LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Xylometazolin Evolan utan konserveringsmedel (xylometazoline hydrochloride)

Asp no: 2024-0368, 2024-0369

This module reflects the scientific discussion for the approval of Xylometazolin Evolan utan konserveringsmedel. The procedure was finalised on 2025-07-28. 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 Xylometazolin Evolan utan konserveringsmedel, 0,5 mg/ml, 1 mg/ml, Nasal spray, solution.

The active substance is xylometazoline 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 for Xylometazolin Evolan utan konserveringsmedel, 0,5 mg/ml, 1 mg/ml, Nasal spray, solution, are Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Otrivin utan konserveringsmedel, 0,5 mg/ml, nässpray, lösning authorised in Sweden since 1996 with Haleon Denmark A/S as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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/Toxicology
The pharmacodynamic, pharmacokinetic and toxicological properties of xylometazoline hydrochloride (xylometazoline for short) are well known. As this active substance is well-known and widely used, and the procedure is an Art 10(3) procedure, no further studies are required, nor does the applicant provide any. A non-clinical overview based on literature review is, thus, appropriate. A short overview of the non-clinical properties – with the toxicological focus being on genotoxicity, carcinogenicity, and DART - is provided below. There are some qualitative and quantitative differences regarding the excipients between the applied-for product and the reference product but these differences are not considered to require particular non-clinical considerations. It can be noted that the Non-clinical overview(s) also covers preservatives but as the applied-for product does not contain any preservatives, this is not included in the overview below. Pharmaceutical impurities are assessed in the Quality assessment.

Pharmacology
Xylometazoline is a sympathomimetic amine which is structurally and pharmacologically related to other imidazoline derivatives (oxymetazoline, tetrahydrozoline, tramazoline). Xylometazoline has agonistic affinity for several alpha-adrenergic receptors and the pharmacological effects are likely mediated via alpha1- and alpha2-receptors in the human nasal mucosa. Intranasal administration of xylometazoline constricts dilated blood vessels in the nasal mucosa, reducing blood flow to engorged, oedematous tissue.

Pharmacokinetics
No non-clinical information was provided on the absorption via nasal exposure. A rat study with intra-narial administration of ^{14}C-xylometazoline found that the majority of radioactivity remained in and around the site of application. If rats are exposed orally, radioactivity can be found in gastrointestinal contents, liver, and kidney. After intravenous (IV) exposure, radioactivity can be found in kidney, adrenal, thyroid, pancreas, liver, lung, salivary glands, and hypophysis. The non-clinical metabolism profile of xylometazoline after nasal exposure is unclear. Regarding elimination, in IV-exposed dogs, unchanged xylometazoline is excreted rapidly mostly via urine with a half-life of 1.85 hours. In rats about 80% is excreted by the kidneys, 5% with the faeces and further 5% were excreted in bile within the first day after administration.

Toxicology
No genotoxicity information has been provided for xylometazoline but a chemically similar imidazoline derivative, oxymetazoline, is known to be negative in an Ames test. There is also no carcinogenicity information for xylometazoline but another similar imidazoline derivative, tramazoline, is known to have been negative in a two-year rat carcinogenicity study. Considering the long clinical experience, together with the information from chemically similar imidazoline derivatives, a genotoxic or carcinogenic risk is unlikely. No scientific DART-references have been provided for xylometazoline, but the applicant refers to the conclusions of a German BfArm monography for xylometazoline from 1994 (for nasal and ocular application) that concludes that there is no evidence for teratogenic effects in mice or rats. This is not evidential support as such, but the information in the proposed SmPC 4.6 (warning that vasoconstrictive pharmacological effects may be a concern) and SmPC 5.3 texts (no teratogenic effects in rodents) are in line with on the SmPC of the reference product and acceptable.

Environmental Risk Assessment (ERA)
The applicant has chosen to provide a Phase I assessment and invoke the 2024 CHMP ERA GL (instead of arguing with the help of historical consumption data, under the 2006 CHMP ERA GL framework, that the overall environmental exposure has not increased). A phase I PECsw is set at 1.5 x 10^{-3} ug/L for xylometazoline (0.10% [1 mg/mL] nasal spray formulation), using a maximum dose of

0.21 mg/d (0.10%; corresponding to 6 sprays per day) and a default Fpen of 0.01. As the PECsw is <0.01 ug/L, a Phase IIA assessment is not triggered. The present ERA is incomplete with regard to log Kow and no conclusion about ERA status can presently be made. A commitment exists for providing the missing experimental Log Kow study (and an updated ERA) within one year after end of procedure.

Overall conclusions
There are no non-clinical objections to approval of the Xylometazolin Evolan utan konserveringsmedel product from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No pharmacokinetic studies have been conducted. Xylometazoline is a locally acting locally applied drug with very low systemic availability. Bioequivalence studies are therefore not relevant to assess therapeutic equivalence with the originator. The assessment of equivalence will therefore rely on quality data.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Xylometazolin Evolan utan konserveringsmedel.

Part II Safety specification
Table SVIII.1: Summary of safety concerns

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

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 2.1 signed 29-Apr-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 RMS;
- 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 information leaflet (PL) *content* has been performed on the basis of a bridging report making reference to Teppix* 1 mg/ml, nasal spray, solution (MA no 42803; Asp. No: 2009-0767) with Dnr: 111:2009/39654.

For the *layout* of the Xylometazolin Evolan utan konserveringsmedel package leaflets, reference is made to the tested and approved package leaflets for Paracetamol Punkt & Evolan 24 mg/ml, oral solution, Asp nr 2024-0331 & 2024-0332, MTnr 66169 & 66170, which are aligned with the Evolan Company design.

The bridging is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Xylometazolin Evolan utan konserveringsmedel is found adequate. There are no objections to approval of Xylometazolin Evolan utan konserveringsmedel from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore 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

Xylometazolin Evolan utan konserveringsmedel, 0,5 mg/ml, 1 mg/ml, Nasal spray, solution was approved in the national procedure on 2025-07-28.

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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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