticosteroids). **Higher concentrations (5 mg, 10 mg)** • **Hormone receptor-positive advanced breast cancer** Treatment of hormone receptor-positive, HER2-negative advanced breast cancer, in combination with exemestane, in postmenopausal women after recurrence or progression following letrozole or anastrozole. • **Neuroendocrine tumors of pancreatic origin** Treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. • **Neuroendocrine tumors of gastrointestinal or lung origin** Treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumors of gastrointestinal or lung origin in adults with progressive disease. • **Renal cell carcinoma** o Treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with sunitinib or sorafenib. o Adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. • **Children (1 year of age or older) and adults with Subependymal Giant Cell Astrocytoma (SEGA),** a brain tumour seen with a genetic condition called Tuberous Sclerosis Complex (TSC). For these patients, their disease has progressed and cannot be treated with surgery. As well, they will not need immediate surgery.

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Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Immunosuppressant indications** • **Kidney and heart transplant** Initial: 0.75 mg twice daily as soon as possible after transplantation. • **Hepatic transplant** Initial**:** 1 mg twice daily, 4 weeks after transplantation. **Maintenance doses** Monitor everolimus concentrations: Adjust maintenance dose to achieve trough concentrations within the 3 to 8 ng/mL target range. **Antineoplastic indications** **Oral**: 10 mg once daily. **Duration**: Therapy is continued as long as clinical benefit is observed or until unacceptable toxicity occurs. **Tuberous Sclerosis Complex (TSC)** • **Tuberous sclerosis complex–associated renal angiomyolipoma** **Oral**: 10 mg once daily, continue treatment until disease progression or unacceptable toxicity. • **Tuberous sclerosis complex–associated partial-onset seizures** **Oral**: Initial: 5 mg/m^2 once daily; adjust dose to attain trough concentrations of 5-15 ng/mL. • **Tuberous sclerosis complex–associated subependymal giant cell astrocytoma SEGA** **Oral**: Initial: 4.5 mg/m^2 once daily; adjust dose to attain trough concentrations of 5-15 ng/mL.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal impairment** No dosage adjustment is required. **Hepatic Impairment** Close monitoring of everolimus blood concentration is needed. • **Renal and cardiac transplantation** **Mild and moderate hepatic impairment:** 0.5 mg twice daily. **Severe hepatic impairment:** 0.25 mg twice daily. • **Liver transplantation** **Mild hepatic impairment:** 0.75 mg twice daily. **Moderate and severe hepatic impairment:** 0.5 mg twice daily. • **Antineoplastic indications and TSC-Associated Renal Angiomyolipoma** **Mild hepatic impairment:** 7.5 mg daily **Moderate hepatic impairment:** 5 mg daily **Severe hepatic impairment:** Use only if the desired benefit outweighs the

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risk. Dose must not exceed 2.5 mg daily.

- **TSC-Associated SEGA and TSC-Associated Partial-Onset Seizures**
  Severe hepatic impairment: 2.5 mg/m^2 orally once daily. Adjust dose based on everolimus trough concentrations as recommended.

Dose Modifications for adverse effects (5 mg, 10 mg)

N.B. Use every other dosing if it reaches the lowest available strength.

- **Non-infectious pneumonitis**
  Grade 1: No adjustment is needed.
  Grade 2: Withhold until improvement to Grade ≤ 1. Resume at 50% of the previous dose. Permanently discontinue if toxicity does not resolve or improve to Grade 1 within 4 weeks.
  Grade 3: Withhold until improvement to Grade ≤ 1. Resume at 50% of the previous dose. Permanently discontinue if toxicity recurs at Grade 3.
  Grade 4: Permanently discontinue.

- **Stomatitis**
  Grade 1: No adjustment is needed.
  Grade 2: Withhold until improvement to Grade ≤ 1. Resume at the same dose. If it recurs at Grade 2, then withhold until improvement to Grade ≤ 1. Resume at 50% of the previous dose.
  Grade 3: Withhold until improvement to Grade ≤ 1. Resume at 50% of the previous dose.
  Grade 4: Permanently discontinue**.**

- **Metabolic events (e.g., hyperglycemia, dyslipidemia)**
  Grade 1 or 2: No adjustment is needed.
  Grade 3: Withhold until improvement to Grade ≤ 2. Resume at 50% of the previous dose.
  Grade 4: Permanently discontinue.

- **Other non-hematologic toxicities**
  Grade 1: No adjustment is needed.
  Grade 2: If toxicity becomes intolerable, withhold until improvement to Grade ≤ 1. Resume at the same dose. If toxicity recurs at Grade 2, withhold until improvement to Grade ≤ 1. Resume at 50% of the previous dose.
  Grade 3: Withhold until improvement to Grade 0 or 1. Consider resuming at 50% of the previous dose. If it recurs at Grade 3, permanently discontinue.
  Grade 4: Permanently discontinue.

- **Thrombocytopenia**
  Grade 1: No adjustment is needed.
  Grade 2: Withhold until improvement to Grade ≤ 1. Resume at the same dose.
  Grade 3 or 4: Withhold until improvement to Grade ≤ 1. Resume at 50% of the previous dose.

- **Neutropenia**

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	Grade 1 or 2: No adjustment is needed. **Grade 3:** Withhold until improvement to Grade ≤ 2. Resume at the same dose. **Grade 4:** Withhold until Grade ≤ 2. Resume at 50% of the previous dose. • **Febrile neutropenia** **Grade 1 or 2:** No adjustment is needed. **Grade 3:** Withhold until improvement to Grade ≤ 2, and no fever. Resume at 50% of the previous dose. **Grade 4:** Permanently discontinue**.** • **Dosage modifications with concomitant use of moderate P-gp and CYP3A4 Inhibitors (if can not be avoided)** **Antineoplastic Indications and TSC-Associated Renal Angiomyolipoma** Reduce dose to 2.5 mg once daily. May increase to 5 mg if tolerable. Resume the dose administered before inhibitor initiation, once the inhibitor is discontinued for 3 days. Close clinical monitoring is needed. **TSC-Associated SEGA and TSC-Associated Partial-Onset Seizures** Reduce the daily dose by 50%. Resume the dose administered before inhibitor initiation, once the inhibitor is discontinued for 3 days. Assess through concentrations. • **Dosage Modifications with concomitant use of strong P-gp and CYP3A4 Inducers** **Antineoplastic Indications and TSC-Associated Renal Angiomyolipoma** If coadministration cannot be avoided, double the daily dose using increments of 5 mg or less. Resume the dose administered before inducer initiation, once an inducer is discontinued for 5 days. **TSC-Associated SEGA and TSC-Associated Partial-Onset Seizures** Double the daily dose using increments of 5 mg or less. Multiple increments may be required. Assess through concentrations. Resume the dose administered before starting any inducer, once all inducers are discontinued for 5 days.
Contra-Indications	Hypersensitivity to everolimus, sirolimus, or any component of the formulation.
Adverse Drug Reactions	**Transplantation indications** **>10%** **Cardiovascular**: Hypertension (17% to 30%), peripheral edema (kidney transplant: 45%; liver transplant: 18% to 20%). **Endocrine and metabolic**: Diabetes mellitus (new onset: kidney transplant: 9%; liver transplant: 32%), hypercholesterolemia (9% to 17%), hyperglycemia (kidney transplant: 12%), hyperkalemia (kidney transplant: 18%), hypokalemia (kidney transplant: 12%), hypomagnesemia (kidney transplant: 14%), hypophosphatemia (kidney transplant: 13%). **Gastrointestinal**: Abdominal pain (13% to 15%), constipation (kidney transplant: 38%), diarrhea (19% to 24%), nausea (kidney transplant: 29%; liver transplant: 14% to 15%), vomiting (kidney transplant: 15%). **Genitourinary**: Dysuria (kidney transplant: 11%), hematuria (kidney transplant: 12%), urinary tract infection (kidney transplant: 22%).

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Hematologic and oncologic: Anemia (kidney transplant: 26%), leukopenia (3% to 13%).
Hepatic: Hepatitis C (liver transplant: 11% to 14%).
Infection: Bacterial infection (liver transplant: 16%), infection (kidney transplant: 62% to 64%; liver transplant: 50%), viral infection (kidney transplant: 10%; liver transplant: 17%).
Nervous system: Fatigue (9% to 11%), headache (18% to 22%), insomnia (kidney transplant: 17%; liver transplant: 6% to 7%).
Neuromuscular and skeletal: Back pain (kidney transplant: 11%), limb pain (kidney transplant: 12%).
Renal: Increased serum creatinine (kidney transplant: 18%).
Respiratory: Upper respiratory tract infection (kidney transplant: 16%).
Miscellaneous: Fever (13% to 19%), wound healing impairment (kidney transplant: 35%; liver transplant: 11%; includes dehiscence, incisional hernia, lymphocele, seroma).

1% to 10%

Cardiovascular: Angina pectoris, atrial fibrillation, chest discomfort, chest pain, deep vein thrombosis, edema, heart failure, hypertensive crisis, hypotension, palpitations, phlebitis, pulmonary embolism, syncope, tachycardia, venous thromboembolism.
Dermatologic: Acne vulgaris, acneiform eruption, alopecia, cellulitis, diaphoresis, ecchymoses, folliculitis, hypertrichosis, night sweats, onychomycosis, pruritus, skin rash, tinea pedis.
Endocrine and metabolic: Acidosis, amenorrhea, cushingoid appearance, dehydration, fluid retention, hypercalcemia, hyperparathyroidism, hypertriglyceridemia, hyperuricemia, hypocalcemia, hypoglycemia, hyponatremia, hypothyroidism, iron deficiency, vitamin B_{12} deficiency.
Gastrointestinal: Abdominal distention, anorexia, biliary obstruction, cholangitis, cholestasis, decreased appetite, dyspepsia (kidney transplant: 4%), dysphagia, epigastric distress, flatulence, gastritis, gastroenteritis, gastroesophageal reflux disease, gingival hyperplasia, hematemesis, hemorrhoids, hernia of abdominal cavity, inguinal hernia, intestinal obstruction, oral candidiasis, oral herpes simplex infection, oral mucosa ulcer, peritoneal effusion, peritonitis, stomatitis (kidney transplant: 8%), upper abdominal pain (kidney transplant: 3%).
Genitourinary: Benign prostatic hypertrophy, bladder spasm, erectile dysfunction (kidney transplant: 5%), nocturia, ovarian cyst, perinephric abscess, perinephric hematoma, pollakiuria, polyuria, proteinuria, pyuria, scrotal edema, urethritis, urinary retention, urinary urgency.
Hematologic and oncologic: Benign neoplasm (≤4%), leukocytosis, lymphadenopathy, lymphorrhea, malignant neoplasm (≤4%), neutropenia, pancytopenia, thrombocytopenia.
Hepatic: Abnormal hepatic function tests (liver transplant: 7% to 8%), ascites (liver transplant: 4%), hepatitis (noninfectious), increased liver enzymes, increased serum alkaline phosphatase, increased serum bilirubin.
Infection: Bacteremia, BK virus (kidney transplant: 1%), candidiasis, cytomegalovirus disease (1%), fungal infection (liver transplant: 2%), herpes virus infection, influenza, sepsis, wound infection.

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Nervous system: Agitation, anxiety, asthenia, chills, depression, dizziness, drowsiness, hallucination, hemiparesis, hypoesthesia, lethargy, malaise, migraine, myasthenia, neuralgia, pain, paresthesia, tremor (8% to 10%).

Neuromuscular and skeletal: Arthralgia, gout, joint swelling, muscle spasm, musculoskeletal pain, myalgia, osteoarthritis, osteomyelitis, osteoporosis, spondylitis.

Ophthalmic: Blurred vision, cataract, conjunctivitis.

Renal: Hydronephrosis, increased blood urea nitrogen, interstitial nephritis, kidney failure (5% to 10%; may be acute), kidney impairment, pyelonephritis, renal artery thrombosis, renal tubular necrosis.

Respiratory: Atelectasis, bronchitis, cough (kidney transplant: 7%), dyspnea, epistaxis, lower respiratory tract infection, nasal congestion, nasopharyngitis, oropharyngeal pain, paranasal sinus congestion, pleural effusion (liver transplant: 5%), pneumonia, pulmonary edema, rhinorrhea, sinusitis, wheezing.

Antineoplastic indications

>10%

Cardiovascular: Edema (≤39%), hypertension (4% to 13%), peripheral edema (≤39%).

Dermatologic: Acne vulgaris (10% to 22%), nail disease (5% to 22%), pruritus (12% to 21%), skin rash (21% to 59%), xeroderma (13%).

Endocrine and metabolic: Amenorrhea (15% to 17%), decreased serum bicarbonate (56%), hypercholesterolemia (66% to 85%), hyperglycemia (13% to 75%), hypertriglyceridemia (27% to 73%), hypoalbuminemia (13% to 18%), hypocalcemia (37%), hypokalemia (23% to 27%), hypophosphatemia (9% to 49%), irregular menses (10% to 11%), weight loss (5% to 28%).

Gastrointestinal: Abdominal pain (5% to 36%), anorexia (25%), constipation (10% to 14%), decreased appetite (6% to 30%), diarrhea (14% to 50%; grades 3/4: 2% to 9%), dysgeusia (5% to 19%), gastroenteritis (10% to 12%), mucosal swelling (19%), nausea (8% to 26%; grades 3/4: 2% to 3%), stomatitis (44% to 78%; grades 3/4: 4% to 9%), vomiting (15% to 29%; grade 3: 1% to 4%), xerostomia (8% to 11%).

Genitourinary: Proteinuria (18%), urinary tract infection (9% to 31%).

Hematologic and oncologic: Anemia (41% to 92%; grades 3/4: 5% to 15%), decreased serum fibrinogen (8% to 38%), leukopenia (37% to 49%; grades 3/4: 2%), lymphocytopenia (20% to 66%; grades 3/4: 1% to 18%), neutropenia (14% to 46%; grades 3/4: ≤9%), prolonged partial thromboplastin time (63% to 72%; grade 3: 3%), prolonged prothrombin time (40%), thrombocytopenia (19% to 45%; grades 3/4: 1% to 3%).

Hepatic: Increased serum alanine aminotransaminase (18% to 48%), increased serum alkaline phosphatase (32% to 74%), increased serum aspartate aminotransferase (23% to 57%).

Infection: Infection (37% to 58%).

Nervous system: Aggressive behavior (≤21%), anxiety (≤21%), asthenia (23% to 33%), behavioral changes (≤21%; including agitation, obsessive compulsive disorder, panic attack), dizziness (7% to 12%), fatigue (≤45%),

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	headache (≤30%), insomnia (6% to 14%), malaise (≤45%), migraine (≤30%). **Neuromuscular and skeletal**: Arthralgia (13% to 15%), back pain (15%), limb pain (8% to 14%), myalgia (11%). **Renal**: Increased serum creatinine (5% to 50%). **Respiratory**: Cough (≤30%), dyspnea (≤24%), dyspnea on exertion (≤20%), epistaxis (5% to 22%), nasopharyngitis (≤25%), oropharyngeal pain (11%), pneumonia (6% to 19%), pneumonitis (1% to 17%; including interstitial lung disease, pulmonary alveolar hemorrhage, pulmonary alveolitis, pulmonary fibrosis, pulmonary infiltrates, pulmonary toxicity, restrictive pulmonary disease), productive cough (≤25%), respiratory tract infection (31%), rhinitis (≤25%), upper respiratory tract infection (≤25%). **Miscellaneous**: Fever (20% to 31%). **1% to 10%** **Cardiovascular**: Chest pain (5%), heart failure (1%), pulmonary embolism (2%), tachycardia (3%), thrombosis (1%). **Dermatologic**: Acneiform eruption (3%), cellulitis (6%), erythema of skin (4%), onychoclasis (4%), palmar-plantar erythrodysesthesia (5%), skin lesion (4%). **Endocrine and metabolic**: Diabetes mellitus (10%; new onset: <1%), exacerbation of diabetes mellitus (2%), heavy menstrual bleeding (6% to 10%), increased follicle-stimulating hormone (3%), increased luteinizing hormone (1% to 4%), menstrual disease (6% to 10%). **Gastrointestinal**: Dysphagia (4%), hemorrhoids (5%). **Genitourinary**: Abnormal uterine bleeding (6%), azoospermia (1%), dysmenorrhea (6%), ovarian cyst (3%), vaginal hemorrhage (8%) **Hematologic and oncologic**: Hemorrhage (3%). **Hepatic**: Hyperbilirubinemia (3%). **Hypersensitivity**: Angioedema (≤1%), hypersensitivity reaction (3%). **Nervous system**: Chills (4%), depression (5%), paresthesia (5%). **Neuromuscular and skeletal**: Jaw pain (3%), muscle spasm (10%). **Ophthalmic**: Conjunctivitis (2%), eyelid edema (4%). **Otic**: Otitis media (6%). **Renal**: Kidney failure (3%). **Respiratory**: Pharyngolaryngeal pain (4%), pleural effusion (7%), rhinorrhea (3%), streptococcal pharyngitis (10%).
Monitoring Parameters	• CBC with differential before and periodically during treatment. • Renal function, including serum creatinine, blood urea nitrogen (BUN), and urinary protein, baseline and periodically during treatment. • Liver function baseline and periodic during treatment. • Blood Glucose level baseline and annually. • Lipid Profile baseline and annually. • Monitor for respiratory symptoms or radiologic changes. • Monitor for stomatitis and fungal infection. **For immunosuppressant indications only** • Monitor everolimus blood concentrations to adjust maintenance dose: Target trough concentration range should be within the 3 to 8 ng/mL based on chromatographic methods.

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	• Monitor blood concentrations every 4 to 5 days after initiation or dose adjustment until 2 consecutive trough concentrations show stable everolimus concentrations. **For Tuberous Sclerosis Complex (TSC) Associated Subependymal Giant Cell Astrocytoma (SEGA) and TSC-Associated Partial-Onset Seizures** • Target trough concentrations of 5 ng/mL to 15 ng/mL. • Monitor blood concentrations 1 to 2 weeks after initiation or adjustment of dosing or Initiation or discontinuation of P-gp and moderate CYP3A4 inducers or inhibitors.
Drug Interactions	***Risk X: Avoid the combination*** Abrocitinib, Antihepaciviral Combination Products, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Grapefruit Juice, Inhibitors of CYP3A4 (Strong) and P-glycoprotein, Mumps-Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Cyclosporine (Systemic), CYP3A4 Inducers (Strong), CYP3A4 Inhibitors (Strong), Deferiprone, Denosumab, Inducers of CYP3A4 (Strong) and P-glycoprotein, Influenza Virus Vaccines, Inhibitors of CYP3A4 (Moderate) and P-glycoprotein, Leflunomide, Lemborexant, Lomitapide, Lonafarnib, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Sirolimus (Protein Bound), St John's Wort, Ubrogepant, Vaccines (Inactivated/Non-Replicating). **CYP3A4 Inhibitors and P-gp Inhibitors may Increase Everolimus Blood Concentrations** • **Strong inhibitors:** Coadministration should be avoided. e.g. ketoconazole. • **Moderate inhibitors:** Reduction of everolimus dose is needed**,** e.g., erythromycin, verapamil. **Strong CYP3A4 inducers and PgP inducers may decrease Everolimus Blood Concentrations:** Dose increase is required.
Pregnancy and Lactation	**Pregnancy:** No adequate human data. Reproductive toxicity in animal studies. Women of childbearing potential should use effective contraception during and up to 8 weeks after stopping treatment. **Fertility:** Male infertility and secondary amenorrhoea have been observed. Reversible azoospermia and oligospermia in patients treated with mTOR inhibitors have been reported. **Lactation:** No human data. In animal studies, everolimus was readily transferred into the milk of lactating rats. Therefore, women who are taking everolimus should not breast-feed.

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Administration	**Hazardous agent:** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: Oral** • May be administered with or without food; to reduce variability, take consistently with the same food. • Drink a glass of water and swallow it whole. Avoid breaking, chewing, or crushing tablets (do not provide crushed or broken tablets). **Missed dose**: If a dose is missed, it can be administered up to 6 hours after the usual time of administration. After more than 6 hours, the dose should be skipped for that day. The next day, administer it at its usual time. Double doses should not be administered to make up for the dose that was missed. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	**Minimal to low emetic risk:** (<30% frequency of emesis).
Warnings/ Precautions	**Severe hypersensitivity reactions** Permanently discontinue for clinically significant hypersensitivity (anaphylaxis, dyspnea, flushing, chest pain, and angioedema). **Angioedema** Everolimus is associated with the development of angioedema; using it concurrently with other medications that are known to induce angioedema (e.g., ACE inhibitors) may raise the risk. Permanently discontinue for angioedema. **Myelosuppression** • There have been reports of decreases in lymphocytes, platelets, neutrophils, and hemoglobin, including grade 3 and 4 occurrences. • Monitor at baseline, follow up every six months for the first year of treatment, then once a year after that. • Withhold or permanently discontinue based on severity. **Infections** • Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis, candidiasis, or PJP/PCP, and viral infections, including reactivation of hepatitis B virus, have been reported. Some of these infections have been severe and occasionally fatal, mostly associated with concomitant use of corticosteroids or other immunosuppressive agents. • Monitor for signs and symptoms of infection. Due to the potential increased risk of infection, avoid the use of live vaccines. • Withhold or permanently discontinue based on severity. Pre-existing infections should be treated appropriately and resolved before initiation of treatment. **Metabolic effects** • There have been reports of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia, including grade 3 and 4 occurrences. • Monitor blood glucose level and lipid profile before initiation and annually

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thereafter. In diabetic patients, monitor fasting serum glucose more frequently as clinically indicated. Increased risk of new-onset diabetes mellitus after transplantation.

- Grade 3 to 4 metabolic events: withhold or permanently discontinue based on severity. Consider anti-lipid therapy for hyperlipidemia.

Stomatitis

- Mucositis and mouth ulcers are frequently associated with Everolimus. Usually, stomatitis develops during the first 8 weeks of treatment.
- Management of stomatitis may include prophylactic and/or therapeutic use of an alcohol-free corticosteroid oral solution as a mouthwash. Products containing alcohol, hydrogen peroxide, iodine, and thyme derivatives should be avoided as they may exacerbate the condition.
- If a fungal infection has not been detected, do not use systemic antifungals due to the significant risk of medication interactions.

Renal toxicity

- Elevations of serum creatinine and proteinuria. Cases of acute renal failure, some with a fatal outcome, have been reported.
- Monitor renal function before treatment and periodically thereafter (annually, or at least every 6 months in patients who have additional risk factors for renal failure).

Non-infectious pneumonitis

- Non-infectious pneumonitis cases have been reported with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnoea. Some cases were reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event.
- Monitor for symptoms or radiologic changes.
- Manage by dose reduction or discontinuation until symptoms resolve.
- Grade 2 to 4 non-infectious pneumonitis: Withhold or permanently discontinue based on severity. Use of corticosteroids may be indicated until clinical symptoms resolve.
- For patients who require the use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for opportunistic infections, PJP/PCP may be considered.

Radiation sensitization/recall

In patients treated with radiation before, during, or after treatment with everolimus, radiation sensitization and recall (some are severe or involving cutaneous and visceral organs [e.g., esophagitis, pneumonitis]) may occur.

Wound healing impairment

- Vascular endothelial growth factor receptor inhibitors are associated with impaired wound healing.
- Withhold everolimus for at least 1 week before elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.

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	• The safety of resuming everolimus treatment after resolution of wound healing complications has not been established. **Lymphomas and other malignancies** • Patients receiving immunosuppressives are at increased risk of developing lymphomas or other malignancies, particularly of the skin. • Patients should be monitored regularly for skin neoplasms and advised to minimise exposure to UV light and sunlight, and to use appropriate sunscreen. **Co-administration with a calcineurin inhibitor** • The concomitant administration with a calcineurin inhibitor (e.g., cyclosporine, tacrolimus) may increase the risk of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy. • In renal and cardiac transplantation, everolimus with full-dose ciclosporin increases the risk of renal dysfunction. Reduced doses of ciclosporin are required to avoid renal dysfunction in patients with elevated serum creatinine levels.
Storage and Light Sensitivity	• Store between 15°C and 30°C. • Protect from light. Protect from moisture. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient Counseling Keys	• The patient should contact a healthcare provider immediately if any of the following have developed: angioedema (swelling, dizziness, digestive problems), lung disease (dyspnea, hypoxia, cough). • Blood cell count may be changed. The patient should avoid causes of infection and bleeding and report any related symptoms immediately. Advise patients that live vaccines should be avoided. • The patient should tell the doctor before taking any drugs, as additional blood tests or a different dosage may be needed. The patient should avoid grapefruit during treatment. • Patient should monitor glucose and lipids periodically during therapy and perform laboratory tests regularly as directed • To avoid skin malignancy, exposure to UV light and sunlight should be minimized, accompanied by appropriate sunscreen. • There is a risk of stomatitis. Alcohol-free mouthwashes during treatment may be used. • The patient should inform the healthcare provider about any planned surgical procedure due to the decreased wound healing effect of the drug, and about any radiation therapy, as radiation sensitization and recall can occur.
Pharmaco-genomics	**Testing recommended** **TSC1/2 - Everolimus (Subependymal Giant Cell Astrocytoma (SEGA))** **Outcome**: Efficacy. **Evidence of Testing Benefit:** Moderate In patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma, consider molecular genetic testing as appropriate.

Other protein kinase inhibitors

Sorafenib

Generic Name	Sorafenib
Dosage Form/Strengths	Tablets: 200 mg, 400 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Tyrosine Kinase Inhibitor; Vascular Endothelial Growth Factor (VEGF) Inhibitor. ATC Code: L01EX02.
Indications	**N.B.** *Refer to the literature and specific protocols for all indications.* **Indicated in the treatment of** • Unresectable hepatocellular carcinoma (HCC). • Advanced renal cell carcinoma (RCC) patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2-based therapy or who are not suitable for such therapy. • Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols**.** **Adult Dosing** **Oral**: 400 mg twice daily on an empty stomach. **Duration**: Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. **Pediatrics** No data. Safety and efficacy in children and adolescents aged < 18 years have not yet been established.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** • No dose adjustment is necessary in renal impairment of any degree. • Dialysis patients: No data. **Hepatic Impairment** • **Mild or moderate hepatic impairment**: No dose adjustment is necessary. • **Severe hepatic impairment**: Not studied. **Dose modifications due to adverse effects** • **Hepatocellular carcinoma and advanced renal cell carcinoma** **Oral:** 400 mg once daily. If necessary, the dose may be further reduced to 200 mg once daily or 400 mg every other day. • **Differentiated thyroid carcinoma (DTC)** **Oral:** 600 mg daily in divided doses (two tablets of 200 mg and one tablet of 200 mg, twelve hours apart). If necessary, the dose may be further reduced to 400 mg daily in divided doses. Another reduction to one tablet

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	of 200 mg once daily may be needed.
Contra-indications	Hypersensitivity to the active substance or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Hypertension (9% to 41%). **Dermatologic**: Alopecia (14% to 67%), palmar-plantar erythrodysesthesia (21% to 69%), pruritus (14% to 20%), skin rash (including desquamation; 19% to 40%), xeroderma (10% to 13%). **Endocrine and metabolic**: Hypoalbuminemia (59%), hypocalcemia (12% to 36%), hypophosphatemia (35% to 45%), increased amylase (30% to 34%), increased thyroid stimulating hormone level (>0.5 mU/L: 41%), weight loss (10% to 49%). **Gastrointestinal**: Abdominal pain (11% to 31%), anorexia (16% to 29%), constipation (14% to 16%), decreased appetite (30%), diarrhea (43% to 68%), gastrointestinal hemorrhage, increased serum lipase (40% to 41%), nausea (21% to 24%), stomatitis (24%; grades 3/4: 2%), vomiting (11% to 16%). **Hematologic and oncologic**: Anemia, hemorrhage (15% to 17%; grades 3/4: 2%), increased INR (42%; grades 3/4: 4%), leukopenia, lymphocytopenia (23% to 47%; grades 3/4: 13%), neutropenia (18%; grades 3/4: 5%), thrombocytopenia (12% to 46%; grades 3/4: 1% to 4%). **Hepatic**: Hepatic insufficiency (11%), increased serum alanine aminotransferase (59%), increased serum aspartate aminotransferase (54%). **Infection**: Infection. **Nervous system**: Fatigue (37% to 46%), headache (10% to 17%), mouth pain (14%), pain (including tumor pain), peripheral sensory neuropathy (13%), voice disorder (13%). **Neuromuscular and skeletal**: Asthenia (12%), limb pain (15%), ostealgia. **Respiratory**: Dyspnea (14%), respiratory tract hemorrhage. **Miscellaneous**: Fever (11%). **1% to 10%** **Cardiovascular**: Cardiac failure (2%), flushing, ischemic heart disease (including myocardial infarction: 2% to 3%). **Dermatologic**: Acne vulgaris, erythema of skin (10%), exfoliative dermatitis, folliculitis, hyperkeratosis (7%). **Endocrine and metabolic**: Hypokalemia (5% to 10%), hyponatremia, hypothyroidism. **Gastrointestinal**: Dysgeusia (6%), dyspepsia, dysphagia, gastroesophageal reflux disease, glossalgia, xerostomia. **Genitourinary**: Erectile dysfunction, proteinuria. **Hematologic and oncologic**: Squamous cell carcinoma of skin (3%; grades 3/4: 3%). **Nervous system**: Depression. **Neuromuscular and skeletal**: Arthralgia (10%), muscle spasm (10%), myalgia. **Renal**: Renal failure syndrome.

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	Respiratory: Epistaxis (7%), flu-like symptoms, rhinorrhea. **Postmarketing** **Dermatologic**: Stevens-Johnson syndrome, toxic epidermal necrolysis. **Hematologic and oncologic**: Thrombotic microangiopathy. **Hypersensitivity**: Angioedema. **Neuromuscular and skeletal**: Osteonecrosis of the jaw, rhabdomyolysis.
Monitoring Parameters	• CBC with differential • Liver function test regularly • Blood glucose level • Electrolytes: (Magnesium, potassium, calcium, phosphate). • Blood pressure (baseline, weekly for the first 6 weeks, then periodically). • ECG in patients at risk for prolonged QT interval. • Renal function test (in the elderly) • Thyroid function testing monthly in DTC patients. • Prothrombin time, INR, or clinical bleeding episodes in patients taking warfarin. • Monitor for signs/symptoms of bleeding and GI perforation.
Drug Interactions	***Risk X: Avoid the combination*** BCG (Intravesical), Chloramphenicol (Systemic), Cladribine, CYP3A4 Inducers (Strong), Fexinidazole, Irinotecan Products, Linzagolix, Neomycin (Systemic), Paclitaxel, Sacituzumab. ***Risk D: Consider therapy modification*** Acetaminophen, Belinostat, Carboplatin, Cholic Acid, Deferiprone, Obeticholic Acid, Propacetamol, Ropeginterferon Alfa-2b, Taurursodiol.
Pregnancy and Lactation	**Pregnancy**: No human data. Reproductive toxicity in animal studies, including malformations**.** Advise female patients and male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months following the last dose. **Fertility**: May impair fertility in males of reproductive potential. **Lactation**: Sorafenib is excreted in milk. Due to the potential for serious adverse reactions in the breastfed infant, discontinuing breastfeeding during treatment and for 2 weeks after the final sorafenib dose is recommended.
Administration	**Hazardous agent:** Only developmental and/ or reproductive hazard. use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Oral Administration** Administer without food (at least 1 hour before or 2 hours after a meal). **Missed doses**: If a dose is missed, the next dose should be taken at the regularly scheduled time, and not double the dose. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	**Minimal to low emetic risk:** (<30% frequency of emesis)
Warnings/ Precautions	**Dermatologic toxicity** • Hand-foot skin reaction and rash (generally grades 1 or 2) are the most common drug-related adverse events and typically appear within the

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first 6 weeks of sorafenib treatment.

- Symptomatic topical treatment is recommended. Temporary interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib, may be needed.

Hypertension

- Sorafenib may cause hypertension (usually mild to moderate), which occurs in the early course of sorafenib treatment and is amenable to management with standard antihypertensive therapy.
- Monitoring blood pressure weekly during the first 6 weeks of treatment, and periodically thereafter.
- Consider discontinuation (temporary or permanent) in patients who develop severe or persistent hypertension while on appropriate antihypertensive therapy.

Aneurysms and artery dissections

Risk factors include hypertension or a history of aneurysm. Evaluate risk before initiation.

Hemorrhage

- An increased risk of bleeding may occur.
- Permanent discontinuation is recommended with serious bleeding events (requiring medical intervention).
- Thyroid cancer patients with tracheal, bronchial, and esophageal infiltration should be treated with local therapy before administering sorafenib due to the potential bleeding risk.
- Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR, or clinical bleeding episodes

Hypoglycemia

- Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalization due to loss of consciousness, have been reported during sorafenib treatment.
- In case of symptomatic hypoglycaemia, sorafenib should be temporarily interrupted.

Cardiac ischemia/infarction

- Cardiac ischemia/infarction events were higher in the sorafenib group compared with the placebo group.
- Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischaemia and/or infarction

QT interval prolongation

- Sorafenib has been shown to prolong the QT/QTc interval, which may lead to an increased risk for ventricular arrhythmias.
- Caution and periodic monitoring of electrolytes and electrocardiograms, during treatment in patients with risk factors.
- Risk factors include congenital long QT syndrome, treatment with a high cumulative dose of anthracycline therapy, certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia.
- Interrupt if QTc interval is greater than 500 milliseconds or for an

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	increase from baseline of 60 milliseconds or greater. **Gastrointestinal perforation** • GI perforation has been reported (in less than 1% of patients). Permanently discontinue sorafenib treatment if GI perforation occurs. **Hepatotoxicity** • Sorafenib-induced hepatitis (characterized by a hepatocellular pattern of liver damage with significant increases in transaminases) may result in hepatic failure and death. Bilirubin elevations and INR increases may also occur. • Monitor liver functions regularly. Discontinue sorafenib if significantly increased transaminases occur without an alternative explanation (e.g., viral hepatitis, progressing underlying malignancy). **Wound healing complications** • Vascular endothelial growth factor receptor inhibitors are associated with impaired wound healing; therefore, sorafenib may affect wound healing. • As a precautionary measure, withhold sorafenib treatment for at least 10 days before elective surgery. Do not administer sorafenib for at least 2 weeks following major surgery and until adequate wound healing. **Differentiated thyroid carcinoma (DTC)** • **Hypocalcemia:** When using sorafenib in patients with DTC, close monitoring of blood calcium levels is recommended. Severe hypocalcaemia should be corrected to prevent complications such as QT prolongation or torsade de pointes. • **Thyroid impairment**: Sorafenib impairs exogenous thyroid suppression. TSH level elevations were commonly observed in the thyroid carcinoma study; monitor TSH levels monthly and as clinically necessary, and adjust thyroid replacement as needed.
Storage and light sensitivity	• Store between 15°C and 30°C. • Protect from moisture. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Patient counselling keys	• The patient should contact healthcare provider immediately if any of the following have developed: cardiovascular disorders (chest pain, shortness of breath, palpitations, swelling of an extremity), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, and dark-colored urine), gastrointestinal perforation (severe abdominal pain) or Bleeding episode. • Conditions called hand-foot skin reactions and skin rash are common and can be severe. The patient should tell the healthcare provider if they developed any of the following symptoms: skin rash, skin redness, pain or swelling, or blistering and peeling of your skin, palm, or inside of your mouth. • The patient should tell the doctor before taking any drugs. • Blood pressure and glucose levels should be checked regularly during treatment. • Wounds may not heal properly during treatment. The patient should tell the healthcare provider if planning to have any surgery before starting or

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	during treatment with sorafenib.

Sunitinib

Generic Name	Sunitinib
Dosage Form/Strength	Capsules: 12.5mg, 25mg, 37.5 mg, 50mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, BCR-ABL Tyrosine Kinase Inhibitor, Vascular endothelial growth factor (VEGF) inhibitor. ATC: L01EX01
Indications	**N.B.** Refer to the literature and specific protocols for all indications used. **Gastrointestinal stromal tumour (GIST)** Sunitinib is indicated for the treatment of gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance. **Renal cell carcinoma (RCC)** Sunitinib is indicated for the treatment of advanced/metastatic renal cell carcinoma (RCC) in adults. Adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy. **Pancreatic neuroendocrine tumours (pNET)** Sunitinib is indicated for the treatment of progressive, unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) in adults.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adults dosing** • **Gastrointestinal stromal tumor (GIST) and Renal cell carcinoma (RCC)** **Oral**: 50 mg once daily for 4 weeks of a 6-week treatment cycle (4 weeks on, 2 weeks off). **Duration** o Adjuvant Treatment of RCC: for a maximum of 9 cycles. o GIST and advanced/metastatic RCC: until disease progression or unacceptable toxicity. • **Pancreatic neuroendocrine tumors (pNET)** **Oral:** 37.5 mg once daily, continuous daily dosing until disease progression or unacceptable toxicity. **Pediatrics** The safety and efficacy of Sunitinib in patients below 18 years of age have not been established.
Dosage Adjustment	N.B. Refer to the protocol used for specific dose modifications. **Renal impairment** • No initial dose adjustment is recommended at any stage of renal impairment. • **Hemodialysis**: Due to decreased exposure, subsequent doses may be increased gradually up to 2-fold based on safety and tolerability.

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Hepatic Impairment

- **Mild or moderate impairment:** No initial dose adjustment.
- **Severe hepatic impairment:** Not studied. Use is not recommended.

➢ **Dose adjustments (according to safety and tolerability)**

- **GIST and MRCC:** Dose may be increased to 75 mg or reduced to 25 mg in dose steps of 12.5 mg**.**
  Adjuvant RCC: Dose can be decreased to 37.5 mg once daily only.
- **pNET:** Dose may be increased up to 50 mg or decreased to 25 mg**.**
- Dose interruptions may be required based on individual safety and tolerability.

Hepatotoxicity during treatment

- Grade 1 or 2: No adjustment is required.
- Grade 3: Interrupt sunitinib until resolution to Grade ≤1 or baseline and resume sunitinib at a reduced dose; discontinue if no resolution.
- Grade 4 hepatoxicity, subsequent severe changes in liver function tests or other signs and symptoms of liver failure: Discontinue sunitinib.

Hypertension

- Grade 1 or 2: No adjustment is required.
- Grade 3: Interrupt sunitinib until resolution to Grade ≤1 or baseline, then resume sunitinib at a reduced dose.
- Grade 4: Discontinue sunitinib.

Hemorrhagic Events

- Grade 1 or 2: No adjustment is required.
- Grade 3 or 4: Interrupt sunitinib until resolution to Grade ≤1 or baseline, then resume at a reduced dose; discontinue if no resolution.

Cardiac disorders

- Clinical manifestations of congestive heart failure: Discontinue sunitinib.
- Decreased LVEF: Interrupt until resolution to Grade 0 to 1 or baseline. Resume at reduced dose.

Proteinuria

- 3 or more grams proteinuria in 24 hours in the absence of nephrotic syndrome: Withhold until resolution to Grade 0 to 1 or baseline then resume at a reduced dose.
- Nephrotic syndrome or recurrent proteinuria of 3 or more grams per 24 hours despite dose reductions: Permanently discontinue.

Dermatologic Toxicities

Severe progressive skin reactions: Discontinue sutenet.

Co-administration with potent CYP3A4 inducers, such as rifampicin

If avoidance is not possible, sunitinib dose may need to be increased, in 12.5

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	mg steps, to a maximum of: • GIST and MRCC: 87.5 mg daily. • pNET: 62.5 mg daily. **Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole** If avoidance is not possible, sunitinib dose may need to be reduced to a minimum of: • GIST and MRCC: 37.5 mg daily • pNET: 25 mg daily
Contra-indications	Hypersensitivity to the active substance or to any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Chest pain (13%), decreased left ventricular ejection fraction (11% to 16%), hypertension (15% to 39%), increased serum creatine kinase (49%), peripheral edema (≤24%). **Dermatologic**: Alopecia (5% to 14%), erythema of skin (12%), hair discoloration (7% to 29%), palmar-plantar erythrodysesthesia (14% to 50%), pruritus (12%), skin discoloration (18% to 30%; yellow color), skin rash (14% to 29%), xeroderma (14% to 23%). **Endocrine and metabolic**: Decreased serum albumin (28% to 41%), decreased serum calcium (34% to 42%), decreased serum magnesium (19%), decreased serum phosphate (31% to 36%), decreased serum potassium (12% to 21%), decreased serum sodium (20%), hypothyroidism (≤24%), increased serum calcium (13%), increased serum sodium (10% to 13%), increased uric acid (46%), weight loss (16%). **Gastrointestinal**: Abdominal pain (25% to 39%), anorexia (≤48%), constipation (12% to 23%), decreased appetite (≤19%), diarrhea (40% to 66%; grades 3/4: 4% to 10%), dysgeusia (21% to 47%), dyspepsia (15% to 34%), flatulence (14%), gastroesophageal reflux disease (12%), glossalgia (11%), increased serum amylase (17% to 35%), increased serum lipase (17% to 56%), nausea (34% to 58%; grades 3/4: 2% to 6%), stomatitis (29% to 61%; grades 3/4: 3% to 6%; grade 4: <1%), vomiting (19% to 39%; grades 3/4: 2% to 5%), xerostomia (13%). **Hematologic and oncologic**: Decreased hemoglobin (26% to 79%; grades 3/4: 3% to 8%; grade 4: 2%), hemorrhage (22% to 37%; grades 3/4: ≤4%), lymphocytopenia (38% to 68%; grades 3/4: 3% to 18%, grade 4: 2%), neutropenia (grades 3/4: 13%). **Hepatic**: Increased indirect serum bilirubin (10% to 13%), increased serum alanine aminotransferase (≤61%), increased serum alkaline phosphatase (24% to 46%), increased serum aspartate aminotransferase (≤72%), increased serum bilirubin (16% to 37%). **Local**: Localized edema (18%). **Nervous system**: Chills (14%), depression (11%), dizziness (11%), fatigue (≤62%), headache (18% to 23%), insomnia (15% to 18%), mouth pain (6% to 14%).

Sunitinib

	Neuromuscular and skeletal: Arthralgia (11% to 30%), asthenia (≤57%), back pain (28%), limb pain (≤40%), myalgia (≤14%). **Renal**: Increased serum creatinine (12% to 70%). **Respiratory**: Cough (27%), dyspnea (26%), epistaxis (21%), nasopharyngitis (14%), oropharyngeal pain (14%), upper respiratory tract infection (11%). **Miscellaneous**: Fever (12% to 22%). **1% to 10%** **Cardiovascular**: Cardiac failure (3%), edema (≤10%), venous thromboembolism (4%). **Endocrine and metabolic**: Hyperglycemia (grades 3/4: 2%), hyperkalemia (grades 3/4: 2%), hypoglycemia (2% to 10%). **Gastrointestinal**: Hemorrhoids (10%), pancreatitis (1%). **Hematologic and oncologic**: Leukopenia (grades 3/4: 3%), thrombocytopenia (grades 3/4: 5%). **Respiratory**: Flu-like symptoms (5%).
Monitoring Parameters	• Complete blood counts • Liver function tests at baseline, during each cycle, and as clinically indicated. • Urinalysis baseline and periodically. • Left ventricular ejection fraction at baseline and periodically during treatment. • ECG and electrolytes (at higher-risk patients). • Blood pressure at baseline and as clinically indicated. • Thyroid function at baseline, periodically during treatment, and as clinically indicated. • Blood glucose levels regularly.
Drug Interactions	***Risk X: Avoid the combination*** Bevacizumab, Domperidone, Fexinidazole, Lefamulin, Levoketoconazol, Pimozide, Posaconazole, Saquinavir, Sertindole, St John's Wort, Temsirolimus, Thioridazine. ***Risk D: Consider therapy modification*** CYP3A4 Inducers (Strong), CYP3A4 Inhibitors (Strong), Dronedarone, Encorafenib, Fusidic Acid (Systemic), Itraconazole, QT-prolonging Agents, QT-prolonging Strong CYP3A4 Inhibitors.
Pregnancy and Lactation	**Pregnancy:** No human data. Fetal malformations in animal studies. should be avoided. Effective contraception should be used during treatment and for 4 weeks following the final dose. **Lactation:** No human data. Due to the potential for serious adverse reactions in breastfed infants, lactation is not recommended during treatment and for at least 4 weeks after the last dose.
Administration	**Hazardous agent:** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Oral Administration** Administered orally with or without food.

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	Missed dose: If a dose is missed, the patient should not take an additional dose. The patient should stick to the usual prescribed dose on the following day. **N.B.** Refer to the manufacturer's PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk: (<30% frequency of emesis).
Warnings/ Precautions	**Hepatotoxicity** Fatal liver failure has been observed rarely. Monitor liver function tests at baseline, during each cycle, and as clinically indicated. Interruption and dose reduction or discontinuation may be needed. **Cardiovascular Events** Myocardial ischemia, myocardial infarction, heart failure, cardiomyopathy, and decreased left ventricular ejection fraction (LVEF) to below the lower limit of normal, including death, have occurred. **QT Interval Prolongation and Torsade de Pointes** • Prolongation of the QT interval and Torsade de pointes have been observed. QT interval prolongation may lead to an increased risk of ventricular arrhythmias, including Torsade de pointes • Monitor patients at higher risk for developing QT interval prolongation. Consider monitoring of electrocardiograms and electrolytes • Risk factors include congenital long QT syndrome, patients taking antiarrhythmic medicines or cumulative high-dose anthracycline therapy, co-administration of strong CYP3A4 inhibitors, or electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia. **Renal Impairment** • Renal impairment or renal failure, some are fatal, have been reported. • Risk factors include underlying RCC, the elderly, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration, and rhabdomyolysis. • Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Discontinue sunitinib in patients with nephrotic syndrome. **Hypertension** • Monitor blood pressure at baseline and as clinically indicated. Initiate or adjust antihypertensive therapy as appropriate. Interruption and dose reduction or discontinuation may be needed. **Thrombotic microangiopathy (TMA)**

Sunitinib

- TMA, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported.
- Diagnosis of TMA should be considered in the occurrence of hemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestations, renal impairment, and fever.
- Sunitinib therapy should be discontinued in patients who develop TMA, and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation.

Skin disorders

- Reversible dermatological effects may include depigmentation, dryness, thickness, or cracking of the skin, blisters, or rash on the palms of the hands and soles of the feet. These reactions are reversible and do not need discontinuation.
- Severe skin reactions may rarely occur, some of which are fatal. If symptoms of progressive skin rash, often with blisters or mucosal lesions, are present, sunitinib treatment should be discontinued.
- If the diagnosis of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is confirmed, treatment must not be restarted. In some cases of suspected erythema multiforme (EM), patients tolerated the reintroduction of sunitinib therapy at a lower dose, with corticosteroids or antihistamines, after resolution of the reaction.

Hemorrage

- Epistaxis is the most common hemorrhagic adverse reaction. Some of the epistaxis events were severe, but very rarely fatal. Other hemorrhagic events include gastrointestinal, pulmonary, urinary tract, and brain hemorrhages.
- Monitoring of CBC with physical examinations is required. Interruption and dose reduction or discontinuation may be needed.

Gastrointestinal disorders

- Diarrhea, nausea, vomiting, abdominal pain, dyspepsia, and stomatitis/oral pain were the most commonly reported gastrointestinal adverse reactions.
- Supportive treatment may include antiemetics, antidiarrheals, or antacids. Serious, sometimes fatal gastrointestinal perforation were reported in patients with intra-abdominal malignancies treated with sunitinib.

Hematological disorders

- Decreased absolute neutrophil and platelet counts and anemia were reported in association with sunitinib. These events were reversible, not cumulative, and generally did not result in treatment discontinuation.

Thromboembolic events

- Deep venous thrombosis and pulmonary embolism have occurred.
- Cases of arterial thromboembolic events (ATE), including transient ischaemic attack, and cerebral infarction, sometimes fatal, have been reported. Risk factors associated with ATE include the elderly, hypertension, diabetes mellitus, and prior thromboembolic disease.

Sunitinib

Thyroid dysfunction

- Hypothyroidism has been observed to occur early or late during treatment with sunitinib. Monitoring baseline and every three months.
- The patients who develop thyroid dysfunction should be treated as per standard medical practice.

Pancreatitis

- Transient increases in serum lipase and amylase activities were observed without signs or symptoms of pancreatitis.
- Cases of serious pancreatic events, some with fatal outcomes, have been reported. If symptoms of pancreatitis are present, sunitinib should be discontinued, and appropriate supportive care should be given.

Impaired wound healing

- As a precautionary measure, temporary interruption of sunitinib therapy is recommended for at least 3 weeks prior to elective surgery and for at least 2 weeks following major surgery and until adequate wound healing.

Osteonecrosis of the Jaw (ONJ)

- Prior or concomitant treatment with intravenous bisphosphonates is a risk factor. Withhold sunitinib for at least 3 weeks before invasive dental procedures and the development of ONJ until complete resolution.
- The safety of resuming therapy after osteonecrosis has not been established. Either resume at a reduced dose or discontinue depending on the severity and persistence of the adverse reaction.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS (some fatal) has been reported. Monitor for signs of RPLS, including seizures, hypertension, headache, decreased alertness, altered mental functioning, and visual loss. Withhold sunitinib until resolution.

Hypoglycemia

- Decreases in blood glucose, in some cases clinically, have been reported. In case of symptomatic hypoglycaemia, sunitinib should be temporarily interrupted.

Hyperammonemic encephalopathy

- In patients who develop unexplained lethargy or changes in mental status, ammonia levels should be measured, and appropriate clinical management should be initiated.

Storage and Light Sensitivity	Store between 15°C and 30°C. **N.B.** Refer to manufacturer PIL for specific considerations.

Sunitinib

Patient Counselling Keys	• Patient should contact healthcare provider immediately if any of the following have developed: Cardiac disorders (shortness of breath, palpitations, fatigue), Reversible posterior leukoencephalopathy syndrome (headache, decreased alertness, altered mental functioning, and visual loss), Hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, dark-colored urine), Bleeding, Gastrointestinal perforation (persistent or severe abdominal pain), Severe skin reactions. • Advise patients that depigmentation of the hair or skin may occur during treatment. Other possible dermatologic effects may include dryness, thickness, or cracking of skin, blister or rash on the palms of the hands and soles of the feet. • Advise the patient regarding good oral hygiene practices. Withholding sunitib treatment for at least 3 weeks may be needed prior to scheduled dental surgery or invasive dental procedures, to avoid osteonecrosis of the jaw. • Advise patients to inform their healthcare provider of any planned surgical procedures due to possible impaired wound healing. • The patient should tell the doctor before taking any drugs, supplements, or herbal products. • The patient should follow the instructions for laboratory tests. • Blood pressure, glucose levels, and thyroid hormones should be checked regularly during treatment. • Some GIT symptoms can be resolved by supportive treatments. The patient may contact the doctor if symptoms of diarrhea, nausea, vomiting, abdominal pain, dyspepsia, stomatitis or oral pain develop.
Pharmaco-genomics	**Testing recommended** - **KIT - Sunitinib (Gastrointestinal Stromal Tumors)** **Outcome**: Efficacy – **Evidence of Testing Benefit**: Strong. The *KIT* gene is a proto-oncogene that encodes the KIT receptor tyrosine kinase, also known as c-Kit. Specific *KIT* mutations are generally associated with specific disease states.

MONOCLONAL ANTIBODIES

CD20 inhibitors

Rituximab

Generic Name	Rituximab
Dosage Form/Strengths	Solution for injection: 100 mg/10 mL, 500 mg/50 mL Solution for S.C injection: 1400 mg/ 11.7 ml.
Route of Administration	IV, SC
Pharmacologic Category	Antineoplastic Agent, Anti-CD20, Monoclonal Antibody, Antirheumatic, Miscellaneous, Immunosuppressant Agent. ATC Code: L01FA01.
Indications	N.B. Refer to literature and specific protocols for all indications used **Non-Hodgkin's Lymphoma (NHL) (IV or SC)** • Previously untreated, low-grade or follicular, CD20-positive, B-cell NHL or diffuse large B-cell, CD20-positive NHL in combination with chemotherapy in adults. • Maintenance therapy for low-grade or follicular, CD20-positive, B-cell as a single agent in patients achieving a complete or partial response to rituximab in combination with chemotherapy. • Monotherapy for relapsed, refractory, low-grade or follicular, CD20-positive B-cell NHL or for non-progressing stable disease after first-line chemotherapy (cyclophosphamide, vincristine, and prednisone). • Previously untreated children aged 6 months to less than 18 years old, with advanced CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma/Burkitt leukemia (mature B-cell acute leukemia), or Burkitt-like lymphoma in combination with chemotherapy. **Chronic lymphocytic leukemia (CLL) (IV or SC)** Previously treated or untreated CD20-positive CLL in combination with chemotherapy (fludarabine and cyclophosphamide) in adults. **Rheumatoid Arthritis (RA) (IV)** Treatment of moderately-to severely-active RA in combination with methotrexate in adult patients who have an inadequate response to other disease-modifying anti-rheumatic drugs (DMARD), including one or more tumor necrosis factor (TNF) inhibitor therapies. **Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) (IV)** In adult and pediatric (from 2 years) patients, in combination with glucocorticoids. **Pemphigus vulgaris (IV)** Treatment of an adult with moderate to severe pemphigus vulgaris (PV). **N.B.** Subcutaneous products can be used only for malignant diseases and after one full dose intravenous infusion.

Rituximab

Dosage Regimen

N.B. Different doses and regimens have been used; consult the literature for specific protocols.

Premedication: Anti-pyretic and antihistaminic, e.g., paracetamol and diphenhydramine, should always be given before each administration in all indications. For RA, GPA, and MPA patients, IV methylprednisolone 100 mg or its equivalent is recommended 30 minutes before each infusion.

Non-Hodgkin's lymphoma

- Follicular non-Hodgkin's lymphoma (in combination with chemotherapy)

- Previously untreated and relapsed or refractory

IV: 375 mg/m^2 body surface area on Day 1 of each chemotherapy cycle, for up to 8 cycles.

- Maintenance therapy for previously untreated

IV: 375 mg/m^2 once every 2 months (starting 2 months after the last dose of induction therapy) until progression of disease or for a maximum period of two years (12 infusions in total).

- Maintenance therapy for relapsed/refractory follicular lymphoma

IV: 375 mg/m^2 once every 3 months (starting 3 months after the last dose of induction therapy) until progression of disease or for a maximum period of two years (8 infusions in total).

- Follicular non-Hodgkin's lymphoma (Monotherapy)

- Relapsed/refractory follicular lymphoma

IV: 375 mg/m^2 body surface area, once weekly for four weeks for induction and 4 weeks for maintenance.

- Non-progressing, follicular, CD20-Positive, B-Cell NHL

IV: 375 mg/m^2, once weekly for 4 doses, at 6-month intervals, up to a maximum of 16 doses. That starts following completion of 6-8 cycles of first-line CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy.

- Diffuse large B-cell non-Hodgkin's lymphoma

IV: 375 mg/m^2, on Day 1 of each chemotherapy cycle for 8 cycles after IV infusion of the glucocorticoid component of CHOP chemotherapy.

- Pediatric patients aged 6 months and older with previously untreated mature B-cell NHL/B-AL

Rituximab is given in combination with systemic Lymphome Malin B chemotherapy. In total, six infusions are given, two doses during each of the induction courses, COPDAM1 and COPDAM2, and one dose during each of the two consolidation courses of CYM/CYVE.

Subcutaneous products can be used in adults only after one full dose IV infusion for non-Hodgkin's lymphoma with a fixed dose of 1400 mg.

Chronic lymphocytic leukemia

IV: 375 mg/m^2 on Day 0 in the first cycle and 500 mg/m^2 on Day 1 in Cycles 2-6, in combination with fludarabine and cyclophosphamide (FC), administered every 28 days. The chemotherapy should be given after rituximab infusion.

Subcutaneous products can be used in adults only after one full dose IV infusion for Chronic lymphocytic leukemia with a fixed dose of 1600 mg.

Rituximab

	Rheumatoid arthritis **IV infusion**: In combination with methotrexate, two 1,000 mg rituximab doses are separated by 2 weeks (one course). The need for further courses should be evaluated 24 weeks following the previous course. Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 minutes before each infusion. **Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)** **- Induction of remission** **IV infusion:** 375 mg/m^2, once weekly for 4 weeks. **-Maintenance treatment** **IV infusions**: two 500 mg doses separated by two weeks, followed by 500 mg IV infusion every 6 months thereafter. Initial maintenance dose should start no sooner than 16 weeks after the last rituximab infusion or during the 4-week period that follows disease remission with other standard of care immunosuppressants. It should last for at least 24 months and up to 5 years after the achievement of remission. **Pemphigus vulgaris** **IV infusions**: 1000 mg followed two weeks later by a second 1000 mg in combination with a tapering course of glucocorticoids. **Maintenance: IV infusion:** 500 mg at months 12 and 18, and then every 6 months thereafter if needed, based on clinical evaluation**.** **Relapse: IV infusion:** 1000 mg, consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** No dosage adjustment necessary. **Hepatic Impairment** No dosage adjustment necessary. **Dose Adjustment for Adverse Effects** • Cardiac arrhythmia (severe or life-threatening): Discontinue rituximab infusion. • Hepatitis B virus reactivation: Discontinue rituximab (and concomitant medications) and initiate antiviral therapy. • Infection (serious): Discontinue rituximab and initiate appropriate anti-infective treatment. • Infusion reaction: Interrupt infusion or slow infusion rate. Discontinuation of infusion either temporarily or permanently depends on the severity of the reaction and required interventions. Mild infusion reaction: After symptoms resolve, infusion may be resumed with at least a 50% infusion rate reduction. Severe infusion reaction: Discontinue rituximab; provide medical treatment for grade 3 or 4 infusion-related reactions. • Progressive multifocal leukoencephalopathy: Discontinue rituximab; also consider reduction/discontinuation of concurrent chemotherapy or immunosuppressants. • Severe mucocutaneous reaction: Discontinue rituximab.

Rituximab

Contra-indications	• Hypersensitivity to the active substance or murine proteins, or any of the excipients. • Active, severe infections or severely immunocompromised state.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Cardiac disorder (5% to 29%), flushing (5% to 14%), hypertension (6% to 12%), peripheral edema (8% to 16%). **Dermatologic**: Night sweats (15%), pruritus (≤17%), skin rash (≤17%). **Endocrine and metabolic**: Hypophosphatemia (12% to 21%), weight gain (11%). **Gastrointestinal**: Abdominal pain (14%), diarrhea (10% to 17% grades 3/4: 1%), nausea (8% to 23%; grades 3/4: 1%). **Hematologic and oncologic**: Anemia (8% to 35%; grades 3/4: 3%), febrile neutropenia (grades 3/4: 9% to 15%), hypogammaglobulinemia (<1% to 58%), leukopenia (10% to 14%; grades 3/4: 4% to 23%), lymphocytopenia (48%; grades 3/4: 40%), neutropenia (8% to 14%; grades 3/4: 4% to 49%; may be prolonged neutropenia [lasting up to 42 days] or late onset [occurring >42 days after last dose]), thrombocytopenia (12%; grades 3/4: 2% to 11%). **Hepatic**: Hepatobiliary disease (17%), increased serum alanine aminotransferase (13%) **Hypersensitivity**: Angioedema (11%) **Immunologic**: Antibody development (1% to 32%) **Infection**: Bacterial infection (19%; including cellulitis), infection (19% to 63%%; including CMV viremia, herpes simplex infection, parvovirus B19 seroconversion, varicella zoster infection, hepatitis C, and lower respiratory tract infection), serious infection (2% to 11%; including sepsis). **Nervous system:** Chills (3% to 33%), fatigue (13% to 39%), headache (15% to 19%), insomnia (14%), pain (12%), peripheral sensory neuropathy (30%). **Neuromuscular and skeletal**: Arthralgia (6% to 13%), asthenia (2% to 26%), muscle spasm (17%). **Respiratory**: Bronchitis, cough (13% to 15%), epistaxis (11%), nasopharyngitis (≤16%), pulmonary disease (31%), pulmonary toxicity (18%), rhinitis (3% to 12%), upper respiratory tract infection (≤16%). **Miscellaneous**: Fever (5% to 56%), infusion-related reaction (first dose: 12% to 77%). **1% to 10%** **Cardiovascular**: Chest tightness (7%), hypotension (10%), significant cardiovascular event (2%). **Dermatologic**: Urticaria (2% to 8%). **Endocrine and metabolic**: Hyperglycemia (9%), hyperuricemia (2%), increased lactate dehydrogenase (7%). **Gastrointestinal**: Dyspepsia (3%), oral candidiasis (9%), upper abdominal pain (2%), vomiting (10%; grades 3/4: 1%). **Genitourinary**: Urinary tract infection (8%). **Hematologic and oncologic**: Pancytopenia (grades 3/4: 3%; can be prolonged). **Hepatic**: Exacerbation of hepatitis B (grades 3/4: 2%). **Infection**: Fungal infection (1%), viral infection (10%; including herpes zoster).

Rituximab

	Nervous system: Anxiety (2% to 5%), dizziness (6% to 10%), migraine (2%), paresthesia (2%), rigors (10%). **Neuromuscular and skeletal**: Back pain (9% to 10%), myalgia (10%). **Respiratory**: Bronchospasm (8%), dyspnea (7% to 10%), sinusitis (6%), throat irritation (2% to 9%).
Monitoring Parameters	• CBC with differential before use and regularly up to 6 months after cessation of treatment. • Renal functions • Monitor for HBV by measuring HBsAg and anti-HBc before treatment. • Monitor cardiac functions for patients with a history of arrhythmias.
Drug Interactions	***Risk X: Avoid the combination*** Abrocitinib, Anifrolumab, Baricitinib, BCG Products, Belimumab, Biologic Disease-Modifying Antirheumatic Drugs (DMARDs), Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Etrasimod, Fexinidazole, Filgotinib, Mumps-Rubella- or Varicella-Containing Live Vaccines, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccines, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy** There are no adequate and well-controlled studies of rituximab in pregnant women. Transient B-cell depletion and lymphocytopenia have been reported in infants. Females of reproductive potential should be informed of the potential risk to a fetus and use of effective contraception during and for 12 months following treatment. **Lactation** Limited data. Not recommended due to the potential secretion into breast milk for 6 months following rituximab treatment.
Administration	**Premedication** **With all indications**, premedication before each administration consisting of an anti-pyretic and an antihistaminic, e.g., paracetamol and diphenhydramine, should always be given. **In patients with malignant disease,** premedication with glucocorticoids should be considered 30 minutes before each infusion (particularly for pediatrics) if not given in combination with glucocorticoid-containing chemotherapy. **In patients with rheumatoid arthritis, GPA or MPA, or pemphigus vulgaris,** premedication with 100 mg IV methylprednisolone should be completed 30 minutes before each infusion. **IV administration** For IV Infusion only. Do **not** administer IV push or bolus.

Rituximab

	Preparation for administration Dilute to a final concentration of 1-4 mg/mL with either 0.9% Sodium Chloride or 5% Dextrose. Mix the solution gently. Do not mix or dilute with other drugs. Discard any unused portion left in the vial. **Rate of Infusion for Adults** **First infusion** Initially: 50 mg/h; after the first 30 minutes, if there is no hypersensitivity or infusion-related reactions, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. **Subsequent infusions** Initially: 100 mg/h, and increased by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h. *Alternative accelerated schedule for Rheumatoid patients*: Initiate at a rate of 250 mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. **Rate of Infusion for Pediatrics** **First infusion** Initially: 0.5 mg/kg/h (maximum 50 mg/h); it can be escalated by 0.5 mg/kg/h every 30 minutes if there is no hypersensitivity or infusion-related reactions, to a maximum of 400 mg/h. **Subsequent infusions** Initially: 1 mg/kg/h (maximum 50 mg/h); it can be increased by 1 mg/kg/h every 30 minutes to a maximum of 400 mg/h. **Subcutaneous Administration** Administered subcutaneously over approximately 5 minutes. It should be injected into the abdominal wall. Avoid injection in red, bruised, tender, hard areas or areas where there are moles or scars. **N.B.** Refer to the manufacturer's PIL if there are specific considerations.
Emetogenicity	Pediatrics and Adults: Minimal (<10%).
Warnings/ Precautions	**Infusion /Administration-related Reaction** • Administration may be associated with severe reactions, which include the syndrome of cytokine release, tumor lysis syndrome, and anaphylactic and hypersensitivity reactions. Symptoms may start within minutes to 2 hours after starting the infusion. • Severe cytokine release syndrome is characterized by severe dyspnea, bronchospasm, hypotension, fever, chills, rigors, urticaria, and angioedema. Features of tumor lysis syndrome include hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH), and may be associated with acute respiratory failure and death. Additional reactions include myocardial infarction, atrial fibrillation, pulmonary edema, and acute reversible thrombocytopenia. • Symptoms are usually reversible with interruption of infusion and administration of epinephrine, an antihistaminic, and, occasionally, oxygen, intravenous saline, or bronchodilators, and glucocorticoids if required.

Rituximab

- Caution in patients with a history of pulmonary insufficiency or with high tumor burden.
- Erythema, pruritus, rash, and injection site reactions may occur within 24 hours of subcutaneous injections.

Severe Mucocutaneous Reactions

- Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported
- Discontinue rituximab in patients who experience a severe mucocutaneous reaction.

Infections

- Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and up to one year following rituximab therapy.
- Rituximab should be discontinued for serious infections, and appropriate anti-infective therapy should be given. Caution in patients with a history of recurring or chronic infections.
- Should not be administered to patients with an active, severe infection or severely immunocompromised patients.

Progressive Multifocal Leukoencephalopathy (PML)

- Increased risk of infections, including JC virus, which results in progressive multifocal leukoencephalopathy (PML), may occur rarely (sometimes fatal).
- Monitor for cognitive, neurological, or psychiatric symptoms. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.
- Discontinue rituximab permanently and consider discontinuation of immunosuppressive therapy in patients who develop PML.

Hepatitis B Virus (HBV) Reactivation

- Reactivation of hepatitis B, sometimes fatal, may occur. Screening for HBV by measuring HBsAg and anti-HBc should be performed in all patients before initiation of treatment.
- Monitor patients with evidence of prior hepatitis B infection closely and consider HBV antiviral therapy before and/or during therapy.
- Discontinue Rituximab and any concomitant chemotherapy in patients who develop viral hepatitis, and institute appropriate treatment. No sufficient data for resuming rituximab.

Cardiovascular

- Cardiac adverse reactions may occur. Closely monitor patients with a history of cardiac disorders for ventricular fibrillation, myocardial infarction, and cardiogenic shock during and after infusions. Discontinue infusions if a serious or life-threatening cardiac arrhythmia occurs.

Renal toxicities

Rituximab

	Monitor closely for signs of renal failure and discontinue rituximab in patients with a rising serum creatinine or oliguria. **Bowel Obstruction and Perforation** • Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. • Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of abdominal pain. **Immunization** Vaccination with live virus vaccines is not recommended. No data. Non-live vaccinations may be associated with reduced response. **Prophylaxis treatment for Pneumocystis jirovecii pneumonia (PCP) and herpes virus infections** should be given during treatment and for up to 12 months (CLL patients) or 6 months (GPA and MPA patients) following treatment as appropriate. **Concomitant use of other DMARDs in rheumatoid arthritis other than Methotrexate** is not recommended. Limited data.
Storage and Light Sensitivity	• Store intact vials at 2°C to 8°C. Protect vials from direct sunlight. • Do not freeze. Do not shake. • Diluted solution can be stored refrigerated at 2°C to 8°C for up to 16 days after preparation in saline or 24 hours for preparation in dextrose. **N.B.** Refer to the manufacturer PIL if there are specific considerations**.**
Patient Counselling Keys	• The patients should contact health care professional immediately to report any of the following: Severe skin reaction (red, swollen, blistered, or peeling skin (with or without fever); irritated eyes; or sores in mouth), Neurological symptoms (confusion, memory problems, depression, trouble speaking or thinking, or change in eyesight), Cardiovascular disorders (chest pain, irregular heartbeats), Bowel obstruction and perforation (severe abdominal pain, repeated vomiting) or infection. • If the patient has had hepatitis B before, this drug can cause the virus to become active. Advise patients to contact a healthcare provider for symptoms of hepatitis, including worsening fatigue or yellow discoloration of skin or eyes. • Use of live vaccines with this drug is not recommended, as they may either raise the chance of an infection or make the vaccine not work as well. • The patient should follow the instructions for laboratory tests.
Sequence of Administration	Rituximab is administered before conventional chemotherapy.

EGFR inhibitors

Cetuximab

Generic Name	Cetuximab
Dosage Form/Strengths	Solution for Infusion: 100mg (5 mg/ml)
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Epidermal Growth Factor Receptor (EGFR) Inhibitor, Monoclonal Antibody. ATC: L01FE01
Indications	**N.B.** Refer to the literature and specific protocols for all indications. **Treatment of squamous cell cancer of the head and neck** • In combination with radiation therapy for locally advanced disease. • In combination with platinum-based chemotherapy for recurrent and/or metastatic disease. • Recurrent or metastatic progressing disease after platinum-based therapy. **Colorectal Cancer (K-Ras wild-type, EGFR-expressing, metastatic disease)** • In combination with irinotecan-based chemotherapy. • In first-line in combination with FOLFOX or FOLFIRI. • As a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Administer** an antihistamine and a corticosteroid at least 1 hour before administration of cetuximab. **Initial: IV**: 400 mg/m^2 once weekly as a 120-minute intravenous infusion. **Subsequent doses**: **IV**: 250 mg/m^2 once weekly as a 60-minute infusion. Treatment with cetuximab should be continued until progression of the underlying disease or unacceptable toxicity. **In combination with radiation therapy** o The initial dose is one week before initiating a course in radiation therapy. o Subsequent doses are given every week for the duration of radiation therapy (6–7 weeks). o Cetuximab administration should be completed 1 hour before radiation therapy. **As a single agent or in combination with chemotherapy** **Alternative dosing: Biweekly** o Administer 500 mg/m^2 as a 120-minute intravenous infusion every 2 weeks. o Complete cetuximab administration 1 hour before chemotherapy.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** No dose adjustments available. Not studied. **Hepatic Impairment** No dose adjustments available. Not studied.

Cetuximab

	Dose modification for dermatologic toxicity **Severe Skin Reaction (grade 3)** • First occurrence: Interrupt treatment, then resume without any dose changes when resolved to grade 2. • Second and third occurrences: Interrupt treatment, then may only be resumed at a lower dose level (200 mg/m² after the second occurrence and 150 mg/m² after the third occurrence) when resolved to grade 2. • Fourth time or do not resolve to grade 2 during interruption of treatment: permanent discontinuation of cetuximab treatment is required.
Contra-indications	Severe (grade 3 or 4) hypersensitivity reactions to cetuximab.
Adverse Drug Reactions	**>10%** **Dermatologic**: Acneiform eruption (87%), changes in nails (31%), desquamation (≤95%), pruritus (16% to 47%), radiodermatitis (86%), skin rash (≤95%), xeroderma (57%). **Endocrine and metabolic**: Dehydration (13% to 25%), hypomagnesemia (55%), weight loss (84%). **Gastrointestinal**: Constipation (53%), diarrhea (19% to 42%; grades 3/4: 2%), dyspepsia (14%), nausea (49% to 64%; grades 3/4: 2% to 6%), stomatitis (32%; grades 3/4: 1%), vomiting (29% to 40%; grades 3/4: 2% to 5%), xerostomia (12%). **Hepatic**: Increased serum alanine aminotransferase (43%), increased serum alkaline phosphatase (33%), increased serum aspartate aminotransferase (38%). **Infection**: Infection (13%), infection without neutropenia (38%). **Local**: Application site reaction (18%). **Nervous system**: Anxiety (14%), chills (≤16%), confusion (18%), depression (14%), fatigue (91%), headache (19% to 38%), insomnia (27%), pain (59%), peripheral sensory neuropathy (45%; grades 3/4: 1%), rigors (≤16%). **Neuromuscular and skeletal**: Arthralgia (14%), asthenia (56%), ostealgia (15%). **Respiratory**: Cough (30%), dyspnea (49%), pharyngitis (26%). **Miscellaneous**: Fever (25% to 29%), infusion-related reaction (18%; severe infusion-related reaction: <2%). **1% to 10%** **Gastrointestinal**: Dysgeusia (10%). **Immunologic**: Antibody development (<5%).
Monitoring Parameters	• Serum electrolytes, including serum magnesium, potassium, and calcium, are measured weekly during treatment and for at least 8 weeks following the completion of administration. • Monitor for hypersensitivities reactions for 1 hour after the end of infusion (2 hours after the initial infusion), dermatologic toxicities, and pulmonary toxicity.
Drug Interactions	No significant interactions of risk X or D observed.
Pregnancy and Lactation	**Pregnancy**: No human data. Cetuximab may cause fetal harm when administered to a pregnant woman based on animal data. Female patients at potential risk to the fetus should use effective contraception. **Lactation**: No human data. Use is not recommended due to the potential for serious

Cetuximab

	adverse reactions.
Administration	**Premedication:** Premedicate with an IV histamine-1 (H1) receptor antagonist 30–60 minutes before the first dose and subsequent doses as deemed necessary. **IV Administration** • Do not shake or dilute. • Do not use it if the solution is discolored, cloudy, or contains foreign particulate matter. • Do not administer as an intravenous push or bolus. • Administer via infusion pump or syringe pump. **Rate of infusion** **Initial dose:** Must not exceed 5 mg/min. The recommended infusion period is 120 minutes. **Subsequent doses:** Must not exceed 10 mg/min. The recommended infusion period is 60 minutes. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Emetogenicity	Minimal emetic risk (<10% frequency of emesis).
Warnings/ Precautions	**Infusion Reactions** • May cause serious and fatal infusion reactions (anaphylactic or cytokine release syndrome) characterized by bronchospasm, urticaria, hypotension, shock, myocardial infarction, and cardiac arrest. • Monitor during the first infusion and for several hours later, and for an hour after each subsequent infusion. • Immediately stop and permanently discontinue if serious infusion reactions develop. Interrupt the infusion and, upon recovery, resume the infusion at a slower rate for less severe reactions, e.g., fever, chills, dizziness, or dyspnea. **Pulmonary Toxicity** Interrupt or permanently discontinue for acute onset or worsening of pulmonary symptoms. Permanently discontinue for confirmed interstitial lung disease (ILD). **Dermatologic Toxicity** • Monitor for dermatologic toxicities (e.g., acneiform rash, skin drying, and fissuring) or infectious sequelae. Limit sun exposure. Withhold, reduce dose, or permanently discontinue based on the severity of acneiform rash or mucocutaneous disease. • Skin reactions are very common, and treatment interruption or discontinuation may be required. Prophylactic use of oral tetracyclines (6 - 8 weeks) and topical application of 1% hydrocortisone cream with moisturizer should be considered. Medium to high-potency topical corticosteroids or oral tetracyclines have been used for the treatment of skin reactions. **Cardiopulmonary Arrest** An increased frequency of severe and sometimes fatal cardiovascular events

Cetuximab

	has been observed. Monitor serum electrolytes during and after therapy. **Hypomagnesemia and Accompanying Electrolyte Abnormalities** • Hypomagnesemia, hypocalcaemia, and hypokalemia may occur. monitor during and for at least 8 weeks following the treatment. Replete electrolytes as necessary. • Hypokalaemia may develop as a result of diarrhea. Hypocalcaemia may also occur in combination with platinum-based chemotherapy. **Eye disorders** If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. Caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. **Colorectal cancer patients with RAS-mutated tumours** Cetuximab should not be used in the treatment of colorectal cancer patients whose tumours have RAS mutations or for whom RAS tumour status is unknown. Increased mortality or lack of benefit has been observed in patients with RAS-mutant colorectal cancer. **Laboratory parameters** Cetuximab has not been studied in patients with one or more of the following laboratory parameters: Hemoglobin < 9 g/dL, leukocyte count < 3000/mm³, absolute neutrophil count < 1500/mm³, platelet count < 100000/mm³.
Storage and Light Sensitivity	• Store vials under refrigeration at 2° C to 8° C. • Do not freeze or shake. • Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C. N.B. Refer to the manufacturer's PIL if there are specific considerations.
Patient Counselling Keys	• The patient should contact healthcare provider immediately if any of the following have developed: Infusion reactions (fever, chills, or breathing problems), lung disease (dyspnea, new or worsening cough, chest pain), or dermatologic toxicity (acne-like rash (including itchy, dry, scaly skin and inflammation, infection or loss of the nails), conjunctivitis, blepharitis, or decreased vision). • The patient should report any history of coronary artery disease, congestive heart failure, or arrhythmias. • The patient is recommended to limit sun exposure during treatment and for 2 months after the last dose.
Sequence of Administration	Cetuximab is administered before the conventional chemotherapy.

HER2 inhibitors

Pertuzumab

Generic Name	Pertuzumab
Dosage Form/Strengths	• Concentrate Solution for IV Infusion: 420 mg. • Solution for subcutaneous injection: 1200 mg pertuzumab/600 mg trastuzumab/Hyaluronidase 30000 units, 600 mg pertuzumab/600 mg trastuzumab/Hyaluronidase 20000 units.
Route of Administration	IV, SC
Pharmacologic Category	Antineoplastic Agent, Anti-HER2, Monoclonal Antibody Pertuzumab: ATC: L01FD02. Pertuzumab and trastuzumab: ATC: L01FY01.
Indications	**N.B.** Refer to the literature and specific protocols for all indications used. **In early breast cancer, in combination with trastuzumab and chemotherapy** • Locally advanced, inflammatory HER2-positive breast cancer (Neoadjuvant treatment). • Early-stage HER2-positive breast cancer at high risk of recurrence (Adjuvant or neoadjuvant treatment). **In metastatic breast cancer, in combination with trastuzumab and docetaxel** • Metastatic HER2-positive breast cancer patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing** **IV formulation** **Initial loading dose**: IV infusion: 840 mg over an hour (combined with IV trastuzumab 8mg/m^2) **Maintenance dose**: IV infusion: 420 mg over 30-60 minutes every 3 weeks thereafter (combined with IV trastuzumab 6 mg/m^2, or fixed 600 mg subcutaneous dose initially and thereafter). N.B. Pertuzumab and trastuzumab can be given in any order but not in the same infusion bag. **SC formulation** **Initial loading dose**: SC: 1200 mg pertuzumab/ 600 mg trastuzumab over 8 minutes. **Maintenance dose** (every 3 weeks): SC: 600 mg pertuzumab/ 600 mg trastuzumab over 5 minutes. **Duration of treatment** • **Metastatic breast cancer:** Treatment with pertuzumab may continue until disease progression or unmanageable toxicity, even if treatment with docetaxel is discontinued. • **Neoadjuvant treatment:** Preoperatively, for 3 to 6 cycles in combination with trastuzumab and chemotherapy. • **Adjuvant Early breast cancer:** for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) in combination with trastuzumab and chemotherapy. Treatment should include

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standard anthracycline- and/or taxane-based chemotherapy. Pertuzumab and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.

Delayed dosing, switching from IV to SC

If the time between two sequential injections is:

- For less than 6 weeks, the maintenance dose should be administered as soon as possible. Thereafter, continue with the 3-weekly schedule.
- For 6 weeks or more, a loading dose should be re-administered, followed by a maintenance dose every 3 weeks thereafter.

Pediatrics: Safety and efficacy in children below 18 years of age is not established.

Dosage Adjustment

N.B. Refer to the protocol used for specific dose modifications.

Renal impairment

- Mild or moderate renal impairment: No dose modification is needed.
- Severe renal impairment: Limited data.

Hepatic impairment

Not studied.

Dose adjustment due to adverse effects

Left ventricular dysfunction

If signs suggesting congestive heart failure developed, Pertuzumab and trastuzumab should be withheld for at least 3 weeks. If confirmed clinically significant decrease in left ventricular function, pertuzumab should be discontinued.

	Pre-treatment LVEF	**Monitor LVEF every**	**Withhold pertuzumab and trastuzumab for at least 3 weeks for an LVEF decrease to**		**Resume pertuzumab and trastuzumab after 3 weeks if LVEF has recovered to**	
Meta-static Breast Cancer	≥ 50%	~12 weeks	Either		Either	
			< 40%	40%-45% with a fall of ≥10%-points below pre-treatment value	> 45%	40%-45% with a fall of < 10%-points below pre-treatment value
Early Breast Cancer	≥ 55% (For anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracycline, before starting pertuzumab and trastuzumab	~12 weeks (once during neoadjuvant therapy)	<50% with a fall of ≥10%-points below the pretreatment value		Either	
					≥50%	<10% points below the pre-treatment value

Reversible-chemotherapy-induced myelosuppression

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	Patients may continue pertuzumab, along with trastuzumab, with careful monitoring for complications of neutropenia.
Contra-indications	Hypersensitivity to pertuzumab or to any of its excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Decreased left ventricular ejection fraction (8% to 16%). **Central nervous system**: Fatigue (26% to 36%), headache (11% to 21%), insomnia (8% to 13%), dizziness (3% to 13%). **Dermatologic**: Alopecia (52% to 65%), skin rash (11% to 34%), pruritus (4% to 14%), palmar-plantar erythrodysesthesia (11%), xeroderma (9% to 11%). **Gastrointestinal**: Diarrhea (46% to 67%), nausea (39% to 53%), vomiting (13% to 36%), decreased appetite (11% to 29%), mucositis (20% to 28%), constipation (23%), stomatitis (17% to 19%; grades 3/4: <1%), dysgeusia (13% to 18%). **Hematologic and oncologic**: Neutropenia (47% to 53%; grades 3/4: 43% to 49%), anemia (3% to 23%; grades 3/4: 2% to 4%), leukopenia (9% to 16%; grades 3/4: 5% to 12%), febrile neutropenia (8% to 14%; grades 3/4: 9% to 13%). **Hypersensitivity**: Hypersensitivity (1% to 11%). **Neuromuscular and skeletal**: Asthenia (15% to 26%), myalgia (11% to 22%), arthralgia (10% to 12%). **Respiratory**: Upper respiratory tract infection (4% to 17%), epistaxis (11%). **Miscellaneous**: Fever (9% to 19%), infusion reactions (13%). **1% to 10%** **Cardiovascular**: Left ventricular dysfunction (3% to 4%), peripheral edema (3% to 4%). **Central nervous system**: Peripheral sensory neuropathy (8%; grades 3/4: <1%), peripheral neuropathy (1%). **Dermatologic**: Nail disease (7%), paronychia (1% to 7%). **Gastrointestinal**: Dyspepsia (8%). **Hematologic and oncologic**: Thrombocytopenia (1%). **Hepatic**: Increased serum alanine aminotransferase (3%). **Ophthalmic**: Increased lacrimation (4% to 5%). **Respiratory**: Dyspnea (8%), nasopharyngitis (7%), oropharyngeal pain (7%), cough (5%).
Monitoring Parameters	• Assess left ventricular ejection fraction (LVEF) before initiation, then once during neoadjuvant treatment and every 12 weeks in the adjuvant or metastatic setting. • Monitor for signs of infusion-related or hypersensitivity reactions.
Drug Interactions	No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel, paclitaxel, carboplatin, gemcitabine, capecitabine, and erlotinib.
Pregnancy and Lactation	**Pregnancy:** Exposure to pertuzumab can result in embryo-fetal death and birth defects. Women of childbearing potential should use effective contraception during and for 6 months following the last dose of pertuzumab. **Lactation:** Human IgG is secreted in human milk. The effect on the infants is unknown**.** A decision should be made to discontinue breastfeeding or to discontinue

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	treatment, considering the benefit and potential risk.
Administration	**Intravenous Administration** • IV infusion only. Not to be taken as an IV bolus or push. • Dilute with 250 ml of 0.9% sodium chloride injection only. Do not use dextrose (5%) solution. Mix gently. Administer immediately. • Close observation of the patient during and for 60 minutes after the first IV infusion and during and for 30-60 minutes after subsequent infusions is recommended. **Rate of infusion** • Initial dose: over 60 minutes. • If the first infusion is well tolerated, subsequent infusions may be administered over 30 minutes to 60 minutes. **Subcutaneous Administration** • The injection site should be alternated between the left and right thigh only. • The loading dose and maintenance dose should be administered over 8 and 5 minutes, respectively. • With subcutaneous administration, patients should be observed for injection-related reactions and hypersensitivity reactions for 30 minutes in the loading dose and for 15 minutes after subsequent doses. **Infusion or injection reactions** If developed, the infusion rate or injection may be slowed or interrupted. administration may be resumed when symptoms resolve. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Emetogenicity	Minimal emetic risk (<10% frequency of emesis).
Warnings/ Precautions	**Left ventricular dysfunction (including congestive heart failure)** • Pertuzumab can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Most of the cases were in patients who received anthracycline-based chemotherapy. • Evaluate cardiac function before and during treatment. Discontinue treatment for a confirmed clinically significant decrease in left ventricular function. **Infusion reactions** • Close observation of the patient during and after administration is recommended. Injection-related reactions were defined as any systemic reaction with symptoms such as fever, chills, headache, likely due to a release of cytokines occurring within 24 hours of administration. • Infusion rate may be slowed or interrupted. Treatment, including oxygen, beta agonists, antihistamines, rapid IV fluids, and antipyretics, may also help alleviate symptoms. • Permanent discontinuation should be considered in patients with severe infusion reactions or anaphylaxis. **Hypersensitivity reactions**

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	The infusion should be discontinued immediately and permanently if the patient experiences life-threatening consequences (anaphylaxis), bronchospasm, or acute respiratory distress syndrome. **Febrile neutropenia** • Pertuzumab is associated with an increased risk of febrile neutropenia with mucositis and diarrhea. Symptomatic treatment for mucositis and diarrhea should be considered. • Severe diarrhea may be associated with pertuzumab, particularly in elderly patients. Early intervention with loperamide, fluids, and electrolyte replacement should be considered in the elderly and cases of severe or prolonged diarrhea. Interruption of treatment with pertuzumab should be considered if no improvement. Pertuzumab may be reinitiated when diarrhea is under control.
Storage and Light Sensitivity	• Store in a refrigerator (2°C-8°C). • Do not freeze. Protect from light. • **Diluted infusion solution:** Can be stored at 2 °C to 8 °C for up to 24 hours. **N.B.** Refer to the manufacturer PIL if there are specific considerations**.**
Patient Counselling Keys	• Advise patients to contact a health care professional immediately for any cardiac symptoms (new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, dizziness, or loss of consciousness). • The patient should contact the healthcare provider if diarrhea occurs. Early treatments can be used to help.
Sequence of Administration	• Targeted medicines are administered before chemotherapy. • In patients receiving an anthracycline-based regimen, pertuzumab and trastuzumab should be administered following completion of the entire anthracycline regimen.

Trastuzumab

Generic Name	Trastuzumab
Dosage Form/Strength	• **Powder for IV Infusion:** 150 mg, 440 mg • **Solution for SC injection**: 600 mg
Route of Administration	IV, SC
Pharmacologic Category	Antineoplastic Agent, Anti-HER2; Monoclonal Antibody Trastuzumab: L01FD01
Indications	**N.B.** Refer to the literature and specific protocols for all indications used. HER2/neu receptor antagonist indicated for the treatment of adults with HER2-positive: • **Breast cancer (IV or SC)** o Metastatic ▪ As a single agent in patients who have received one or more chemotherapy regimens. ▪ In combination with paclitaxel as first-line treatment. ▪ In combination with an aromatase inhibitor for the treatment of postmenopausal patients, not previously been treated with trastuzumab. o Adjuvant early breast cancer ▪ As a single agent following multi-modality anthracycline-based therapy. ▪ As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. ▪ As part of a treatment regimen with docetaxel and carboplatin. ▪ Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). • **Metastatic gastric or gastroesophageal junction adenocarcinoma (IV)** In combination with capecitabine or 5-fluorouracil and cisplatin who have not received prior anti-cancer treatment for their metastatic disease.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing** **Early breast cancer until progression of disease (for a maximum of a year)** • **Three-weekly schedule** (As a single agent within three weeks after anthracycline-based chemotherapy regimens) - Initial loading dose: 8 mg/kg body weight. - Maintenance dose: 6 mg/kg body weight, beginning three weeks after the loading dose. • **Weekly regimen** (concomitantly with paclitaxel, docetaxel, or docetaxel and carboplatin following chemotherapy with doxorubicin and cyclophosphamide). - Initial loading dose: IV: 4 mg/kg body weight. - Maintenance dose: IV: 2 mg/kg every week beginning one week after the loading

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	dose. **Metastatic breast cancer** • **Three-weekly schedule** - Initial loading dose: IV: 8 mg/kg body weight. - Maintenance dose: IV: 6 mg/kg body weight, beginning three weeks after the loading dose. • **Weekly schedule** - Initial loading dose: IV: 4 mg/kg body weight. - Maintenance dose: IV: 2 mg/kg every week beginning one week after the loading dose. **N.B.** Paclitaxel or docetaxel is administered the day following the first dose of trastuzumab, and immediately after the subsequent doses of trastuzumab; the preceding dose of trastuzumab was well tolerated. **N.B.** Trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration. **Subcutaneous Formulations for Breast Cancer (early or metastatic)** **SC**: 600 mg (fixed dose) every three weeks without the need for a loading dose. **Duration of use** • Metastatic breast cancer: Until progression of disease. • Early breast cancer: Use for 1 year or until disease recurrence, whichever occurs first. **Metastatic gastric cancer** **Three-weekly schedule** - Initial loading dose: IV: 8 mg/kg body weight. - Maintenance dose: IV: 6 mg/kg body weight, beginning three weeks after the loading dose. **Pediatrics** The safety and effectiveness of trastuzumab in pediatric patients have not been established.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** No dosage adjustments provided. No pharmacokinetic changes in renal impairment. Has not studied in severe cases. **Hepatic Impairment** No dosage adjustments provided. Has not studied.
Contra-indications	Hypersensitivity to trastuzumab, murine proteins, or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Decreased left ventricular ejection fraction (4% to 22%). **Dermatologic**: Skin rash (4% to 18%). **Gastrointestinal**: Abdominal pain (22%; upper abdominal pain: 2%), anorexia (14%), diarrhea (7% to 25%), nausea (6% to 33%), vomiting (4% to 23%). **Hypersensitivity**: Infusion-related reaction (first infusion: ≤40%; subsequent infusions: 21% [severe: 1%]).

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	Infection: Infection (20%). **Nervous system**: Asthenia (5% to 42%), chills (5% to 32%), dizziness (4% to 13%), headache (10% to 26%), insomnia (14%), pain (47%). **Neuromuscular and skeletal**: Back pain (5% to 22%). **Respiratory**: Cough (5% to 26%), dyspnea (3% to 22%), pharyngitis (12%), rhinitis (2% to 14%). **Miscellaneous**: Fever (6% to 36%). **1% to 10%** **Cardiovascular**: Cardiac arrhythmia (3%), edema (8%), heart failure (≤7%), hypertension (4%), palpitations (3%), peripheral edema (5% to 10%), tachycardia (5%). **Dermatologic**: Acne vulgaris (2%), nail disease (2%), pruritus (2%). **Gastrointestinal**: Constipation (2%), dyspepsia (2%). **Genitourinary**: Urinary tract infection (3% to 5%). **Hematologic and oncologic**: Anemia (4%; grade 3: <1%), leukopenia (3%). **Hypersensitivity**: Hypersensitivity reaction (≤3%). **Infection**: Herpes simplex infection (2%), influenza (4%). **Nervous system**: Depression (6%), neuropathy (1%), paresthesia (2% to 9%), peripheral neuritis (2%). **Neuromuscular and skeletal**: Arthralgia (6% to 8%), muscle spasm (3%), myalgia (4%), ostealgia (3% to 7%). **Respiratory**: Epistaxis (2%), flu-like symptoms (2% to 10%), nasopharyngitis (8%), pharyngolaryngeal pain (2%), sinusitis (2% to 9%), upper respiratory tract infection (3%).
Monitoring Parameters	• CBC • Monitor for infusion-related reactions. • Baseline cardiac assessment including history and physical examination, electrocardiogram (ECG) or echocardiogram. Repeat every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration. • Pregnancy testing
Drug Interactions	***Risk D: Consider therapy modification*** **Anthracyclines**: Patients who receive anthracycline after stopping trastuzumab may be at increased risk of cardiac dysfunction because of trastuzumab's estimated long washout period. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.
Pregnancy and Lactation	**Pregnancy** Serious fetal harm has been reported after exposure to trastuzumab during pregnancy. Avoid use unless the potential benefit for the mother outweighs the potential risk to the fetus. Advise for using effective contraception during treatment and for 7 months following the last dose. **Lactation** It is not known whether trastuzumab is excreted into human milk. Consider the benefits and potential adverse effects. Trastuzumab wash-out period is about 7 months.

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Administration	**N.B.** To prevent medication errors, it is important to check the label of the product (to ensure that the drug used is trastuzumab and not another trastuzumab-containing product, e.g., trastuzumab emtansine, trastuzumab deruxtecan, or trastuzumab; hyaluronidase). Also, check the formulation if it is for subcutaneous or IV administration. These products are not to be substituted. **Intravenous (IV) Administration** For intravenous (IV) infusion only. Do not administer as an IV push or bolus. **Preparation for infusion** • Reconstitute with Sterile Water for Injection (SWFI). The reconstituted vial yields a solution containing 21 mg/mL trastuzumab either for single-dose use (150 mg) or a multidose vial (440 mg). Do not shake. • Saline solution may be used for dilution. Glucose solutions should not be used since they cause aggregation of the protein. **Rate of infusion** • Loading dose IV infusion should be administered over 90 minutes. • Subsequent doses can be administered as a 30-minute infusion if the initial loading dose was well tolerated. • Patients should be observed for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms **Subcutaneous Administration** • Dose should be administered subcutaneously over 2-5 minutes. • Subcutaneous formulation is a ready-to-use solution and is not to be mixed or diluted with other products. • Alternative injection sites between the left and the right thighs should be used. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Emetogenicity	Minimal emetic risk (<10% frequency of emesis).
Warnings/ Precautions	**Cardiomyopathy** • Trastuzumab can result in congestive heart failure or asymptomatic cardiac dysfunction. These may be moderate to severe (sometimes fatal). Higher risk appears with concurrently administering anthracyclines. • Evaluate cardiac function before and during treatment. Discontinue trastuzumab for cardiomyopathy unless the benefits for the individual patient are deemed to outweigh the risks. • Patients who develop CHF or asymptomatic cardiac dysfunction can benefit from standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. **Infusion Reactions**

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	• Serious reactions include dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema have been reported. The majority of events occur within 2.5 hours of the start of the first infusion. If developed, discontinue or slow the rate of infusion, and the patient should be monitored until resolution of all observed symptoms, and appropriate treatments should be used. • Pre-medication may be used to reduce the risk of the occurrence of these events. • Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab. **Pulmonary Toxicity** • Severe (sometimes fatal) pulmonary events have been reported. Interstitial lung diseases, including symptoms of lung infiltrates, pneumonia, pneumonitis, pleural effusion, and respiratory insufficiency, have been reported. Discontinue treatment if it develops. • These events may occur as part of an infusion-related reaction or with a delayed onset. **Exacerbation of Chemotherapy-Induced Neutropenia** The incidences of neutropenia and febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. **Embryo-Fetal Toxicity** Exposure to trastuzumab during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception.
Storage and Light Sensitivity	Store intact vials at 2°C to 8°C. Do not freeze. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Patient Counselling Keys	• The patient should contact healthcare provider immediately if any of the following have developed: Cardiac disorders (new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, dizziness or loss of consciousness), Infusion reactions and lung problems (fever and chills, and on occasion included nausea, vomiting, pain, headache, dizziness, dyspnea, hypotension, rash, and asthenia) • Females of reproductive potential should be advised to use effective contraception during treatment and for 7 months following the last dose.
Sequence of Administration	Trastuzumab is administered before conventional chemotherapy.

PD-1/PD-L1 inhibitors

Nivolumab

Generic Name	Nivolumab
Dosage Form/Strengths	Solution for IV infusion: 40mg/4 ml, 100mg/ 10ml
Route of Administration	IV
Pharmacologic Category	Anti-PD-1 Monoclonal Antibody, Immune Checkpoint Inhibitor, Antineoplastic Agent. ATC Code: L01FF01
Indications	**N.B.** Refer to literature and specific protocols for all indications. 1. Melanoma in adults and pediatric (12 years and older) 2. Non-small cell lung cancer (NSCLC) 3. Malignant pleural mesothelioma (MPM) 4. Renal cell carcinoma (RCC) 5. Classical Hodgkin lymphoma (cHL) 6. Squamous cell cancer of the head and neck (SCCHN) 7. Urothelial carcinoma 8. Oesophageal cancer 9. Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult dosing** **1. Melanoma** • **Monotherapy (unresectable, metastatic, or adjuvant treatment)** (continued until disease progression or unacceptable toxicity). o Weight more than 40 or 50 kg**: IV**: 240 mg every 2 weeks or 480 mg every 4 weeks. o Weight is less than 40 or 50 kg**: IV**: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. • **Combination with ipilimumab (unresectable or metastatic only)** **IV:** 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab every 3 weeks for 4 doses, then followed by monotherapy as above. Monotherapy starts 3 weeks after the last dose of the combination if using 240 mg or 3 mg/kg, **or** 6 weeks after the last dose of the combination if using 480 mg or 6 mg/kg. **2. Non-small cell lung cancer NSCLC** • **Monotherapy (locally advanced or metastatic NSCLC)** **IV:** 240 mg every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity. • **Resectable** (in combination with platinum-based chemotherapy) o **Neoadjuvant treatment** (tumors ≥4 cm or node positive)**: IV:** 360 mg every 3 weeks on the same day of chemotherapy for 3 cycles. o **Neoadjuvant and adjuvant treatment: IV:** 360 mg every 3 weeks for up to 4 cycles, then followed by adjuvant monotherapy nivolumab 480 mg every 4 weeks after surgery for up to 13 cycles (~1 year) or until disease recurrence or unacceptable toxicity. • **Metastatic, in combination with ipilimumab**

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- **Expressing PD-L1: IV**: 360 mg nivolumab every 3 weeks with ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
- **Metastatic or recurrent: IV:** 360 mg nivolumab every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy.
  Combination nivolumab with ipilimumab continues until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression

3. Malignant pleural mesothelioma (MPM)

IV: 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.

4. Renal cell carcinoma (RCC) (Advanced)

- **Monotherapy** (after prior therapy)
  - **IV:** 240 mg every 2 weeks or 480 mg every 4 weeks.
- **Combination therapy** (first line)
  - **Intermediate or poor risk: IV**: 3 mg/kg every 3 weeks with ipilimumab 1 mg/kg for 4 doses followed by monotherapy phase as above until disease progression or unacceptable toxicity.
  - **IV**: 240 mg every 2 weeks or 480 mg every 4 weeks in combination with 40 mg cabozantinib administered orally every day until disease progression, unacceptable toxicity, or up to 2 years.

5. Classical Hodgkin lymphoma (cHL). (Relapsed or refractory).

IV: 240 mg every 2 weeks or 480 mg every 4 weeks monotherapy until disease progression or unacceptable toxicity.

6. Squamous Cell Cancer of the Head and Neck (SCCHN) (recurrent or metastatic).

IV: 240 mg every 2 weeks or 480 mg every 4 weeks monotherapy until disease progression or unacceptable toxicity.

7. Urothelial carcinoma.

- **Monotherapy (adjuvant or previously treated locally advanced or metastatic)**
  IV: 240 mg every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity.
- **Combination therapy as first-line treatment for unresectable or metastatic urothelial carcinoma**
  IV: 360 mg every 3 weeks with cisplatin and gemcitabine on the same day for up to 6 cycles, followed by monotherapy nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

8. Oesophageal squamous cell carcinoma

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	• **Monotherapy** **IV**: 240 mg every 2 weeks or 480 mg every 4 weeks. It may continue for a duration of 1 year. • **Combination therapy** (first line for unresectable advanced, recurrent or metastatic with tumour cell PD-L1 expression ≥ 1%) **IV**: 240 mg every 2 weeks **or** 480 mg every 4 weeks in combination with fluoropyrimidine- and platinum-containing chemotherapy until disease progression or unacceptable toxicity. **IV**: 3 mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks until disease progression or unacceptable toxicity up to years in patients without disease progression. **9. Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma** (advanced or metastatic). **IV**: 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks **or** 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks. Continue until disease progression, unacceptable toxicity, or up to 2 years.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Renal Impairment** • Mild or moderate renal impairment: No dose adjustment is required. • Severe renal impairment: limited data. **Hepatic Impairment** • Mild hepatic impairment: No dose adjustment is required. • Moderate to severe hepatic impairment: Limited data. Caution. **Dose Adjustment for Toxicity** • Dose reduction is not recommended for nivolumab. Withholding or permanent discontinuation may be needed based on individual safety and tolerability. • In general, for immune-mediated adverse reactions, withhold for severe reactions (Grade 3). Permanently discontinue for life-threatening reactions (Grade 4) or recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment. Refer to the Warnings/Precautions section for detailed recommendations. • Infusion-Related Reactions: Interrupt or slow the rate of infusion for grade 1 or 2. Permanently discontinue for grade 3 or 4.
Contra-indications	Hypersensitivity to the active substance or any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Edema (12%), hypertension (11%). **Dermatologic**: Pruritus (13% to 30%), skin rash (21% to 40%), vitiligo (10% to 11%). **Endocrine and metabolic**: Hypercalcemia (12%), hyperglycemia (46%), hyperkalemia (12% to 32%), hyperthyroidism (6% to 11%), hypocalcemia (10% to 17%), hypokalemia (12%), hypomagnesemia (16%), hyponatremia (16% to 22%),

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	hypothyroidism (11% to 14%), increased serum albumin (21%), weight loss (7% to 13%). **Gastrointestinal**: Abdominal pain (17% to 21%), decreased appetite (13% to 22%), diarrhea (23% to 37%; grades 3/4: ≤5%), increased serum amylase (17% to 34%), increased serum lipase (22% to 33%), nausea (14% to 30%; grades 3/4: <1%), vomiting (20%; grades 3/4: ≤1%). **Hematologic and oncologic**: Anemia (19% to 41%; grades 3/4: ≤3%), leukopenia (14%), lymphocytopenia (27% to 44%; grades 3/4: ≤17%), neutropenia (10% to 24%; grades 3/4: ≤2%). **Hepatic**: Hepatitis (2% to 11%), increased serum alanine aminotransferase (20% to 25%), increased serum alkaline phosphatase (21% to 27%), increased serum aspartate aminotransferase (24% to 29%), increased serum bilirubin (13%). **Immunologic**: Antibody development (11%; neutralizing: <1%). **Nervous system**: Asthenia (≤59%), dizziness (11%), fatigue (≤59%), headache (23%). **Neuromuscular and skeletal**: Arthralgia (10% to 21%), musculoskeletal pain (21% to 42%). **Renal**: Increased serum creatinine (12% to 19%), kidney impairment (≤17%) **Respiratory**: Cough (≤28%), dyspnea (≤18%), dyspnea on exertion (≤18%), productive cough (≤28%), upper respiratory tract infection (17% to 22%) **Miscellaneous**: Fever (16%) **1% to 10%** **Dermatologic**: Erythema of skin (10%). **Endocrine and metabolic**: Adrenocortical insufficiency (1%). **Gastrointestinal**: Colitis (≤6%; severe: 2%), constipation (10%), intestinal perforation (<10%), stomatitis (<10%). **Hepatic**: Increased gamma-glutamyl transferase (grades 3/4: 4%). **Hypersensitivity**: Infusion-related reaction (≤6%; severe: <1%). **Immunologic**: Sjögren disease (<10%). **Nervous system**: Neuritis (<10%), peripheral nerve palsy (peroneal: <10%), peripheral neuropathy (<10%). **Neuromuscular and skeletal**: Myopathy (<10%), myositis (<10%), polymyositis (<10%), rheumatism (spondyloarthropathy: <10%). **Renal**: Nephritis (≤1%). **Respiratory**: Pneumonitis (3%).
Monitoring Parameters	• Renal function test (baseline and periodically during treatment). • Liver function test (baseline and periodically during treatment), consider monitoring more frequently when nivolumab is administered in combination with cabozantinib. • Electrolytes (baseline to and periodically during treatment). • Thyroid function (baseline and periodically during treatment). • Blood glucose (for hyperglycemia) • Monitor for infusion reaction, cardiac and pulmonary adverse reactions, diarrhea and colitis, adrenal Insufficiency, dermatologic toxicity, encephalitis, and ocular disorders continuously during treatment. • Monitor for signs/symptoms of infusion-related reactions. • Assessment of PD-L1 status if needed.

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Drug Interactions	***Risk X: Avoid the combination*** None. ***Risk D: Consider therapy modification*** Corticosteroids (Systemic).
Pregnancy and Lactation	**Pregnancy:** No human data. Nivolumab can cause fetal harm based on animal data. Use is not recommended unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab. **Fertility:** The effect of nivolumab on male and female fertility is unknown. **Lactation**: No human data. Breastfeeding is not recommended during treatment due to the potential serious risk to the child.
Administration	**Administration: IV** **Preparation for administration** • Dilute with either sodium chloride (0.9%) or glucose (5%) solution for injection to a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL/kg. • Must not be administered as an intravenous push or bolus injection. • Do not co-administer other drugs through the same intravenous line. Flush the IV line at the end of the infusion. • Infuse through a line with a sterile, nonpyrogenic, low protein-binding 0.2 to 1.2 micrometer in-line filter. **Rate of infusion** Infuse over 30-60 minutes. **N.B.** Refer to the manufacturer PIL for specific considerations.
Emetogenicity	Minimal emetic risk (<10% frequency of emesis).
Warnings/ Precautions	➢ **Immune-Mediated Adverse Reactions** • Nivolumab and other PD-1/PD-L1 inhibitors are associated with Immune-Mediated Adverse Reactions, which may be severe or fatal, and can occur in any organ system or tissue. Immune-mediated reactions include pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, dermatologic adverse reactions, and nephritis and renal dysfunction. • Higher frequencies occurred when nivolumab was taken in combination with ipilimumab compared with nivolumab as monotherapy. • Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions. • Monitor for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, and laboratory abnormalities indicating electrolyte disturbances and dehydration before and periodically during treatment and at least up to 5 months after the last dose. Dose may be withheld or permanently discontinued according to severity and type of reaction. • Most immune-related adverse reactions improved with appropriate management, including corticosteroids (tapered) and treatment modifications. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Withhold nivolumab during immunosuppressive therapy. **Immune-related pneumonitis**

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- Severe, some fatal, cases have been observed during monotherapy or nivolumab in combination. Monitor radiographic changes, dyspnea, and hypoxia.
- For Grade 3 or 4 pneumonitis, nivolumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.
- For Grade 2 (symptomatic) pneumonitis, nivolumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. If symptoms improve, therapy can be resumed after corticosteroid tapering. If no improvement, the corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalent, with permanent discontinuation of nivolumab.

Immune-related colitis

- Severe diarrhea or colitis observed with nivolumab monotherapy or in combination. Infections (e.g., cytomegalovirus) and other etiologies of diarrhea should be ruled out.
- For Grade 4 diarrhea or colitis, nivolumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
- for Grade 3 diarrhea or colitis associated with nivolumab monotherapy, it should be withheld and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. If symptoms improved, therapy can be resumed after corticosteroid tapering. If no improvement, permanently discontinue nivolumab.
- For Grade 3 diarrhea or colitis associated with nivolumab in combination, permanently discontinue nivolumab and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
- For Grade 2 diarrhea or colitis, withhold nivolumab and initiate 0.5 to 1 mg/kg/day methylprednisolone equivalents. If symptoms improved, resume nivolumab after tapering corticosteroids. If no improvement, permanently discontinue and increase corticosteroid dose to 1 to 2 mg/kg/day.

Immune-related hepatitis

- Severe hepatitis has been observed with monotherapy or nivolumab in combination. Monitor for elevations of transaminase and total bilirubin.
- For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
- For Grade 2 elevations, withhold nivolumab. Persistent elevations in laboratory findings should be managed with 0.5 to 1 mg/kg/day methylprednisolone equivalents. If symptoms improved, resume nivolumab after tapering corticosteroids. If no improvement, permanently discontinue and increase corticosteroid dose to 1 to 2 mg/kg/day.

Immune-related nephritis and renal dysfunction

- Severe nephritis and renal dysfunction have been observed with monotherapy or nivolumab in combination. Monitor for an increase in serum creatinine (may be asymptomatic).

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- For Grade 4 serum creatinine elevation, nivolumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
- For Grade 2 or 3 serum creatinine elevation, withhold nivolumab and initiate 0.5 to 1 mg/kg/day methylprednisolone equivalents. If symptoms improved, resume nivolumab after tapering corticosteroids. If no improvement, permanently discontinue and increase corticosteroid dose to 1 to 2 mg/kg/day.

Immune-related endocrinopathies

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis, have been observed with nivolumab monotherapy or nivolumab in combination.
- For symptomatic hypothyroidism or hyperthyroidism, nivolumab should be withheld and thyroid hormone replacement or an anithyroid medication should be initiated as needed. If inflammation of the thyroid is suspected, corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered. If symptoms improved, resume nivolumab after tapering corticosteroids. If a life-threatening condition occurs, permanently discontinue nivolumab.
- For symptomatic Grade 2 adrenal insufficiency, nivolumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed.
- For Grade 3 or 4 adrenal insufficiency, permanently discontinue nivolumab.
- For symptomatic Grade 2 or 3 hypophysitis, nivolumab should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Resume nivolumab and taper corticosteroids after improvement.
- For Grade 4 hypophysitis, permanently discontinue nivolumab.
- For symptomatic diabetes, nivolumab should be withheld, and insulin replacement should be initiated as needed.
- For life-threatening diabetes, permanently discontinue nivolumab.

Immune-related skin adverse reactions

- Severe rash has been observed with nivolumab in combination with ipilimumab and, less commonly, with nivolumab as monotherapy.
- For Grade 3 rash, withhold nivolumab. For Grade 4 rash, permanently discontinue nivolumab. Severe rash should be managed with corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Other immune-related adverse reactions

- Myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, has been reported. If developed, close monitoring should be implemented.
- Based on the severity of myotoxicity, nivolumab should be withheld or discontinued, and initiation of prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day may be needed.

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	Infusion-related reactions Interrupt, slow the rate of infusion, or permanently discontinue based on the severity of the reaction. **Complications of allogeneic HSCT** Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. **Organ transplant rejection** Treatment with nivolumab or PD-1 inhibitors may increase the risk of rejection in solid organ transplant recipients. Consider the benefit/risk ratio **Assessment of PD-L1 status** When assessing the PD-L1 status of the tumour, a well-validated methodology must be used. **Multiple myeloma** Randomized studies of individuals with multiple myeloma who were treated with a thalidomide analog plus dexamethasone in addition to a PD-1 blocking drug (such as nivolumab) showed an increase in mortality. Treatment for multiple myeloma with nivolumab should only be administered as part of a clinical trial.
Storage and Light Sensitivity	• Store between 2°C to 8°C. Do not freeze or shake. • Protect from light. • The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours. • After preparation in NS, may be stored for 30 days at 2ºC to 8ºC protected from light or 1 day at room temperature and room light (including infusion time). • After preparation in D5W, may be stored for 7 days at 2ºC to 8ºC protected from light or 8 hours at room temperature and room light (including infusion time). **N.B.** Refer to the manufacturer PIL for specific considerations.
Patient Counselling Keys	• Advise females of reproductive potential to use effective contraception and stop lactation during treatment and for at least 5 months following the last dose. • The patient should be informed of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation. So, at any signs, the patient should contact the healthcare provider, including: o Pneumonitis (chest pain, dyspnea or shortness of breath). o Colitis (diarrhea or severe abdominal pain). o Hepatitis (jaundice, severe nausea or vomiting, pain on the right side of the abdomen). o Endocrinopathies, e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus (weight changes, headache, photophobia, or visual field defects, fatigue, hypotension). o Nephritis and Renal Dysfunction (decreased urine output, blood in urine, swelling in ankles). o Skin Adverse Reactions (rash).
Pharmaco-genomics	**Gene Testing Required** MSI-H/dMMR - Nivolumab ± Ipilimumab (Colorectal Cancer) • **Outcome**: Efficacy – **Evidence of Testing Benefit**: Strong • Polymerase chain reaction, next-generation sequencing, or

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	immunohistochemistry can be used to test for MSI and/or MMR proficiency.
Sequence of Administration	Nivolumab should be administered before ipilimumab, and before chemotherapy if to be taken on the same day.

VEGF/VEGFR inhibitors

Bevacizumab

Generic Name	Bevacizumab
Dosage Form/Strengths	Concentrate Solution for Infusion: 100 mg/4mL, 400 mg/16mL
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Monoclonal Antibody; Vascular Endothelial Growth Factor (VEGF) Inhibitor. ATC Code: L01FG01
Indications	**N.B.** Refer to the literature and specific protocols for all indications. **Adult dosing** **Metastatic colorectal cancer** • For first- or second-line treatment: in combination with IV fluorouracil. • For second-line treatment: in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin chemotherapy after failure with first-line bevacizumab-containing therapy. **Non-small cell lung cancer** First-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer: in combination with carboplatin and paclitaxel, or with erlotinib in EGFR mutant patients. **Advanced and/or metastatic renal cell carcinoma** First-line treatment in combination with interferon alfa. **Cervical cancer** Persistent, recurrent, or metastatic cervical cancer: in combination with paclitaxel and either cisplatin or topotecan. **Epithelial ovarian, fallopian tube, or primary peritoneal cancer** • For first-line treatment with advanced stages III B, III C, and IV: in combination with carboplatin and paclitaxel. • For recurrence of platinum-sensitive disease: in combination with carboplatin and either paclitaxel or gemcitabine. • Platinum-resistant recurrent patients who received no more than two prior chemotherapy regimens: in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin. **Metastatic breast cancer** • First-line treatment: in combination with paclitaxel. • First-line treatment of metastatic breast cancer in whom treatment with other chemotherapy options, including taxanes or anthracyclines, is not considered appropriate: in combination with capecitabine. **Relapsed glioblastoma**
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for

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specific protocols.

Metastatic colorectal cancer

IV infusion: 5 mg/kg or 10 mg/kg once every 2 weeks.
Or 7.5 mg/kg or 15 mg/kg once every 3 weeks.
Treatment is recommended to be continued until progression of the disease or until unacceptable toxicity.

Non-small cell lung cancer

- In combination with carboplatin and paclitaxel
  IV infusion: 7.5 mg/kg or 15 mg/kg once every 3 weeks.
- In combination with erlotinib in EGFR mutant patients
  IV infusion: 15 mg/kg once every 3 weeks.

Treatment is recommended to be continued until progression of the disease or until unacceptable toxicity.

Advanced and/or metastatic renal cell carcinoma

IV infusion: 10 mg/kg every 2 weeks with interferon alfa.
Treatment is recommended to be continued until progression of the disease or until unacceptable toxicity.

Cervical cancer

IV infusion: 15 mg/kg once every 3 weeks with paclitaxel and cisplatin or paclitaxel and topotecan.
Treatment is recommended to be continued until progression of the disease or until unacceptable toxicity.

Epithelial ovarian, fallopian tube, or primary peritoneal cancer

- Front-line or first-line treatment with advanced stages III B, III C, and IV, with carboplatin and paclitaxel
  IV infusion: 15 mg/kg once every 3 weeks for up to 6 cycles, followed by continued use of bevacizumab as a single agent until disease progression or until unacceptable toxicity for a maximum of 22 cycles.
- Platinum-resistant recurrent
  - *IV infusion*: 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or weekly given topotecan.
  - *IV infusion*: 15 mg/kg every 3 weeks with topotecan (given on days 1-5, every 3 weeks).

- Platinum-sensitive recurrent disease
  IV infusion: 15 mg/kg every 3 weeks with carboplatin and paclitaxel (for 6-8 cycles) or with carboplatin and gemcitabine (for 6-10 cycles), followed by continued use of bevacizumab 15 mg/kg every 3 weeks as a single agent until disease progression.

Metastatic breast cancer

IV infusion: 10 mg/kg once every 2 weeks or 15 mg/kg once every 3 weeks.
Treatment is recommended to be continued until progression of the disease or until

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	unacceptable toxicity. **Hepatocellular Carcinoma (HCC)** *IV infusion*: 15 mg/kg after administration of 1,200 mg of atezolizumab every 3 weeks. **Recurrent glioblastoma** *IV infusion:* 10 mg/kg every 2 weeks. **Pediatrics** The safety and efficacy of bevacizumab in children aged less than 18 years have not been established.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. • **Renal Impairment** The safety and efficacy have not been studied. • **Hepatic Impairment:** The safety and efficacy have not been studied. • **Toxicities due to therapy** Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended. o Nephrotic syndrome (proteinuria >3.5 g per 24 hours): Bevacizumab should be discontinued. o Proteinuria ≥2 to ≤3.5 g per 24 hours: Withhold bevacizumab until less than 2 grams of protein in urine.
Contra-indications	Hypersensitivity to the active substance or to any of the excipients.
Adverse Drug Reactions	**≥10%** **Cardiovascular**: Hypertension (24% to 42%), peripheral edema (15%), venous thromboembolism (grades 3/4: 5% to 11%). **Dermatologic**: Exfoliative dermatitis, xeroderma. **Endocrine and metabolic**: Hyperglycemia (26%), hypoalbuminemia (16%), hypomagnesemia (24%), hyponatremia (19%), weight loss (20% to 21%). **Gastrointestinal**: Abdominal pain (grade 3/4: 8% to 12%), decreased appetite (34% to 36%), diarrhea (21% to 40%), dysgeusia, nausea (53% to 72%), stomatitis (15% to 25%). **Genitourinary**: Ovarian failure (34%), pelvic pain (14%), proteinuria (10% to 20%), urinary tract infection (22%). **Hematologic and oncologic**: Bruise (17%), leukopenia (grades 3/4: 37% to 53%), lymphocytopenia (12%; grades 3/4: 6%), neutropenia (12%; grades 3/4: 8% to 21%), thrombocytopenia (58%; grades 3/4: 20% to 40%). **Nervous system**: Anxiety (17%), dizziness (23%), dysarthria (8% to 12%), fatigue (33% to 82%), headache (22% to 49%), insomnia (21%), myasthenia (13% to 15%), voice disorder (5% to 13%). **Neuromuscular and skeletal**: Arthralgia (28% to 41%), back pain (12% to 21%), limb pain (19% to 25%), myalgia (19%). **Ophthalmic**: Disease of the lacrimal apparatus. **Renal**: Increased serum creatinine (16%). **Respiratory**: Cough (26%), dyspnea (26% to 30%), epistaxis (17% to 55%),

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	oropharyngeal pain (16%), pulmonary hemorrhage (4% to 31%), sinusitis (15%). **Miscellaneous**: Postoperative wound complication (5% to 15%). **1% to 10%** **Cardiovascular**: Arterial thrombosis (grades ≥3: 5%), decreased left ventricular ejection fraction (10%), deep vein thrombosis (grades 3/4: 9%), intra-abdominal venous thrombosis (grades 3/4: 3%), left ventricular dysfunction (grades 3/4: 1%), pulmonary embolism (1%), syncope (grades 3/4: 3%), thrombosis (10%). **Dermatologic**: Acne vulgaris (1%), cellulitis (grades 3/4: 3%). **Endocrine and metabolic**: Dehydration (grades 3/4: 4%), hypokalemia (grades 3/4: 7%). **Gastrointestinal**: Constipation (grades 3/4: 4%), fistula of bile duct (≤2%), gastritis (1%), gastroesophageal reflux disease (2%), gastrointestinal fistula (≤2%), gastrointestinal perforation (≤3%), gingival hemorrhage (4% to 7%), gingival pain (1%), gingivitis (2%), hemorrhoids (8%), oral mucosa ulcer (2%), rectal fistula (6%), rectal pain (6%), tooth abscess (2%), tracheoesophageal fistula (≤2%). **Genitourinary**: Bladder fistula (≤2%), vaginal fistula (≤2%). **Hematologic and oncologic**: Hemorrhage (grades ≥3: ≤7%; including major hemorrhage) **Hypersensitivity**: Infusion-related reaction (<3%; severe infusion-related reaction: <1%, including anaphylaxis, non-immune anaphylaxis, and hypertensive crisis). **Infection**: Infection (10%). **Nervous system**: Asthenia (grades 3/4: 10%), pain (grades 3/4: 8%). **Ophthalmic**: Blurred vision (2%). **Otic**: Deafness (1%), tinnitus (2%). **Renal**: Renal fistula (≤2%). **Respiratory**: Bronchopleural fistula (≤2%), nasal congestion (8%), nasal signs and symptoms (7% to 10%), rhinitis (≥3%), rhinorrhea (10%). **Miscellaneous**: Fistula (≤2%).
Monitoring Parameters	• Monitor proteinuria by dipstick urinalysis before starting and during therapy. • Blood pressure every 2-3 weeks during treatment. • Evaluate pregnancy status before use. • Monitor for signs/symptoms of GI perforation or fistula (including abdominal pain, constipation, vomiting, and fever), bleeding (including epistaxis, hemoptysis, GI, and/or CNS bleeding), posterior reversible encephalopathy syndrome, thromboembolism (arterial and venous), wound healing complications, and/or heart failure.
Drug Interactions	***Risk X: Avoid the combination*** Anthracyclines, BCG (Intravesical), Chloramphenicol (Systemic), Cladribine, Dipyrone, Fexinidazole, Sunitinib. ***Risk D: Consider therapy modification*** Deferiprone, Ropeginterferon Alfa-2b.
Pregnancy and Lactation	**Pregnancy:** Avoid. No adequate human data. Post-marketing fetal abnormalities reports. Women of childbearing potential should use effective contraception during (and up to 6 months after) treatment.

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	Lactation: No data. women must discontinue breastfeeding during therapy and not breastfeed for at least six months following the last dose of bevacizumab due to potential serious adverse reactions.
Administration	**IV Administration** IV infusion only. Not for IV push or bolus. **Preparation for administration** • Dilute with 100 ml 0.9 % sodium chloride solution. Discard any unused portion left in a vial. • Do not mix with dextrose solution. • Discard the vial if the solution is cloudy, discolored, or contains particulate matter. **Rate of infusion** • First dose: Infuse over 90 minutes. • Second infusion: Infuse over 60 minutes, if the initial infusion is well tolerated. • All subsequent infusions over 30 minutes if the second infusion is tolerated. Monitor closely during the infusion for signs of an infusion reaction. **N.B.** Refer to the manufacturer PIL if there are specific considerations**.**
Emetogenicity	Minimal emetic risk (<10% frequency of emesis)
Warnings/ Precautions	**Gastrointestinal (GI) perforation/fistula** • Bevacizumab-induced GI perforations have been serious and occasionally fatal. • The majority of perforation cases happened within 50 days of the initial dose. The majority of fistulae occurred within 6 months of the initial dose (including GI-vaginal fistulae). • Risk factors include radiation in cervical cancer patients and intra-abdominal inflammatory processes in colorectal cancer patients. • Perforation can be complicated by intra-abdominal abscess, fistula formation, and the requirement of diverting ostomies. • Therapy should be permanently discontinued in patients who develop gastrointestinal perforation, tracheoesophageal fistula, Grade 4 fistula, or fistula formation involving any internal organ. **Heart failure** • Range from asymptomatic declines in left ventricular ejection fraction to symptomatic congestive heart failure (CHF), requiring treatment or hospitalization. • Previous treatment with anthracyclines or prior radiotherapy to the left chest wall are risk factors. • Administration of bevacizumab in addition to chemotherapy increases the incidence of grade ≥3 left ventricular dysfunction (1% vs. 0.6%), heart failure (HF) (4% vs 0.6%), compared to individuals receiving chemotherapy alone. • Caution with significant cardiovascular disease. Discontinue in patients who develop CHF. **Hemorrhage** • Bevacizumab may cause either severe hemorrhage (which could be fatal) or

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minor hemorrhage (typically grade 1 epistaxis). Compared to patients receiving chemotherapy alone, patients receiving bevacizumab experienced up to five times as many cases of severe or deadly hemorrhage (including hemoptysis, GI bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding).

- Patients with recent hemoptysis (> 2.5 ml of red blood) should not be treated with bevacizumab.
- Discontinue in patients who develop Grade 3 or 4 hemorrhage.
- In patients with HCC, an evaluation for the presence of varices is recommended within 6 months of initiation of bevacizumab.

Hypertension

- Severe hypertension occurred at a higher incidence in patients receiving bevacizumab products compared to patients receiving chemotherapy alone.
- Withhold bevacizumab in patients with uncontrolled severe hypertension; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

Posterior reversible encephalopathy syndrome (PRES)

- Cases with PRES have been rarely reported (<0.5%) within 16 hours to a year following the start of treatment. Symptoms include headache, seizure, disorientation, lethargy, vision problems, or neurologic problems. Mild to severe hypertension may be present.
- MRI is required to confirm the diagnosis of PRES.
- Discontinue bevacizumab in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuation.

Arterial Thromboembolic Events (ATE)

Serious, sometimes fatal, arterial thromboembolic events including cerebral infarction, transient ischemic attacks, angina, and myocardial infarction occurred at a higher incidence than chemotherapy alone. The highest incidence occurred in patients with glioblastoma. Discontinue in patients who develop a severe ATE.

Venous Thromboembolic Events (VTE)

An increased risk of venous thromboembolic events (VTE) was observed. Discontinue bevacizumab in patients with a Grade 4 VTE, including pulmonary embolism.

Infusion reactions

- Infusion reactions (e.g., hypertension, hypertensive crisis [associated with neurologic signs/symptoms], wheezing, oxygen desaturation, hypersensitivity [grade 3], chest pain, rigors, headache, diaphoresis) may occur. Decrease rate of infusion to avoid. with the first infusion (uncommon).
- Decrease the rate of infusion for mild, clinically insignificant reactions. Discontinue in patients who develop a severe infusion-related reaction.

Ocular adverse events

Bevacizumab

	Intravitreal administration (off-label route) has been linked to serious eye infections and various degrees of visual loss, including permanent blindness. **Proteinuria/nephrotic syndrome** • Bevacizumab is associated with higher rates and more severe cases of proteinuria. Patients have occasionally experienced nephrotic syndrome, which may be fatal. • Monitoring is recommended before and during therapy. • Withhold for proteinuria greater than or equal to 2 grams per 24 hours and resume when less than 2 grams per 24 hours. • A history of hypertension is a risk factor. • Therapy should be permanently discontinued in patients who develop nephrotic syndrome **Wound healing complications** • Patients who underwent surgery while receiving Bevacizumab had a higher incidence of wound healing complications (including serious/fatal complications). • Therapy should not be initiated for at least 28 days following major surgery. • Bevacizumab should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be initiated. **Ovarian Failure** • Bevacizumab may impair female fertility. Premenopausal women receiving Bevacizumab with chemotherapy had a greater incidence of ovarian failure (34% vs.2%) than those getting chemotherapy alone as an adjuvant treatment for solid cancer. • After discontinuation, ovarian function recovered in 86.2% of women. • Fertility preservation strategies should be discussed with women of childbearing potential before starting treatment.
Storage and Light Sensitivity	• Store vial in the original carton under refrigeration at 2° to 8°C. • Diluted solution may be stored at 2°C to 8°C for up to 8 hours, if not used immediately. • Protect from light. Do not freeze. Do not shake. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Patient Counselling Keys	• During the infusion, patients may experience severe hypersensitivity effects. They should tell the doctor if they develop any adverse effects. • Patients should contact health care professional immediately to report any of the following: Gastrointestinal Perforations and Fistulae (persistent or severe abdominal pain, severe constipation, or vomiting), Bleeding (serious or unusual bleeding including coughing or spitting blood), Cardiac disorders (chest pain, cough, swelling in extremities, numbness), Neurological symptoms (confusion, dizziness, blurred vision, seizures, intense headaches). • Blood pressure and urinalysis should be monitored regularly. • Instruct patients not to undergo surgery without first discussing potential risks with their healthcare provider due to possible wound healing impairment.

Bevacizumab

	• Women of childbearing potential should use effective contraception and stop lactation during and up to 6 months after treatment.
Sequence of Administration	Bevacizumab is taken before conventional chemotherapy.

OTHER ANTINEOPLASTIC AGENTS

Proteasome inhibitors

Bortezomib

Generic Name	Bortezomib
Dosage Form/Strength	Powder for solution for SC / IV injection: 3.5 mg Solution for injection: 3.5 mg
Route of Administration	SC / IV
Pharmacologic Category	Antineoplastic Agent, Proteasome Inhibitor **ATC**: L01XG01
Indications	**Treatment of adult patients with** • Multiple myeloma. • Mantle cell lymphoma.
Dosage Regimen	N.B. Refer to literature and specific protocols for all indications. **- Previously untreated multiple myeloma patients** **Patients NOT eligible for hematopoietic stem cell transplantation** • **Combination therapy with melphalan and prednisone** **Initial**: **Blous SC or IV**: 1.3 mg/m^2 twice weekly in cycles 1-4 of each cycle on days 1, 4, 8, 11, 22, 25, 29, and 32. A treatment cycle is composed of 6 weeks. While in cycles 5-9, bortezomib is administered once weekly on days 1, 8, 22, and 29. **Melphalan (9 mg/m^2) and prednisone (60 mg/m^2)**: **Oral**: On days 1, 2, 3, and 4 of the first week of each bortezomib treatment cycle. **Duration:** 9 treatment cycles. **Before initiating a new cycle,** Platelet counts should be ≥ 70 x 10^9 /l and the absolute neutrophil count should be ≥ 1.0 x 10^9 /l. **Patients eligible for hematopoietic stem cell transplantation** • **Combination therapy with dexamethasone (induction therapy)** **Blous SC or IV**: 1.3 mg/m^2 twice weekly for two weeks in each cycle on days 1, 4, 8, and 11. A treatment cycle is composed of 3 weeks. **Dexamethasone: Oral:** 40 mg on days 1, 2, 3, 4, 8, 9, 10, and 11 of the bortezomib treatment cycle. **Duration:** 4 treatment cycles. • **Combination therapy with dexamethasone and thalidomide** **Blous SC or IV**: 1.3 mg/m^2 twice weekly for two weeks in each cycle on days 1, 4, 8, and 11. A treatment cycle is composed of 4 weeks. **Dexamethasone: Oral:** 40 mg on days 1, 2, 3, 4, 8, 9, 10, and 11 of the bortezomib treatment cycle. **Thalidomide: Oral**: 50 mg daily on days 1-14 and if tolerated, the dose is increased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2. **- Patients who have received at least one prior therapy (progressive multiple**

Bortezomib

	myeloma) • **Monotherapy** **Initial**: **Blous SC or IV**: 1.3 mg/m^2 twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. **Duration**: Continue until 2 weeks after confirmation of a complete response. Responding patients who do not achieve a complete remission are recommended to receive a total of 8 cycles of bortezomib therapy. • **Combination with dexamethasone** **Initial**: **Blous SC or IV**: 1.3 mg/m^2 twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. **Dexamethasone**: Oral: 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the bortezomib treatment cycle. Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles. **Retreatment for Multiple Myeloma**: May retreat starting at the last tolerated dose. **- Previously untreated mantle cell lymphoma (MCL)** • **Combination therapy with rituximab, cyclophosphamide, doxorubicin, and prednisone.** **SC or IV**: 1.3 mg/m^2 twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. A treatment cycle is composed of 3 weeks. **Duration**: 6 treatment cycles. Two additional bortezomib cycles may be given if there is a documented response. **Other agents:** are given as IV infusion on day 1 of each cycle as follows: Rituximab: 375 mg/m^2, cyclophosphamide: 750 mg/m^2, doxorubicin: 50 mg/m^2 **Prednisone**: Oral: 100 mg/m^2 on days 1, 2, 3, 4, and 5 of each bortezomib treatment cycle. **Before initiating a new cycle of therapy** - Platelet counts should be ≥ 100,000 cells/µL, and the absolute neutrophil count (ANC) should be ≥ 1,500 cells/µL. - Platelet counts should be ≥ 75,000 cells/µL in patients with bone marrow Infiltration or splenic sequestration - Hemoglobin ≥ 8 g/dL - Non-hematological toxicities should have resolved to grade 1 or baseline. **N.B.** At least 72 hours should elapse between consecutive doses of bortezomib. **Pediatric Use:** Safety and effectiveness have not been established in pediatric patients.
Dosage Adjustment	• **Renal Impairment** CrCL > 20 ml/min/1.73 m^2: No dose adjustment necessary. CrCL < 20 ml/min/1.73 m^2: No data. Dialysis: Bortezomib should be administered after the dialysis procedure as dialysis may reduce its concentration. • **Hepatic Impairment** Mild impairment: No dose adjustment necessary.

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Moderate or severe hepatic impairment: 0.7 mg/m^2 during the first cycle, and consider subsequent dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 based on patient tolerance.

- **Neuropathic pain or peripheral neuropathy**: should be managed as follows

Severity of neuropathy	Modification of Dose
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function.	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental activities of daily living)	Reduce bortezomib to 1.0 mg/m^2 or change bortezomib treatment schedule to 1.3 mg/m^2 once per week.
Grade 2 with pain or grade 3 (severe symptoms; limiting self-care activities of daily living)	Withhold bortezomib treatment until resolution of symptoms. When toxicity resolves: re-initiate bortezomib with reduced dose 0.7 mg/m^2 once per week
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue bortezomib

Previously untreated multiple myeloma patients are NOT eligible for hematopoietic stem cell transplantation (in combination with melphalan and prednisone)

Toxicity	Modification of Dose
Hematological toxicity	
If prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle.	Consider a reduction of the melphalan dose by 25% in the next cycle.
If platelet counts ≤ 30 x 10^9/l or ANC ≤ 0.75 x 10^9/l on a bortezomib dosing day (other than day 1).	Bortezomib therapy should be withheld.
If several bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration	The Bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2), or (from 1 mg/m^2 to 0.7 mg/m^2).
Non-hematological toxicities	
Grade ≥ 3 non-hematological toxicities	• Withhold until symptoms have resolved to grade 1 or baseline. Then, bortezomib may be reinitiated

Bortezomib

	at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • For neurological toxicities: Refer to neuropathy toxicity adjustments.

Previously untreated multiple myeloma patients are eligible for hematopoietic stem cell transplantation

Previously treated multiple myeloma patients with at least one prior therapy) (monotherapy or combination therapy)

- **Any grade 3 non-hematological or any grade 4 hematological toxicities, excluding neuropathy**: Withhold bortezomib therapy. Bortezomib therapy should be withheld when the platelet count is < 25,000/µl.
  After resolution of symptoms, reinitiate at 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2).
  If symptoms recur at the lowest dose, discontinue unless the benefit of treatment clearly outweighs the risk.
- **Neuropathy**: refer to the neurological toxicities table.

Previously untreated mantle cell lymphoma (MCL)

Toxicity	Modification of Dose
Hematological toxicity	
≥ Grade 3 neutropenia with fever, grade 4 neutropenia lasting more than 7 days, or a platelet count < 10,000 cells/µL.	• Withhold until ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL, then reinitiate at a reduced dose by one level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • If not resolved in 2 weeks, discontinue.
If platelet counts are < 25,000 cells/µL. or ANC < 750 cells/µL on a bortezomib dosing day (other than Day 1 of each cycle)	Bortezomib therapy should be withheld.
Non-hematological toxicities	
≥ Grade 3 non-hematological toxicities considered to be related to bortezomib.	• Withhold until symptoms have resolved to grade 2 or better. Then, bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • For neurological toxicities: Refer to neuropathy toxicity adjustments.

Contra-indications	• Hypersensitivity to the active substance, to boron, or to any of the excipients. • Acute diffuse infiltrative pulmonary and pericardial disease.

Bortezomib

	• Contraindicated for intrathecal administration.
Adverse Drug Reactions	**>10%** **Dermatologic**: Skin rash (12% to 23%). **Gastrointestinal**: Abdominal pain (11%), anorexia (14% to 21%), constipation (24% to 34%), decreased appetite (11%), diarrhea (19% to 52%; grade 3: 1% to 7%; grades ≥3: 7%), nausea (14% to 52%; grade 3: 2%; grades ≥3: 3%), vomiting (9% to 29%; grade 3: 2%; grades ≥3: 3% to 4%). **Hematologic and oncologic**: Anemia (12% to 23%; grades ≥3: ≤6%), leukopenia (18% to 20%; grade 3: 5%; grade 4: 1%), neutropenia (5% to 27%; grades ≥3%: 2% to 18%), thrombocytopenia (16% to 52%; grades ≥3%: 3% to 28%) **Infection**: Herpes zoster infection (herpes zoster infection and reactivation: 6% to 11%). **Nervous system:** Dizziness (10% to 18%), fatigue (7% to 52%), headache (10% to 19%), malaise (≤59%), neuralgia (23%), paresthesia (7% to 19%), peripheral neuropathy (including peripheral motor neuropathy and peripheral sensory neuropathy: 28% to 54%; grades ≥2: 24% to 39%; grades ≥3: 6% to 15%; grade 4: <1%). **Neuromuscular and skeletal**: Asthenia (7% to 16%). **Respiratory**: Dyspnea (11%). **Miscellaneous**: Fever (8% to 23%). **1% to 10%** **Cardiovascular**: Cardiac disorder (treatment emergent: 8%), cardiogenic shock (≤1%), heart failure (≤1%), hypotension (including orthostatic hypotension: 8% to 9%). **Hematologic and oncologic**: Hemorrhage (grades ≥3: 2%). **Infection**: Herpes simplex infection (1% to 3%). **Local**: Injection site reaction (mostly redness: 6%), irritation at injection site (5%). **Respiratory**: Acute pulmonary edema (≤1%), pulmonary edema (≤1%).
Monitoring Parameters	• CBC (regularly) and before each dose. • Hepatic functions • Monitor for cardiac symptoms (in patients with risk factors) or pulmonary toxicity and for neuropathy. • A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Bromperidol, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), CYP3A4 Inducers (Strong), Dengue Tetravalent Vaccine (Live), Deucravacitinib, Etrasimod, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine, Zoster Vaccine (Live/Attenuated). ***Risk D: Consider therapy modification*** Amifostine, Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus

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	Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Fusidic Acid (Systemic), Green Tea, Influenza Virus Vaccines, Leflunomide, Multivitamins, Obinutuzumab, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Non-Live/Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** No human data. Bortezomib can cause fetal harm based on animal data. Advise patients of reproductive potential to use effective contraception during treatment and for 7 months (for females) or 4 months (for males with female partners of reproductive potential) after the last dose. Bortezomib may affect either male or female fertility. **Lactation:** No human data. Due to potential harm, lactating patients should avoid breastfeeding during and for 2 months following bortezomib treatment.
Administration	**Hazardous agent:** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **IV Administration** • Dilute with 3.5 mL of neutral saline (0.9%) to give a final 1 mg/mL concentration. • Administer as a 3-5 second bolus IV injection through a peripheral or central IV catheter, followed by a flush with sodium chloride (0.9%) solution. **Subcutaneous Administration** • Dilute with 1.4 mL of neutral saline (0.9%) to give a final 2.5 mg/mL concentration. • Inject through the thighs or abdomen. Injection sites should be rotated for successive injections. • If local injection site reactions occur following bortezomib SC injection, either a less concentrated solution (to be reconstituted to 1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously, or a switch to IV injection is recommended. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Emetogenicity	Minimal emetic risk (<10% frequency of emesis).
Warnings/ Precautions	**Bone marrow suppression** • Hematologic toxicity is common, including thrombocytopenia, neutropenia and anemia. Bortezomib therapy should be withheld when platelet count is less than 25,000/µl or, in the case of combination with melphalan and prednisone, when platelet count is less than 30,000/µl. • Hemorrhage (GI and intracerebral) due to low platelet count has been observed. Neutropenic fever has been observed. **Cardiovascular effects** Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported with bortezomib. Fluid retention may be a predisposing factor. Monitor patients closely with risk factors.

Bortezomib

GI effects

Nausea, vomiting, diarrhea, constipation, or ileus may occur. May require the use of antiemetic and antidiarrheal medications or fluid replacement. Interrupt therapy if severe symptoms develop.

Pulmonary toxicity

- Pulmonary disorders (some are fatal), including pneumonitis, interstitial pneumonia, lung infiltrates, and acute respiratory distress syndrome (ARDS), have been rarely reported.
- Rare incidences of pulmonary hypertension (without left heart failure or significant pulmonary disease) have been reported.
- In the event of new or worsening cardiopulmonary symptoms, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.

Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely.

Hepatotoxicity

- Acute liver failure has been reported rarely in patients receiving bortezomib and multiple concomitant medications and with serious underlying conditions.
- Hepatitis, increases in liver enzymes, and hyperbilirubinemia have also been reported. May be reversible upon discontinuation. Limited experience with rechallenge.

Viral reactivation

- Herpes (zoster and simplex) reactivation has been reported with bortezomib. Also, hepatitis B virus has been reported with bortezomib in combination with rituximab.
- Consider using antiviral prophylaxis.

Hypotension

Bortezomib may cause postural and orthostatic hypotension. Caution in patients taking antihypertensives, with a history of syncope, or with dehydration.

Posterior reversible encephalopathy syndrome

- Posterior reversible leukoencephalopathy syndrome (PRES) has been reported rarely. Symptoms of PRES include confusion, headache, hypertension, lethargy, seizure, blindness, and/or other vision or neurologic disturbances.
- Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, bortezomib should be discontinued.

Peripheral neuropathy

- Bortezomib may cause or worsen peripheral neuropathy (sensory or motor).
- The incidence of grades ≥ 2 peripheral neuropathies may be lower with the subcutaneous route (compared to IV).

Bortezomib

	• Monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain, or weakness. • Patients with peripheral neuropathy should undergo neurological evaluation and may require a change in the dose, schedule, or route of administration to subcutaneous. Neuropathy has been managed with supportive care and other therapies. **Intrathecal administration** There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib should not be administered intrathecally.
Storage and Light Sensitivity	• Vials may be stored between 15 ^{0}C and 30 ^{0}C. • Protect from light. • Reconstituted solution (of 1 mg/ml and 2.5 mg/ml concentration) may be stored for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Patient Counselling Keys	• Patients should contact health care professional immediately to report any of the following: Peripheral Neuropathy (numbness, pain or a burning feeling in the feet or hands), cardiac diorders (chest pain, swelling of extremities), lung disorders (hypoxia, cough, dyspnea), neurological symptoms (confusion, memory problems, depression, trouble speaking or thinking, or change in eyesight), hepatotoxicity (abdominal pain, jaundice, anorexia, bleeding, dark-colored urine). • Advise patients to report symptoms of gastrointestinal toxicity to their healthcare provider and to drink adequate fluids to avoid dehydration. Instruct patients to seek medical advice if they experience symptoms of constipation, diarrhea, vomiting, or upset stomach, or muscle cramps. There may be ways to lower these side effects. • This medicine alters blood counts. Patients should check their blood counts regularly and avoid causes of infection and bleeding. • The patient should tell the doctor before taking any drugs, supplements, or herbal products. Other drugs, vitamin C supplements, and green tea may diminish bortezomib activity. • Advise females of reproductive potential to use effective contraception and stop lactation during treatment and for at least 7 months following the last dose.
Sequence of Administration	Bortezomib is administered before conventional chemotherapy.

Monoclonal Antibody, Bone-Modifying Agent

Denosumab

Generic Name	Denosumab
Dosage Form/Strengths	Prefilled syringe for injection: 60 mg, 120mg
Route of Administration	SC
Pharmacologic Category	Bone-Modifying Agent; RANK ligand (RANKL) inhibitor, Monoclonal Antibody. ATC: M05BX04
Indications	**120 mg** • **In adults with advanced malignancies involving bone:** Prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) • **Treatment of adults and skeletally mature adolescents with giant cell tumour of bone** that is unresectable or where surgical resection is likely to result in severe morbidity. **60 mg** • **Treatment of osteoporosis** in postmenopausal women and in men at increased risk of fractures. • **Treatment of bone loss** associated with o Hormone ablation in men with prostate cancer at an increased risk of fractures. o Long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
Dosage Regimen	**Adults** **120 mg** • **Advanced malignancies involving bone: SC:** 120 mg every 4 weeks. • **Giant Cell Tumor of Bone, Hypercalcemia of Malignancy: SC**: 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Evaluate patients at regular intervals to determine whether they continue to benefit from treatment. **60 mg** **SC**: 60 mg once every 6 months. The optimal total duration has not been established. Re-evaluation of the need for treatment should be made periodically based on the benefits and potential risks of denosumab, particularly after 5 or more years of use. **Pediatrics** • Giant cell tumour of bone: skeletally mature adolescents (aged 12-17 years): dose as adults. • Other indications: Use in pediatrics is not recommended. **N.B.** Supplementation of at least 500 mg calcium (1000 mg with Prolia) and 400 IU vitamin D daily is required in all patients to treat or prevent hypocalcemia, unless hypercalcaemia is present.
Dosage Adjustment	**Renal impairment** No dose adjustment is required in renal patients.

Denosumab

	Crcl <30 mL/min: risk for hypocalcemia. Monitor calcium level closely. **Hepatic impairment** The safety and efficacy have not been studied in hepatic patients.
Contra-indications	• Hypersensitivity to the active substance or any of the excipients. • Hypocalcemia.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (60 mg: 5%; 120 mg: 17%). **Dermatologic**: Dermatitis (60 mg: ≤11%), eczema (60 mg: ≤11%), skin rash (≤14%). **Endocrine and metabolic**: Hypocalcemia (60 mg: 2%, including severe hypocalcemia; 120 mg: 18%, severe hypocalcemia: 3%), hypophosphatemia (120 mg: 32%; severe: 15% to 21%). **Gastrointestinal**: Diarrhea (120 mg: 20% to 34%), nausea (120 mg: 31% to 32%). **Hematologic and oncologic**: Anemia (120 mg: 22%), thrombocytopenia (120 mg: 19%). **Nervous system**: Asthenia (120 mg: ≤45%), fatigue (120 mg: ≤45%), headache (60 mg: 4%; 120 mg: 11% to 13%). **Neuromuscular and skeletal**: Arthralgia (60 mg: 7% to 14%), back pain (60 mg: 5% to 12%; 120 mg: 21%), limb pain (60 mg: 10% to 12%). **Respiratory**: Cough (120 mg: 15%), dyspnea (120 mg: 21%), upper respiratory tract infection (60 mg: 3% to 5%; 120 mg: 15%). **1% to 10%** **Cardiovascular**: Angina pectoris (60 mg: 3%), hypertension (60 mg: 4%). **Endocrine and metabolic**: Hypercholesterolemia (60 mg: 7%). **Gastrointestinal**: Constipation (60 mg: 3%), dyspepsia (60 mg: 3%), flatulence (60 mg: 2%), upper abdominal pain (60 mg: 3%), vomiting (60 mg: 3%). **Genitourinary**: Urinary tract infection (60 mg: 3%). **Hematologic and oncologic**: Malignant neoplasm (60 mg: new; 3% to 5%). **Infection**: Serious infection (60 mg: 4%). **Nervous system**: Dizziness (60 mg: 2%), falling (60 mg: 2%), sciatica (60 mg: 5%). **Neuromuscular and skeletal**: Musculoskeletal pain (60 mg: 6%), myalgia (60 mg: 3%), ostealgia (60 mg: 4%), osteonecrosis of the jaw (60 mg; 120 mg: 2%), polymyalgia rheumatica (60 mg: 2%), vertebral column fracture (following discontinuation: 60 mg: 3% to 6%). **Ophthalmic**: Cataract (60 mg: 5%). **Respiratory**: Bronchitis (60 mg: 4%), nasopharyngitis (60 mg: 7%), pneumonia (120 mg: 8%).
Monitoring Parameters	• Monitor calcium levels: Before the initial dose, within two weeks after the initial dose, and if suspected symptoms of hypocalcemia occur.
Drug Interactions	***Risk D: Consider therapy modification*** Corticosteroids (Systemic), Immunosuppressants, Methotrexate.
Pregnancy and Lactation	**Pregnancy**: Limited data. Not recommended for use in pregnant women or women of childbearing potential not using contraception, and until 5 months after treatment. Effects are likely to be greater during the second and third trimesters of pregnancy.

Denosumab

	Lactation: Limited data. Denosumab was detected in the maternal milk up to 1 month after the last dose in animals. Consider the benefits and risk.
Administration	**Subcutaneous Administration** Administered into the thigh, abdomen, or upper arm. Avoid vigorous shaking. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Emetogenicity	No emetogenicity.
Warnings/ Precautions	**Biological product** The name and the batch number of the administered product should be clearly recorded. **Hypocalcemia** • Can occur at any time during therapy. severe symptomatic hypocalcaemia (including fatal cases) has been reported mostly during the first weeks of therapy. Monitoring of the calcium level is required. Correct hypocalcemia before initiation of therapy. • Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present • Patients with severe renal impairment are at higher risk of hypocalcemia. **Chronic kidney disease** • The presence of chronic kidney disease-mineral bone disorder (CKD-MBD) markedly increases the risk of hypocalcemia. • Before initiating treatment in patients with advanced chronic kidney disease, including dialysis patients, evaluate for the presence of CKD-MBD with intact parathyroid hormone, serum calcium, and vitamin D. • Monitor serum calcium weekly for the first month after Prolia administration and monthly thereafter. Adequate supplementation with calcium and vitamin D is necessary. **Osteonecrosis of the jaw (ONJ)** • ONJ has been reported with demosumab therapy. Therapy should be delayed in patients with unhealed open soft tissue lesions in the mouth. • All patients should be advised to maintain good oral hygiene, receive routine dental check-ups. Monitor for symptoms. Avoid invasive dental procedures during treatment. • If ONJ develops, temporary interruption of therapy should be considered until the condition resolves. **Atypical fractures of the femur** • Patients should be advised to report new or unusual thigh, hip, or groin pain. Interruption of therapy should be considered in patients suspected of having an atypical femur fracture, with risk-to-benefit individual assessment. **Hypercalcaemia after discontinuation** • In patients with giant cell tumour of bone and patients with growing skeletons, clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported weeks to months following treatment discontinuation. • After discontinuation, consider periodic assessment of serum calcium and re-evaluate the patient's calcium and vitamin D supplementation requirements.

Denosumab

	Hypersensitivity Hypersensitivity reactions, including anaphylaxis, may occur. Discontinue permanently if a clinically significant reaction occurs. **Multiple Vertebral Fractures (MVF)** Following treatment discontinuation, evaluate the individual patient's risk for vertebral fractures. **Bisphosphonates** Concomitant use with bisphosphonates is not recommended. **Serious infections, including skin infections** May occur, sometimes leading to hospitalization. Monitor for signs of infection, including cellulitis.
Storage and Light Sensitivity	• Store between 2°C and 8°C. Do not freeze. • If removed from the refrigerator, use it within 14-30 days if stored at room temperature (up to 25°C). • Protect from light and heat. **N.B.** Refer to the manufacturer's PIL if there are specific considerations**.**
Patient Counselling Keys	• Patients should be adequately supplemented with calcium and vitamin D to maintain serum calcium levels. • Patients should maintain good oral hygiene during treatment and inform their dentist before dental procedures that they are receiving denosumab. • Patients should report new or unusual thigh or hip pain, severe bone, joint, and/or muscle pain, or oral symptoms such as dental infections or mobility. • Patients should seek medical attention if they develop signs or symptoms of dermatological reactions (such as dermatitis, rashes, and eczema). • Patients should report symptoms of infections, including cellulitis and chronic ear infections, during treatment with denosumab.

Alphabetical List of Content

Sources

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