LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nezebi
(oxymetazoline hydrochloride)

Asp no: 2021-1328

This module reflects the scientific discussion for the approval of Nezebi. The procedure was finalised on 2022-12-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Nezebi, 0.25 mg/ml, nasal spray, solution.

The active substance is oxymetazoline hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension, new strength, of the previously authorised product Nezebi, 0.5 mg/ml, nasal spray, solution, marketed by Perrigo Sverige AB since 2020.

The application for Nezebi 0.25 mg/ml, nasal spray, solution, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, Perrigo Sverige AB, applies for a marketing authorisation in Sweden through a National Procedure.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology

Oxymetazoline hydrochloride belongs to a group of non-selective, direct-acting adrenergic agonists. It is a sympathomimetic amine exerting its decongestant action by directly stimulating α-adrenergic receptors of the sympathetic branch of the autonomic nervous system. The clinical use of oxymetazoline is well-established since several decades. Some examples of non-clinical pharmacology studies have characterised the α2 adrenoceptor-mediated responses using pig nasal mucosa strips incubated with α adrenoceptor agonists and antagonist. One of the agonists used in this experiment was oxymetazoline, for which the contractile responses of pig nasal mucosa was shown to appear beginning from the 0.1μM concentration. The contractile response of the mucosa to oxymetazoline was dose-dependent and comparable with UK14304 and PGE-6201204 agents (α2 adrenoceptor selective agonists). Dose-dependent contractile responses to oxymetazoline have also been shown using guinea pig nasal septum mucosa. The relief of nasal congestion by 0.1% nasally administered oxymetazoline was shown in ferrets infected with influenza virus.

Bende et al. investigated the effect of oxymetazoline nose drops on acute sinusitis in the rabbit. On the oxymetazoline-treated side, authors found a significantly higher degree of inflammation and concluded that oxymetazoline nasal drops may interfere with the normal defence mechanisms during bacterially induced sinusitis, possibly by a decrease in mucosal blood flow.

One possible safety pharmacology aspect from systemic exposure of oxymetazoline concerns its possible influence on blood pressure and heart rate. The study on pig nasal mucosa strips investigated also blood pressure effects in cat nasal congestion model, apart from oxymetazoline decongestant effects described earlier. This study clearly documented that oxymetazoline is able to increase the systolic blood pressure after the topical application, however this effect was observed only when the highest dose of oxymetazoline was used (0.3% solution concentration). The hypertensive oxymetazoline effect was also observed in the anaesthetized rabbit, where it increased the systolic (by 40–61%) and diastolic (by 52–80%) blood pressure and decreased the heart rate (by 10–24%). Similar findings were revealed in dogs, however oxymetazoline doses with significant influences on the blood pressure and heart rate were very high compared to usual clinical oxymetazoline doses (above 1.65mg per 5 minutes of inhalation per dog).

Pharmacokinetics

The applicant has found no information on absorption and distribution in the scientific literature currently available on-line. One study describes the in vitro metabolism of oxymetazoline in human, rat, and rabbit liver post-mitochondrial supernatant fraction from homogenized tissue (S9) fractions and their microsomes supplemented with NADPH. The metabolites of oxymetazoline are the following: M1 (monohydroxylation of the t-butyl group), M2 (oxidative dehydrogenation of the imidazoline to an imidazole moiety), M3 (monohydroxylation of M2), M4 (dihydroxylation of oxymetazoline), and M5 (dihydroxylation of M2). Glutathione conjugates of oxymetazoline (M6) and M2 (M7) were identified in the liver S9 fractions, indicating the capability of oxymetazoline to undergo bioactivation to reactive intermediate species. M6 and M7 were not detected in those liver S9 incubations without NADPH. Cysteine conjugates (M8 and M9) derived from glutathione conjugates and hydroxylated glutathione conjugates (M10 and M11) were also identified. Studies in rabbits indicate that excreted amounts of unmetabolized radioactive oxymetazoline in urine following drug administration were similar (23%) for the ocular and nasal routes of application.

Toxicology
No new experimental toxicological studies have been conducted.

Repeat-dose toxicity
Nasal toxicity – The have been preliminary reports that rat exposure to 2 drops a 0.5mg/mL in each nostril 5d per week for ~one month generated irritation of the nasal mucosa. In a similar study setup, chronic application of oxymetazoline for 2 months (50µl of 0.025% oxymetazoline to each nostril three times a day) induced rhinitis medicamentosa (rebound congestion) in adult Wistar rats. It has been speculated that this is a result from test substance-induced vasoconstriction in capillary vessels which may lead to a decrease in the blood supply, which triggers autophagy and inflammation. No information on possible systemic uptake (i.e., toxicokinetics) has been provided.

Genotoxicity and carcinogenicity
No studies describing genotoxicity or carcinogenicity assessment have been identified or provided by the applicant. The applicant argues that based on the long-lasting clinical experience with the active substance, it is unlikely that oxymetazoline is genotoxic or carcinogenic. As this concerns an extension of a previously approved product with long clinical experience, this is considered acceptable.

DART
The applicant has not provided any relevant animal data concerning oxymetazoline influence on fertility. This is acceptable considering the long clinical experience. Some changes in SmPC 4.6. have been proposed that provide more standardization of the text. These are acceptable.

Local tolerance
In one study, intra-nasal exposure of oxymetazoline in rabbits for more than 2 weeks caused histologic changes including ciliary loss, epithelial ulceration, inflammatory cell infiltration and subepithelial oedema, and the changes were more pronounced with increasing exposure duration. Ciliary loss was prominent in the 4-week oxymetazoline group. Dilatation or vacuolization of mitochondria and endoplasmic reticula and vesicles in the cytoplasm were observed in the 2- and 4-week oxymetazoline groups. This indicate that extended exposure may cause ciliary loss with subsequent inflammatory changes in the nasal respiratory mucosa. It can be noted that the proposed treatment period is less than 2-4w.

Impurities
The impurities detected are in line with limit recommendations.

Environmental Risk Assessment (ERA)
A Phase I PECsw calculation using a maximum daily dose of 0.075 mg and a Fpen of 0.01, a standard calculation of PECsw gives 0.000375µg/L which is below the Phase IIA trigger value of 0.01ug/L. A non-OECD technical guideline chromatography study gave a log Kow of 3.92, nominally below the PBT-assessment trigger value of log Kow 4.5. This is sufficient in the present extension of a previously approved market authorization application (but a pivotal experimental log Kow study may be needed in future authorization applications).

Conclusion
There are no non-clinical issues.

IV. CLINICAL ASPECTS

Pharmacokinetics
No pharmacokinetic studies have been submitted. For locally applied products, bioequivalence generally is not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a role with regard to safety.

The pharmacokinetic properties of oxymetazoline, with an observed very limited systemic absorption, limits the importance of pharmacokinetics in the benefit/risk assessment.

The documentation provided by the applicant nevertheless describe the available information regarding PK in an adequate way.

Pharmacodynamics/Clinical efficacy /Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nezebi.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 3 November 2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Nezeril, 5.4.3-2018-45832. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Nezebi 0.25 mg/ml, nasal spray, solution is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Nezebi, 0.25 mg/ml, nasal spray, solution was approved in the national procedure on 2022-12-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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