swissmedic

Date: 7 December 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Roclanda

International non-proprietary name: latanoprost, netarsudil as netarsudil dimesilate

Pharmaceutical form: eye drops, solution

Dosage strength(s): 0.05 mg latanoprost, 0.2 mg netarsudil

Route(s) of administration: ocular

Marketing authorisation holder: Santen SA

Marketing authorisation no.: 69043

Decision and decision date: approved on 3 October 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IOP	Intraocular pressure
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for netarsudil in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Roclanda is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.

2.2.2 Approved indication

Roclanda is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin provides insufficient IOP reduction.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. Patients should not exceed the dose of 1 drop in the affected eye(s) each day.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	22 July 2022
Formal control completed	16 August 2022
List of Questions (LoQ)	14 December 2022
Response to LoQ	9 March 2023
Preliminary decision	8 June 2023
Response to preliminary decision	12 July 2023
Final decision	3 October 2023
Decision	approval

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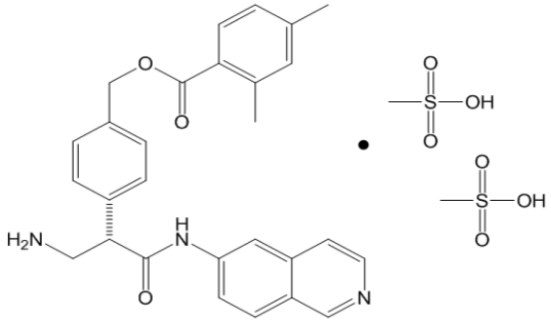
3 Quality aspects

3.1 Drug substance

Drug substance netarsudil dimesylate

INN:	Netarsudil
Chemical name:	Free base: Benzoic acid, 2,4-dimethyl-, [4-[(1S)-1-(aminomethyl)-2-(6-isoquinolinylamino)-2-oxyethyl] phenyl] methyl ester, methansulfonate (1:2)
	Dimesylate salt: (S)-4-(3-amino-1-(isoquinolin-6-yl-amino)-1-oxopropan-2-yl) benzyl 2,4-dimethylbanzoate dimesylate
Molecular formula:	Free base: $C_{28}H_{27}N_3O_3$
	Dimesylate salt: $C_{30}H_{35}N_3O_9S_2$
Molecular mass:	Free base: 453.53 g/mol
	Dimesylate salt: 645.74 g/mol

Molecular structure:



Physico-chemical properties

Netarsudil mesylate is a dimesylate salt and is a light yellow to white powder. The compound is a chiral molecule. The chirality arises in the alpha carbon of the beta amino acid moiety of the amide. The compound is freely soluble in water and is moderately hygroscopic. Polymorphism is not a relevant aspect for this compound.

Synthesis

The synthesis of netarsudil dimesylate consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials critical steps, and intermediates.

Specification

The drug substance specification includes tests for description, identification, assay, related substances, chiral impurity, methanesulfonic acid, methanesulfonates, residual solvents, water content, elemental impurities, and microbiological test. The applied limits are justified and in line with the relevant guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability

The stability of the drug substance was investigated with commercial scale batches which were manufactured by the proposed commercial manufacturing site. The stability samples were stored under long-term conditions (-20°C ±5°C) and accelerated conditions (5°C ±3°C) as defined in the corresponding ICH Guideline on stability studies. Based on these studies, an adequate retest period was defined.

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3.2 Drug product

Description and composition

Netarsudil 0.2 mg/mL-latanoprost 0.05 mg/mL eye drops containing the new active substance netarsudil mesylate, is a clear, sterile, preserved, isotonic solution at approximately pH 5, filled in 4 mL multidose containers (filling volume: 2.5 mL) with a white dropper tip and white screw cap.

Pharmaceutical development

Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process in accordance with the relevant ICH guidelines.

Manufacture

The manufacturing process of the drug product is a simple and conventional process in which all ingredients are added stepwise and dissolved in water, filtered through a bacteria-retentive filter, and filled aseptically into the primary packaging.

Control of the manufacturing process is ensured through defined operating parameters based on the results of the development studies. In addition, in-process controls with adequate acceptance criteria are established.

Specification

The drug product specifications include tests for description; pH; osmolarity; identification of netarsudil, latanoprost, and benzalkonium chloride; assay of netarsudil, latanoprost, and benzalkonium chloride; degradation products of netarsudil and latanoprost; chiral impurity of netarsudil; and sterility. The proposed acceptance criteria and analytical methods were considered appropriate for quality control of the drug product.

Container closure system

The container closure system consists of a natural 4 mL low-density polyethylene (LDPE) bottle, linear low-density polyethylene (LLDPE) dropper tip, and white polypropylene (PP) screw cap. A tamper-evident seal is shrink-wrapped over the cap and the neck of the bottle.

Stability

Appropriate stability data from commercial scale batches of Roclanda are provided. The stability study was carried out according to ICH stability guidelines. Based on the results of this study, an adequate shelf life and adequate storage conditions were established. Degradation impurities are formed after exposure to light; the drug product should be kept protected from light in the outer carton.

3.3 Quality conclusions

Satisfactory and consistent quality of the drug substances and drug product has been demonstrated.

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4 Nonclinical aspects

For the review of the marketing authorisation application for Roclanda, the Nonclinical Assessment Division conducted an abridged evaluation, which was essentially based on the CHMP assessment report of the EMA dated 12 November 2020 (EMA/CHMP/593844/2020) and provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Roclanda in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. For netarsudil, safety margins regarding systemic toxicity are sufficient considering the negligible systemic exposure in patients. For the ocular route and ocular effects, the margins are substantially lower and consisted mainly of the fact that the animals were dosed twice daily and humans are dosed once daily. Similar ocular adverse reactions were observed in both rabbits and monkeys as well as humans. For latanoprost, no information on toxicokinetics was provided; however, the clinical experience of latanoprost outweighs the lack of data. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

5 Clinical aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and corresponding product information from these authorities were used as a basis for the clinical evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy, and safety, see section 7 (Appendix) of this report.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Roclanda was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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