LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Propranolol EQL
(propranolol hydrochloride)

This module reflects the scientific discussion for the approval of Propranolol EQL. The procedure was finalised at 2026-04-01. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Propranolol EQL, 10 mg, 40 mg, Film-coated tablet.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Propranolol is a blocker of the $beta_1$- and $beta_2$-adrenoceptors. Propranolol has a weak membrane stabilising effect. Propranolol is free of beta receptor stimulation properties. Beta-blockers have negative inotropic and chronotropic effects.
Propranolol is racemic and the active form is the S (-) enantiomer. Propranolol inhibits the effects of catecholamines in connection with psychological and physical strain and lowers the heart rate, cardiac output and blood pressure. Propranolol may slightly lower the increased T_3-values in hyperthyroidism. T_4 is not affected.
Propranolol lowers the pressure in the portal vein and reduces the portosystemic collateral flow in patients with liver cirrhosis.

Pharmacotherapeutic group: Beta blocking agents, non-selective (beta blocker), ATC code: C07AA05

II.2 General comments on the submitted dossier

The application for Propranolol EQL, 10 mg, 40 mg, film-coated tablet, is a Generic Art. 10(1) 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 Inderal, 10 mg, film-coated tablet, authorised in PT since 1967, with AstraZeneca Pharmaceuticals as marketing authorisation holder.

The reference product used in the bioequivalence study is Inderal, film-coated tablet, 40 mg, from PT with AstraZeneca Pharmaceuticals as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The MPA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the European Community, the MPA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the European Community, the MPA has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that

acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted study has been provided. Based on review of the submitted inspection reports for inspections performed at both Axis Clinical Limited and Aizant Drug Research Solutions Pvt Ltd in relation to the period of study performance, there are no further questions regarding GCP quality.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of propranolol are well known. As propranolol is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The ERA is not considered to be in line with the latest ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*). The applicant has committed to submit a new ERA within 5 years that is in line with the relevant ERA-GL.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Propranolol EQL (Propranolol) with the reference product Inderal.

Pharmacokinetic properties of the active substance
Absorption: Maximum plasma concentration is reached after 1-2 hours. The bioavailability is approximately 25%. The interindividual variation of the plasma concentration after ingestion is 20-fold. The bioavailability slightly increases with the patient's age. Concomitant intake of food increases the bioavailability. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of propranolol is linear within the dose range 10-40 mg.

Elimination: The half-life in plasma during chronic treatment is 4-6 hours, while the effect on heart rate and blood pressure in general remains unchanged 12 hours after last tablet intake.

Study 112-17
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Propranolol, 40 mg, tablet with Inderal, 40 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 30 hours post-dose. Plasma concentrations of S-propranolol and R-propranolol were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 28 November 2017 and 7 December 2017.

Results
The results from the pharmacokinetic and statistical analysis are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for S-propranolol, n=32.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**182.82 ± 92.57**	**28.98 ± 16.50**	**2.25 (1.00-5.00)**
Reference	**177.67 ± 88.96**	**28.29 ± 13.54**	**2.25 (1.00-5.00)**
***Ratio (90% CI)**	**104.60 (95.12-115.02)**	**101.58 (89.58-115.20)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for R-propranolol, n=32.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**95.98 ± 58.53**	**14.98 ± 8.63**	**2.25 (1.00-5.00)**
Reference	**91.80 ± 54.71**	**14.71 ± 8.09**	**2.25 (1.00-5.00)**
***Ratio (90% CI)**	**105.43 (95.08-116.92)**	**102.09 (90.29-115.43)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both enantiomers.

A biowaiver was sought for the additional strength of 10 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and the ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical method was adequately validated.

Propranolol is a racemic mixture, and the active form is the S-isomer of propranolol. Bioequivalence assessment is based on the active enantiomer, S-propranolol, which is acceptable. It is sufficient to demonstrate bioequivalence for only the active enantiomer in cases where one enantiomer is inactive (or makes a low contribution) with respect to both safety and efficacy. The data for R-propranolol are considered supportive.

Based on the submitted bioequivalence study, Propranolol EQL is considered bioequivalent with Inderal.

Absence of studies with the additional strength of 10 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of propranolol is linear between 10 mg and 40 mg.

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

Pharmacovigilance system
Proposed MAH: EQL Pharma AB
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

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 Propranolol EQL.

Part II Safety specification

Summary of safety concerns	
Important identified risks	– Bradycardia – Hypotension – Bronchospasm – Hypoglycaemia – Abrupt discontinuation of treatment – Use in patients with severe liver diseases – Heart failure deterioration.
Important potential risks	– Foetal and neonatal toxicity when used during pregnancy.
Missing information	– None

The summary of safety concerns is aligned with the one published by CMDh for Propranolol Generis 10 mg and 40 mg film-coated tablets (PT/H/1944/001-002/DC), and which is also used for the product Propranolol Medical Valley (DK/H/3480/001-002/DC).

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 0.1 signed 1 Nov 2024, 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.

Periodic Safety Update Report (PSUR)

The active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Renewal date
The renewal date will be 5 years after approval date.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Propranolol EQL, is found adequate.

There are no objections to approval of Propranolol EQL, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments

Non-clinical
The ERA is not considered to be in line with the latest ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*). The applicant has committed to submit a new ERA within 5 years that is in line with the relevant ERA-GL.

Quality
CEP 2002-026-Rev 06 was submitted and assessed during the procedure. However, on 2026-03-26, it was noted that a new version of the CEP, Rev 07, had been issued on 2026-02-19, according to the EDQM knowledge database. The applicant was unable to provide the current valid version of the CEP within the established timeline for the procedure. To address this issue, the applicant has provided a

Letter of Commitment, stating that a variation for updating the CEP will be submitted within the next 3 months following the EoP.

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available on the Swedish MPA website.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available on the Swedish MPA website.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Propranolol Hcl Accord (NL/H/2564/001-003/MR) and Acetazolamid EQL Pharma (Dnr 5.4.1-2017-52728).

The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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