EGYPTIAN DRUG AUTHORITY

هيئة الدواء المصرية

The Egyptian Pharmaceutical Vigilance center

مركز اليقظة الصيدلية المصري

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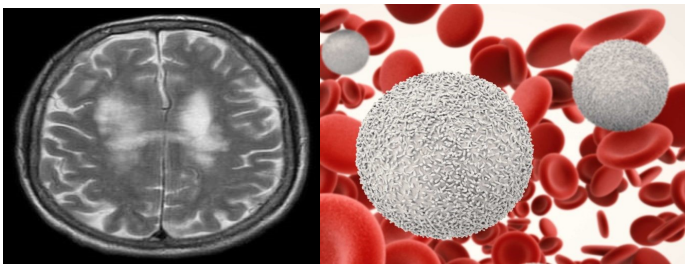
Direct Healthcare Professional Communication (DHPC): Dimethyl fumarate – Updated recommendations in the light of cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia (DILI)

EPVC has agreed with Marketing Authorization holders (MAHs) of Dimethyl Fumarate to distribute Direct Healthcare Professional Communication (DHPC) regarding important updated information to help minimise the risk of progressive multifocal leukoencephalopathy (PML). Dimethyl Fumarate is indicated for the treatment of adults with relapsing-remitting multiple sclerosis.



According to EMA, the comprehensive summary is as follows:

* Cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia (lymphocyte count ≥ 0.8 $\times 10^9$/L and below the lower limit of normal) have been reported in patients treated with Dimethyl Fumarate; previously, PML had been confirmed only in the setting of moderate to severe lymphopenia.
* Dimethyl Fumarate is contraindicated in patients with suspected or confirmed PML.
* Dimethyl Fumarate should not be initiated in patients with severe lymphopenia (lymphocyte counts < 0.5 $\times 10^9$/L).
* If the lymphocyte count is below the normal range, a thorough assessment of possible causes should be completed before initiating treatment with Dimethyl Fumarate.
* Dimethyl Fumarate should be discontinued in patients with severe lymphopenia (lymphocyte counts < 0.5 $\times 10^9$/L) persisting for more than 6 months.
* If a patient develops PML, Dimethyl Fumarate must be permanently discontinued.
* Advise patients to inform their partner or caregivers about their treatment and symptoms suggestive of PML, since they may notice symptoms of which the patient is not aware.

Background on the safety concerns:

Dimethyl Fumarate is authorised for the treatment of adults with relapsing-remitting multiple sclerosis. Dimethyl Fumarate may cause lymphopenia: in clinical trials lymphocyte counts decreased by approximately 30% of baseline value during treatment.

PML is a serious opportunistic infection caused by the John-Cunningham virus (JCV), which may be fatal or result in severe disability. Risk factors for developing PML in the presence of JCV include an altered or weakened immune system.

Among over 475,000 patients exposed to Dimethyl Fumarate, 11 cases of PML have been confirmed. The single commonality in all 11 confirmed cases is a decreased absolute lymphocyte count (ALC), which is a biologically plausible risk factor for PML. Three of these cases occurred in the setting of mild lymphopenia, while the remaining eight cases developed during moderate to severe lymphopenia.

As currently recommended, all patients should have absolute lymphocyte counts (ALC) measured before initiating treatment and every 3 months thereafter.

In patients with lymphocyte counts below the lower limit of normal as defined by local laboratory reference range, enhanced vigilance is now recommended and additional factors that may potentially contribute to an increased risk for PML in patients with lymphopenia should be considered. These include:

- duration of Dimethyl Fumarate therapy. Cases of PML have occurred after approximately 1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown;
- profound decreases in CD4+ and especially in CD8+ T cell counts;
- prior immunosuppressive or immunomodulatory therapy;

In patients with sustained moderate reductions of absolute lymphocyte counts ≥0.5 x 10_9/L and <0.8 x 10_9/L for more than six months, the benefit/risk of Dimethyl Fumarate treatment should be re-assessed. In addition,

- physicians should evaluate their patients to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML;
- at the first sign or symptom suggestive of PML, Dimethyl Fumarate should be withheld and appropriate diagnostic evaluations carried out, including determination of JCV DNA in cerebrospinal fluid (CSF) by quantitative polymerase chain reaction (PCR) methodology;
- it is important to note that patients developing PML following recent discontinuation of natalizumab may not present with lymphopenia.

The Dimethyl Fumarate Product Information is being revised to include the above information.

References:

1- EMA DHPC (Click here)
2– MHRA (Click here)

Safety Communication: Emicizumab—Known interference with lab assays used to diagnose coagulopathy / DIC caused by COVID-19 infection

The following alert is published to remind Healthcare professionals about Emicizumab and its known interaction with certain laboratory assays. Some of these assays may be relevant to some patients that are receiving Emicizumab and become infected with the novel coronavirus that causes COVID-19.The below information is in line with the
approved local Prescribing Information.
Emicizumab is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and children with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.
COVID-19 is caused by a novel coronavirus, therefore knowledge about how it may affect
people with haemophilia A is not well understood. COVID-19 patients with or without
haemophilia may develop a COVID-19 associated coagulopathy

Further Information:
Emicizumab restores the tenase cofactor activity of missing activated factor VIII (FVIIIa).
Coagulation laboratory tests based on intrinsic clotting, including the activated clotting time (ACT), activated partial thromboplastin time (e.g. aPTT), measure the total clotting time including time needed for activation of FVIII to FVIIIa by thrombin. Such intrinsic pathway based tests will yield overly shortened clotting times with emicizumab, which does not require activation by thrombin.
The overly shortened intrinsic clotting time will then disturb all single factor assays based on aPTT, such as the one stage FVIII activity assay (see section 4.4, Table 1). However, single factor assays utilizing chromogenic or immuno-based methods are not affected by emicizumab and may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays as described below.

* Chromogenic factor VIII activity tests may be manufactured with either human or bovine coagulation proteins. Assays containing human coagulation fac

factors are responsive to emicizumab but may overestimate the clinical haemostatic potential of emicizumab. In contrast, assays containing bovine coagulation factors are insensitive to emicizumab (no activity measured) and can be used to monitor endogenous or infused factor VIII activity, or to measure anti FVIII inhibitors.
Emicizumab remains active in the presence of inhibitors against factor VIII and so will produce a false negative result in clotting based Bethesda assays for functional inhibition of factor VIII.
Instead, a chromogenic Bethesda assay utilising a bovine based factor VIII chromogenic test that is insensitive to emicizumab may be used.
These two pharmacodynamic markers do not reflect the true haemostatic effect of emicizumab in vivo (aPTT is overly shortened and reported factor VIII activity may be overestimated) but provide a relative indication of the pro-coagulant effect of emicizumab.

In summary, intrinsic pathway clotting-based laboratory test results in patients treated with Emicizumab should not be used to monitor its activity, determine dosing for factor replacement or anti-coagulation, or measure factor VIII inhibitors titers. Caution should be taken if intrinsic pathway clotting based laboratory tests are used, as misinterpretation of their results may lead to under-treatment of patients experiencing bleeding episodes, which can potentially result in severe or life-threatening bleeds.

Laboratory tests affected and unaffected by emicizumab are shown in Table 1 below. Due to its long half-life, these effects on coagulation assays may persist for up to 6 months after the last dose (see section 5.2).

Results Affected by Emicizumab	Results Unaffected by Emicizumab
* Activated partial thromboplastin time (appt) * Bethesda assays (clotting-based) for FVIII inhibitor titers * One-stage, aPTT-based, single-factor Assays * aPTT-based Activated Protein C Resistance (APC-R) * Activated clotting time (ACT)	* Bethesda assays (bovine chromogenic) for FVIII inhibitor titers * Thrombin time (TT) * One-stage, prothrombin time (PT) - based, single-factor assays * Chromogenic-based single-factor assays other than FVIII1 * Immuno-based assays (i.e., ELISA, turbidimetric methods) * Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210)

References:

SFDA (Click here)
Health Canada (Click here)

Local Case Report

Case report from Alexandria-Reminder: Cyclizine–restricted use in children under 6 years of age.

The regional center in Alexandria received an ICSR concerning a male child above one- year- old (mostly 18 months) administered Cyclizine lactate 50 mg/2ml amp. by a dose 0.5 ml (25 mg) at his anterolateral thigh by IM injection in an outpatient clinic at a hospital for management of vomiting. Few minutes later the child developed bradycardia, excessive sweating and convulsions.

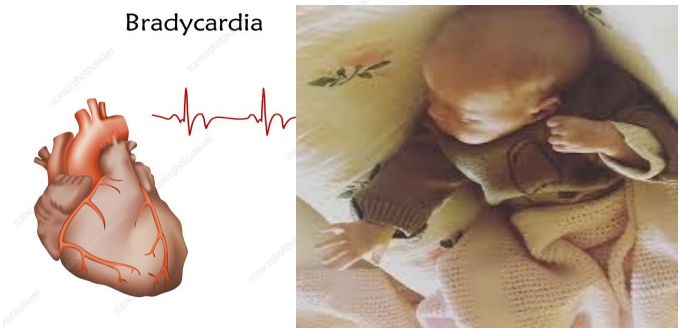
The patient was managed at the hospital, where he administered the drug.

Background :

Cyclizine is a histamine H1 receptor antagonist of the piperazine class which is characterised by a low incidence of drowsiness. It has anticholinergic and antiemetic properties. The exact mechanism by which cyclizine can inhibit or control both nausea and vomiting from various causes is unknown. Cyclizine increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus. It may inhibit the part of the midbrain known collectively as the emetic centre. [1]

Bradycardia is a heart rate quantified in the conscious state that is below the normal range for age (ie, <100 beats per minute [bpm] for infants, <80 bpm for toddlers and young children, <70 for school age children, and <60 for adolescents). [2]

Convulsion is a condition in which muscles contract and relax quickly and cause uncontrolled shaking of the body. Head injuries, high fevers, some medical disorders, and certain drugs can cause convulsions. They may also occur during seizures caused by epilepsy. [3]



The Pharmacovigilance Committee (PVC) based on the Egyptian Pharmaceutical Vigilance Center (EPVC) assessment decided on 17/04/2014 that:

"After EPVC assessment & study; PVC decides, restriction of Cyclizine use in children under six years of age and address pharmacological committee to obligate marketing authorization holders of products containing Cyclizine, to update product label so as to include restriction of use in children under six years"

Labeled information:

- According to Cyclizine Lactate 50 mg/ml Injection Summary of product Characteristics (SmPC) it was stated under section (4.2 Posology and method of administration) that: "Not licensed for use in children." and it is stated under section (4.8 Undesirable effects) that: convulsions and arrhythmias have been reported upon Cyclizine lactate administration. [1]
- According to Cyclizine Hydrochloride 50 mg tablet Summary of product Characteristics (SmPC) it was stated under section (4.2 Posology and method of administration) that: " Cyclizine Hydrochloride tablets are not recommended for children less than 6 years of age." [4]

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Recommendations for Healthcare professionals .[5]

* Cyclizine is indicated in pediatric population for nausea and vomiting associated with vestibular disorders and in palliative care.
* Cyclizine dose by mouth or by intravenous injection over 3-5 minutes: Child 6-11 years 25 mg up to 3 times daily and Child 12-17 years 50 mg up to 3 times daily, for motion sickness, take 1–2 hours before departure.
* Cyclizine dose by rectum: Child 6-11 years 25 mg up to 3 times daily and Child 12-17 years 50 mg up to 3 times daily.
* Cyclizine dose by continuous intravenous or subcutaneous infusion: Child 6-11 years 75 mg administered over 24 hours and Child 12-17 years 150 mg administered over 24 hours.

References:

1. *EMC (Click here)*
2. *Up to Date* (Click here)
3. NIH (Click here)
4. *EMC (Click here)*
5. *BNF (Click here)*

Acknowledgment for Menoufia Focal Points and hospitals affiliate to the Specialized Medical Centers

The Egyptian PharmaceuticalVigilance Center EPVC would like to acknowledge pharmacovigilance focal points in Menoufia directorate hospitals & health units; and in particular Birket Al Saba' health district team for organizing an awareness campaign targeting 224 healthcare professionals during the first week of December 2020 aiming to raise awareness of the importance of reporting adverse reactions.

In addition, EPVC extends its sincere appreciation to pharmacists working in different hospitals affiliate to the Specialized Medical Centers (SMC)- Ministry of Health- for their cooperation and their eagerness to detect and report the adverse reactions of pharmaceutical products through their great leaders at the General Administration of Pharmacist and Pharmacy reaching 1500 reports received during 2020.



Egyptian PharmaceuticalVigilance Center Training for Post-graduate Pharm–D Students

In accordance to the role of the Egyptian Pharmaceutical Vigilance Center (EPVC) in rising awareness of the importance of Pharmacovigilance and spreading the concept of reporting adverse drug reactions (ADR) of pharmaceutical products, and in alignment with the co-operation of EPVC with Faculties of Pharmacy of several Egyptian Universities to prepare pharmacists to enroll successfully in the professional field, EPVC has completed training of the third wave of Post-graduate students enrolled in the Pharma-D program at Faculty of Pharmacy Cairo University; and will continue to train successive waves till August 2021.

The training aimed to emphasize the importance of Pharmacovigilance and reporting adverse effects from drugs, biological products, vaccines and medical devices. In addition, They have been trained practically on entering cases in the National Database for case reports together with case assessments to gain experience in all fields to effectively contribute to the Pharmaceutical care system in Egypt.

What is Pharmacovigilance

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug- related problem.

What is the Egyptian Pharmaceutical Vigilance Center?

With the increasing demand for patient's safety which is becoming more stringent, . The Egyptian Pharmaceutical Vigilance Center was established to be responsible for the safety monitoring of the pharmaceutical products throughout its lifecycle and it is the regulatory authority regarding Pharmacovigilance and its applications .

EPVC monitors the safety of all types of pharmaceutical products, including human medicines, biological products, supplements, cosmetics, veterinary medicines, medical devices, Biocides and pesticides

A call for reporting

Please remember that you can report safety information of medicines to EPVC using the following communication information:

Communication information

The Egyptian Drug Authority (EDA)
Pharmaceutical Care Administration
The Egyptian Pharmaceutical Vigilance Center (EPVC)

Address: 21 Abd El Aziz AlSoud Street. El-Manial, Cairo, Egypt, PO Box: 11451
Telephone: (+2)02 25354100/ (+2)02 23684288/ (+2)02 23648046/ (+2) 02 23640368/ (+2)02 23648769
Extension: 1303
Fax: +202 – 23610497
Email: pv@edaegypt.gov.eg, pv.report@edaegypt.gov.eg
Reporting link: www.eda.mohp.gov.eg
https://sites.google.com/view/epvc-reporting/healthcare-professional-public-adverse-drug-event-reporting/reporting-other-adverse-drug-event-cases
Facebook Page: The Egyptian Pharmaceutical Vigilance Center
(https://www.facebook.com/EPVC.gov/)