Refusal Public Assessment report for Human Medicinal Products

(Diclofenac Sodium, Gabapentin, Lidocaine HCL anhydrous Topical Cream)

Overview:

Based on the review of safety & efficacy data, The Egyptian Drug Authority (EDA) refused granting the marketing authorization for the medicinal products containing the following formula:
Diclofenac sodium + Gabapentin + Lidocaine HCl anhydrous

Legal basis for application:

The application is submitted to Scientific Evaluation unit for Pharmaceutical products and Drug Development according to Ministerial decree decision 425/2015

Applied Scientific Information

- Pharmacotherapeutic group
Diclofenac sodium: non-steroidal anti-inflammatory drugs (NSAID)
Gabapentin: anticonvulsants
According to Martindale:
Gabapentin is also used in the treatment of neuropathic pain and restless legs syndrome.

- Therapeutic indication (topical use)
For the relief of osteoarthritis
For the relief of rheumatoid arthritis

- Therapeutic dose:
For Topical use only
Apply 3–4 times a day

- Warnings associated with the drug
* Do not apply the submitted product to infected skin; open wounds; or red, swollen, or peeling skin.
* Wash your hands immediately before and after using the submitted product Wash the affected area and dry completely before using the submitted product.
* Be sure that you cover your entire knee with your dose of the submitted product. Do not use more than the recommended amount.
* Do not apply sunscreens, cosmetics, insect repellants, other topical medicines, or any other substance to the treated area until it is completely dry.
* Do not put on clothes over the treated area until it is completely dry.
* Do not wrap, bandage, or apply heat to the treated area.
* Let the treated skin dry before touching it or letting it touch anyone else's skin.
* Do not shower, bathe, or wash the treated area for at least 30 minutes after you use the submitted product.
* If you miss a dose of the submitted product. skip the missed dose and go back to your regular dosing schedule. Do not use 2 doses at once.
Ask your health care provider any questions you may have about how to use the submitted product.

Scientific Assessment

1- Gabapentin:

**** Uses**
Postherpetic neuralgia: Management of postherpetic neuralgia (PHN) in adults.

Seizures, focal (partial) onset (immediate release only): As adjunctive therapy in the treatment of focal (partial) seizures with and without secondary generalization in adults and pediatric patients 3 years of age and older with epilepsy.

**** Administration (Oral):**

Immediate release: May administer without regards to meals. Administer first dose on first day at bedtime to avoid somnolence and dizziness. Dosage must be adjusted for renal function; when given 3 times daily, the maximum time between doses should not exceed 12 hours. Capsules may be opened and sprinkled on food (e.g., applesauce, orange juice, pudding) for patients unable to swallow capsules.

Extended release: Administer with evening meal. Swallow whole; do not chew, crush, or split.

**** Mechanism of Action:**

Gabapentin is structurally related to GABA. However, it does not bind to $GABA_A$ or $GABA_B$ receptors, and it does not appear to influence degradation or uptake of GABA. High affinity gabapentin binding sites have been located throughout the brain; these sites correspond to the presence of voltage-gated calcium channels specifically possessing the alpha-2-delta-1 subunit. This channel appears to be located presynaptically, and may modulate the release of excitatory neurotransmitters which participate in epileptogenesis and nociception. These effects on restless leg syndrome are unknown.

** Warnings/Precaution

Disease-related concerns:

• Myasthenia gravis: Use with caution in patients with myasthenia gravis; may exacerbate condition (Mehrizi 2012).

• Renal impairment: Use with caution in patients with renal impairment; dose adjustment required.

• Seizure disorder: The safety and efficacy of the ER formulation has not been studied in patients with epilepsy.

• Substance abuse: Use with caution in patients with a history of substance abuse, including alcohol, benzodiazepines, cannabis, cocaine, and opioids; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur (Evoy 2017; Mersfelder 2016).

Dosage form specific issues:

• Product interchangeability: IR and ER products are not interchangeable with each other or with gabapentin enacarbil due to differences in formulations, indications, and pharmacokinetics.

Other warnings/precautions:

• Tumorigenic potential: Male rat studies demonstrated an association with pancreatic adenocarcinoma (clinical implication in humans is unknown).

• Withdrawal: Antiseizure medications should not be discontinued abruptly because of the possibility of increasing seizure frequency in patients with epilepsy or other withdrawal symptoms (eg, confusion, irritability, tachycardia, diaphoresis). Therapy should be withdrawn gradually over ≥1 week to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal (Norton 2001; Tran 2005).

2- Diclofenac Topical

**** Use:**

Gel 1%:

Rx: Relief of osteoarthritis pain in joints amenable to topical therapy (eg, ankle, elbow, foot, hand, knee, wrist).

OTC: Temporary relief of arthritis pain in the hand, wrist, elbow, foot, ankle, or knee.

Gel 3%: Treatment of actinic keratosis in conjunction with sun avoidance.

Gel 1.16% (Voltaren Emulgel), 2.32% (Voltaren Emulgel Extra Strength) [Canadian products]: Relief of pain associated with acute, localized joint/muscle injuries (e.g., sports injuries, strains) in patients ≥16 years of age (1.16% gel) or ≥18 years of age (2.32% gel).

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**** Mechanism of Action:**
Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties
Other proposed mechanisms not fully elucidated (and possibly contributing to the anti-inflammatory effect to varying degrees), include inhibiting chemotaxis, altering lymphocyte activity, inhibiting neutrophil aggregation/activation, and decreasing proinflammatory cytokine levels.

** Warnings/Precaution

[US Boxed Warning]: NSAIDs cause an increased risk of serious (and potentially fatal) adverse cardiovascular thrombotic events, including MI and stroke. Risk may occur early during treatment and may increase with duration of use.
[US Boxed Warning]: NSAIDs cause an increased risk of serious gastrointestinal inflammation, ulceration, bleeding, and perforation (may be fatal); elderly patients and patients with history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. These events may occur at any time during therapy and without warning.

3- Lidocaine topical

**** Uses:**
Local anesthetic for mucous membrane of the oropharynx; lubricant for intubation; use in laser/cosmetic surgeries; pruritus, pruritic eczemas, insect bites, pain, soreness, minor burns (including sunburns), cuts, and abrasions of the skin; discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes; local management of skin wounds, including pressure ulcers, venous stasis ulcers, first- and second-degree burns, and superficial wounds and scrapes. Indications may vary by product; also refer to manufacturer's labeling.

**** Administration:**
Cream, gel, lotion: For external use only; avoid contact with eyes. Also refer to manufacturer's labeling for additional product-specific application instructions.

**** Mechanism of Action:**
Lidocaine topical prevents pain by blocking the signals at the nerve endings in the skin. It does not cause unconsciousness as general anesthetics do when used for surgery.

**** Warnings/Precaution:**
Life-threatening and fatal events in infants and young children:

Post marketing cases of seizures, cardiopulmonary arrest, and death in patients under the age of 3 years have been reported with use of lidocaine 2% viscous solution when it was not administered in strict adherence to the dosing and administration recommendations. In the setting of teething pain, lidocaine 2% viscous solution should generally not be used. For other conditions, the use of the product in patients less than 3 years should be limited to those situations where safer alternatives are not available or have been tried but failed.
To decrease the risk of serious adverse events with use of lidocaine 2% viscous solution, instruct caregivers to strictly adhere to the prescribed dose and frequency of administration and store the prescription bottle safely out of reach of children.

4- By Searching in Reference countries for the applied formula, it was found that:

1- This combination is not available in reference countries.
2- In National Drug Code Directory:
Proprietary Name**:** Diclona Gel
Active ingredients**:** diclofenac sodium + lidocaine
Strength: 0.01 g/g + 0.045 g/g
Status: unapproved drug other

5- The Applied scientific data did not include scientific data based on published literature for the safety & efficacy for Diclofenac sodium, Gabapentin, Lidocaine HCl anhydrous as fixed dose combination.

Conclusion:

Based on Scientific assessment & applied data for the submitted medicinal product:
The applicant did not submit clinical data or scientific evidence supporting the use of topical gabapentin especially the mechanism of action of gabapentin depend on High affinity gabapentin binding sites have been located throughout the brain; these sites correspond to the presence of voltage-gated calcium channels specifically possessing the alpha-2-delta-1 subunit. This channel appears to be located presynaptically, and may modulate the release of excitatory neurotransmitters which participate in epileptogenesis and nociception. In addition to that the lidocaine is used as Local anesthetic for mucous no evidence on its effect on its use on intact skin to relieve neuropathy.
The Scientific Evaluation committee adopted a negative opinion, recommending the refusal of the marketing authorization for the medicinal product as it did not show add any therapeutic value over use of topical diclofenac alone & the applicant was not able to provide scientific data on the topical effect of either gabapentin nor lidocaine in the management of neuropathic pain .
The Technical committee of drug control refused granting the marketing authorization for the medicinal products containing the following topical formula:
Diclofenac sodium + Gabapentin +Lidocaine HCl anhydrous