Refusal Public Assessment Report for Human Medicinal Products

Pramipexole (as Dihydrochloride monohydrate) + Rasagiline (as Mesylate)

Overview:

Based on the review of safety & efficacy data
The Egyptian Drug Authority (EDA) refused granting the marketing authorization for the medicinal products containing **Pramipexole (as Dihydrochloride monohydrate) & Rasagiline (as Mesylate)**

- The application for **Pramipexole (as Dihydrochloride monohydrate) + Rasagiline (as Mesylate)** is refused, as the submitted data does not meet the requirements for marketing authorization for submitted product as Fixed Dose Combination.

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

Anti-Parkinson's disease

- Therapeutic indication

The applicant has proposed the following therapeutic indications for Pramipexole (as Dihydrochloride monohydrate) + Rasagiline (as Mesylate) Hard Gelatin Capsule:

- **For Pramipexole**: This drug is indicated for the symptomatic treatment of Parkinson's disease. It is also indicated for symptomatic treatment of moderate to severe primary Restless Legs Syndrome.
- **For Rasagiline:** For the treatment of the signs and symptoms of idiopathic Parkinson's disease

- Therapeutic dose:

The proposed dosage regimen is **once daily**.

- Warnings associated with the drug:

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

Pramipexole:

- Contraindicated in patients with a known allergy to pramipexole.
- Tell your doctor if you have ever had:
  - low blood pressure; dizziness after getting up too fast.
  - daytime drowsiness.
  - kidney disease; or problems controlling your muscle movements.

Rasagiline:

- Contraindicated for use with monoamine oxidase inhibitors (MAOIs) in the past 14 days.
- A dangerous drug interaction could occur. MAO inhibitors include isocarboxazid, linezolid, methylene blue injection, phenelzine, selegiline, tranylcypromine, and others

Scientific Assessment:

*The applicant provided data about safety and efficacy of Pramipexole + Rasagiline 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 data or scientific evidence supporting the use of pramipexole and rasagiline as fixed dose combination for applied therapeutic purpose.
- The applicant failed to submit data about Pharmacodynamics and pharmacokinetics of the two ingredients in fixed dose combination.
- The applicant did not submit any scientific data to ensure an additive or synergistic effect for this fixed dose combination.
- The applicant did not submit any scientific data to identify any new or enhanced adverse effects caused by the combination.

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

- **Synergistic effects:**

Combining pramipexole and rasagiline can lead to a synergistic effect, potentially improving the overall efficacy of treatment for Parkinson's disease.

- **Reduced side effects**:

By using a combination therapy, the dosage of each individual drug can be reduced, potentially minimizing side effects commonly associated with higher dosages of these medications.

- **Improved symptom control:**

The combination of pramipexole and rasagiline may provide better symptom control than either drug used alone, potentially leading to improved quality of life for patients with Parkinson's disease.

- **Long-term benefits:**

Research suggests that combining pramipexole and rasagiline may have long-term benefits for patients in terms of symptom management and disease progression.

- **Convenience:**

Taking a single pill that combines pramipexole and rasagiline may be more convenient for patients than managing multiple medications separately.

***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:

- The **fixed-dose combination** of **Pramipexole** and **Rasagiline** is **not available in any reference country.**

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

- **Each active Ingredient available as:**

- Pramipexole dihydrochloride:

Oral extended release

0.26mg,0.375mg, 0.52mg,0.75mg,1.05mg, 1.5mg ,1.57mg, 2.1mg,2.25mg, 2.62mg, 3mg, 3.15mg ,3.75mg , 4.5mg in:
FDA, emc, Compendium, TGA, MHRA, Canada, Ireland, Italy, Germany, Spain, Denmark, Finland, Iceland, Newzeland, Norway & Portugal.

According to FDA:

*** Indication:**

- Pramipexole is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease

*** Dose:** The dose is administered orally once daily.

- Rasagiline mesylate:

Oral tablet: 0.5mg & 1mg in FDA, Emc, Japan, France, Spain , Denmark, Finland, Iceland, Netherland, Norway & Portugal

According to FDA:

*** Indication:** Rasagiline is indicated for the treatment of Parkinson's disease (PD).

*** Dose:**

- Monotherapy: Rasagiline 1 mg once daily
- As adjunct without levodopa: Rasagiline 1 mg once daily
- As adjunct to levodopa: Rasagiline 0.5 mg once daily. Increase dose to 1 mg daily as needed for sufficient clinical response.
- Patients taking ciprofloxacin or other CYP1A2 inhibitors: Rasagiline 0.5 mg once daily
- Patients with mild hepatic impairment: Rasagiline 0.5 mg once daily. Rasagiline should not be used in patients with moderate or severe hepatic impairment.

Conclusion:

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

- **Lack of Clinical Evidence:**
  The applicant has failed to provide sufficient clinical data demonstrating the safety, efficacy, potential increase in adverse effects compared to monotherapy and pharmacokinetic compatibility of the fixed-dose combination of **Pramipexole** and **Rasagiline**.
- **Combination Still Under Investigation:**
  The combination is still under clinical trials, with no conclusive evidence supporting its use in routine clinical practice for Parkinson's disease.

- **Unknown Pharmacokinetics and Pharmacodynamics:**
  The combined pharmacokinetics and pharmacodynamics of this formulation remain undefined, posing potential risks for patients and complicating its clinical application.
- **Need for Additional Research:**
  Additional clinical studies are needed to evaluate the long-term **safety**, **efficacy**, and optimal dosing of the **Pramipexole + Rasagiline** combination.
- **Potential Adverse Effects:**
  Combining these two agents may exacerbate **nausea**, **dizziness**, **orthostatic hypotension**, and other side effects commonly seen with dopaminergic therapies.

Scientific Evaluation Committee has adopted a **negative opinion**, recommending refusal of marketing authorization for the medicinal product **Pramipexole (as Dihydrochloride monohydrate) + Rasagiline (as Mesylate)**

Technical Committee of Drug Control: refused granting the marketing authorization for the medicinal products containing **Pramipexole (as Dihydrochloride monohydrate) + Rasagiline (as Mesylate)**

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