LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nezebi
(oxymetazoline hydrochloride)

SE/H/2193/01/MR

This module reflects the scientific discussion for the approval of Nezebi. The procedure was finalised on 2020-03-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Perrigo Sverige AB has applied for a marketing authorisation for Nezebi, 0.5 mg/ml, nasal spray, solution. The active substance is oxymetazoline hydrochloride (decongestant; intranasal administration results in localized constriction of dilated arterioles and reduction in blood flow and congestion).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

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, Pharmacokinetics and Toxicology

As oxymetazoline is a widely used, well-known active substance, no further studies are required and the applicant provides none. Pharmacodynamic, pharmacokinetic and toxicological properties of oxymetazoline are well known. Overview based on literature review is, thus, appropriate. The non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)

An ERA was submitted concluding that a Phase II assessment is not required and that oxymetazoline is not a PBT substance. The use of Nezebi, nasal spray, solution, 0.5 mg/ml, as indicated, is not considered to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The common cold is a benign self-limited syndrome representing a group of diseases caused by members of several families of viruses. Symptoms may substantially vary from patient to patient; rhinitis and nasal congestion are however the most common. Most patients with mild symptoms do not require any symptomatic therapies. However, there is a variety of therapeutic approaches to nasal congestion of which the use of topical (nasal) decongestants, either alone or in combination with other medicines represents the one of the therapy mainstays

IV.2 Pharmacokinetics

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

IV.3 Pharmacodynamics

Oxymetazoline´s mechanism of action as a direct acting adrenergic agonist is considered well-characterized and accepted. Posology recommendations for oxymetazoline containing medicinal products, including Nezebi, are well-established and the presented literature supports a pharmacological rationale for these posologies. Systemic off-target effects are likely small due to the limited systemic exposure following recommended posology.

IV.4 Clinical efficacy

Overall the short-term use, <10 consecutive days of oxymetazoline in the claimed indications is widespread and the large clinical post-marketing experience strengthens the old, and perhaps outdated efficacy studies presented by the applicant. The proposed posology for Nezebi is in agreement with other similar oxymetazoline nasal sprays currently on the market, assuring that the large clinical experience is also relevant for Nezebi. The applicant

has also provided efficacy studies outside claimed indications. These studies are evaluated for safety purposes only.

IV.5 Clinical safety

Overall, the applicant has presented data for adverse events from several sources, old clinical studies, PSUR and literature reviews. The adverse event profile for oxymetazoline is considered well-characterised and is mainly related to local symptoms such as dry nose, nasal congestion (rebound, concerning chronic use), nasal irritation and sneezing. This is the expected scenario for a locally acting product. The safety data presented by the applicant indicate that the Nezebi nasal spray demonstrates an acceptable safety profile, as the frequency of adverse events is low and they are transient in nature as well as the risk of intoxication after administration of recommended doses is low. Possibly dangerous adverse effects may occur mostly after overdose or prolonged use. The applicant proposes to limit the short-term use of Nezebi to a maximum of 10 consecutive days. The risk for rhinitis medicamentosa after prolonged use is also adequately communicated in the SmPC. Conclusions drawn by the applicant is endorsed and in line with other approved oxymetazoline nasal sprays.

Some concern was raised whether the small systemic exposure following therapeutic use of Nezebi could have clinical consequences in a patient treated with a mono-amino oxidase inhibitor (MAOI) or an ergot derivative and the applicant was asked to clarify. The applicant concludes that pharmacodynamic interactions with MAOI and ergot derivatives are mainly a concern in case of overdose, although this risk cannot be entirely excluded at therapeutic dosing. However, not enough evidence in this regard has currently been presented to warrant inclusion of a warning in the SmPC. This is endorsed. It is also noted that other oxymetazoline containing medicinal products approved in Sweden are devoid of information regarding this risk.

IV.6 Risk Management Plans

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
No safety concerns are listed by the applicant. There are also no pharmacovigilance or additional risk minimisation activities proposed. This is considered acceptable for a well-known and extensively used medicinal product.
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 1.0 signed 20 March 2019 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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Oxymetazoline´s mechanism of action as a direct acting adrenergic agonist is considered well-characterized and accepted. Overall the short-term use, <10 consecutive days of oxymetazoline in the claimed indications is widespread and the large clinical post-marketing experience strengthens the old, and perhaps outdated efficacy studies presented by the applicant. The adverse event profile for nasally administered oxymetazoline is considered well known and is mainly related to local symptoms such as dry nose, nasal congestion (rebound, concerning chronic use), nasal irritation and sneezing.
The benefit/risk balance for Nezebi is considered positive.

Nezebi is considered approvable given that the applicant performs a number of commitments to be reported back to the MPA within the below predefined timeframe, as agreed by the applicant.

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

Description	Due date
A risk evaluation of nitrosamines being present in the product shall be performed as outlined in “Information on nitrosamines for marketing authorisation holders” (EMA/189634/2019) and “Questions and answers on “Information on nitrosamines for marketing authorisation holders” (EMA/CHMP/428592/2019 Rev. 2).	2020-10-01

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

N/A

VII. APPROVAL

Nezebi, 0.5 mg/ml, nasal spray, solution, was approved in the national procedure on 2020-03-03.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2193/01/MR	Initial Mutual Recognition Procedure	Yes	2022-02-23	Approval	N/A

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

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