Refusal Public Assessment Report for Human Medicinal Products

Tadalafil Nasal Spray Solution

Overview:

Based on the review of safety & efficacy data
The Egyptian Drug Authority (EDA) refused granting the marketing authorization for the medicinal products containing **Tadalafil as Nasal Spray** dosage form.

- The application for **Tadalafil as Nasal Spray Solution dosage form** is refused, as the submitted data does not meet the requirements for marketing authorization for Tadalafil Nasal Spray which are under assessment as a potential alternative route for delivering tadalafil

Legal basis for application:

The application was submitted to the **Scientific Evaluation Unit for Pharmaceutical Products and Drug Development** in accordance to **EDA Chairman decision 450/2023 (Case 1)**.

Applied Scientific Information

- Pharmacotherapeutic group

Tadalafil**:** phosphodiesterase 5 (PDE5) inhibitor.

- Therapeutic indication

The applicant has proposed the following therapeutic indications for Tadalafil Nasal Spray:

- **Erectile Dysfunction (ED):** Indicated for the treatment of erectile dysfunction.
- **Benign Prostatic Hyperplasia (BPH):** Indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia.
- **Pulmonary Arterial Hypertension (PAH):** Indicated for the treatment of pulmonary arterial hypertension.

- Therapeutic dose:

The proposed dosing regimen for Tadalafil Nasal Spray is as follows:

- **For Erectile Dysfunction (ED):**
  - **As-needed therapy:** Initial dose of 10 mg just prior to anticipated sexual activity. May increase to 20 mg or decrease to 5 mg based on effectiveness and tolerance.
  - **Once-daily therapy:** Initial dose of 2.5 mg once daily. May increase to 5 mg once daily based on effectiveness and tolerance.
- **For Benign Prostatic Hyperplasia (BPH):**
  - 5 mg once daily.
- **For Pulmonary Arterial Hypertension (PAH):**
  - 40 mg once daily.

- Warnings associated with the drug:

The applicant provided a list of warnings for the use of submitted product, which include:

- **Pregnancy & Lactation:** Tadalafil is not indicated for use in women.
- **Pediatric Use:** Safety and efficacy not established for patients under 18 years of age.
- **Geriatric use:** Safety and efficacy for patients more than 65 years of age is similar to that in younger patients
- **Hepatic & Renal Impairment:** Specific dose adjustments are recommended for patients with mild to moderate hepatic or renal impairment.

Scientific Assessment:

* The applicant provided data about safety and efficacy of Tadalafil Nasal Spray based on published literature.

- Based on the review of available applied data for the submitted product, the following has been found:

- The applicant did not submit clinical trials to establish the safety and efficacy of Tadalafil as Nasal Spray for the proposed indications, including ED, BPH, and PAH.
- There is no published scientific literature supporting the use of Tadalafil as a nasal spray formulation. Although Tadalafil has established efficacy in oral formulations, no comparable data exists for the nasal spray form. Some of the preclinical studies provided were conducted on animals, and the results were not conclusive regarding the applicability of the nasal spray formulation in humans.
- No pharmacokinetic studies or data on the bioavailability, absorption rates, or systemic exposure for the nasal spray formulation were provided.
- No data were provided on the safety and tolerability of the Tadalafil Nasal Spray formulation, particularly in human trials.

* The Scientific rational applied by the company was as follows:

The applicant proposed that a nasal spray formulation of Tadalafil could offer benefits such as faster absorption, rapid onset of action, reduced side effects, and increased convenience, particularly for patients with difficulty in swallowing oral tablets or experiencing digestive issues.

*By Searching in Reference countries approved by Technical committee of drug control it was found that:

The International regulatory status in the reference countries & scientific reference at the time of submission is as the following:

- **Nasal Spray Formulation:** No references available in any scientific references or reference countries support the use of Tadalafil in a nasal spray formulation at the time of submission.

  - So, there is no reliable data about safety and efficacy for the applied medicinal product.

- **Oral Formulations:** Tadalafil is currently available in different global regulatory authorities as oral tablet forms (2.5 mg, 5 mg, 10 mg, 20 mg) , oral Suspension form (2mg/ml, 20mg/5ml) , Or dispersible tablet form (5mg, 10mg, 20mg) .

***Indication & Dose in different international regulatory authorities:**

1- Benign prostatic hyperplasia:
Oral: 5mg once daily.

2- Erectile dysfunction
As-needed dosing: Tadalafil: Oral: Initial: 10 mg as a single dose ≥30 minutes prior to anticipated sexual activity; do not take more than once daily. Erectile function may be improved for up to 36 hours following a single dose. Adjust dose based on effectiveness and tolerability; may decrease to 5 mg or increase to 20 mg per dose.
Once-daily dosing: Tadalafil: Oral: Initial: 2.5 mg once daily without regard to timing of sexual activity; may increase to 5 mg once daily based on effectiveness and tolerability.

3- Pulmonary arterial hypertension:
Oral: Initial: 40 mg once daily; may also start with 20 mg once daily and increase to 40 mg after 4 weeks

Conclusion:

Based on Scientific assessment of the applied medicinal product and submitted data by the applicant.

- **Insufficient Evidence:** The applicant failed to provide adequate scientific evidence to support the safety, efficacy, and pharmacokinetic profile of Tadalafil as Nasal Spray formulation.
- **Lack of Clinical Data:** No clinical trials or human studies were submitted to demonstrate the safety and efficacy of the nasal spray formulation.
- **Limited Animal Studies:** Some of the studies provided were conducted only in animals, with limited relevance to human use.
- **Absence of Published Literature:** No published scientific literature or references from other regulatory authorities support the use of Tadalafil in a nasal spray dosage form.

- **More research & studies are needed:** to evaluate the safety, efficacy, Pharmacokinetics & pharmacodynamics of a new tadalafil nasal spray formulation especially since the route of administration differs significantly from the traditional oral route of administration.

Scientific Evaluation Committee has adopted a **negative opinion**, recommending refusal of marketing authorization for the medicinal product **Tadalafil Nasal Spray Solution**.

Technical Committee of Drug Control: refused granting the marketing authorization for the medicinal products containing **Tadalafil as nasal spray formulation**

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