Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Propranolol 10 mg film-coated tablets
Propranolol 40 mg film-coated tablets
Propranolol 80 mg film-coated tablets

propranolol hydrochloride

PL 49445/0152-0154

Amarox Limited

LAY SUMMARY

Propranolol 10, 40 & 80 mg film-coated tablets
propranolol hydrochloride

This is a summary of the Public Assessment Report (PAR) for Propranolol 10, 40 & 80 mg film-coated tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Propranolol tablets in this lay summary for ease of reading.

For practical information about using Propranolol tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Propranolol tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Inderal 10 mg, 40 mg and 80 mg film-coated tablets.

Propranolol tablets can be used for many conditions including:
- Hypertension (high blood pressure)
- Angina (chest pain)
- Some arrhythmias (disorders of heart rhythm)
- Protection of the heart after a myocardial infarction (heart attack)
- Prevention of migraine
- Essential tremor, anxiety
- Certain thyroid conditions (such as thyrotoxicosis, which is caused by an overactive thyroid gland)
- Hypertrophic cardiomyopathy (thickened heart muscle)
- Phaeochromocytoma (high blood pressure due to a tumour usually near the kidney)
- Bleeding in the oesophagus caused by high blood pressure in the liver.

How do Propranolol tablets work?
The name of this medicine is Propranolol. The active ingredient is propranolol. Propranolol is produced as film-coated tablets in three different strengths. Each tablet contains 10 mg, 40 mg or 80 mg of propranolol hydrochloride.

Propranolol is one of a group of drugs called beta-blockers. It has effects on the heart and circulation and also on other parts of the body.

How are Propranolol tablets used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (by mouth).

Propranolol tablets should be swallowed with a drink of water. The patient’s doctor will have decided how many Propranolol tablets the patient needs to take each day depending on their condition. The patient should follow their doctor's instructions about when and how to take their tablets.

This will also tell the patient how many tablets to take and when they should take them. The patient should ask their doctor or pharmacist if they are not sure.

The following table shows the recommended total daily dosages for an adult:

Hypertension (high blood pressure)	160 mg to 320 mg
Angina (chest pains)	120 mg to 240 mg
Arrythmias (disorders of heart rhythm)*	30 mg to 160 mg
Protection of the heart after a heart attack	160 mg
Prevention of migraine*	80 mg to 160 mg
Essential tremor	80 mg to 160 mg
Anxiety	40 mg to 120 mg
Certain thyroid conditions (such as thyrotoxicosis)*	30 mg to 160 mg
Hypertrophic cardiomyopathy (thickened heart muscle)	30 mg to 160 mg
Phaeochromocytoma	30 mg to 60 mg
Bleeding in the oesophagus caused by high blood pressure in the liver	80 mg to 160 mg

*Under some circumstances, Propranolol can be used to treat children with these conditions. The dosage will be adjusted by the doctor according to the child's age or weight.

Elderly people may be started on a lower dose.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

For further information on how Propranolol tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Propranolol tablets have been shown in studies?
Because Propranolol tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Propranolol tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can

be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Propranolol tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Propranolol tablets approved?
It was concluded that, Propranolol tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Propranolol tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Propranolol tablets. The RMP details the important risks of Propranolol tablets, how these risks can be minimised, any uncertainties about Propranolol tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Propranolol tablets:

Important Identified Risk	Bradycardia
	Hypotension
	Bronchospasm
	Hypoglycaemia
	Abrupt discontinuation of treatment
	Use in patients with severe liver diseases
	Heart failure deterioration
Important Potential Risk	Foetal and neonatal toxicity when used during pregnancy
Missing information	None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Propranolol tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Propranolol tablets

Marketing Authorisations for Propranolol tablets were granted in the United Kingdom (UK) on 2 July 2024.

The full PAR for Propranolol tablets follows this summary.

This summary was last updated in August 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Propranolol 10, 40 & 80 mg film-coated tablets (PL 49445/0152-0154) could be approved.

The products are approved for the following indications:

- the control of hypertension
- the management of angina pectoris
- long-term management against re-infarction after recovery from acute myocardial infarction
- the control of most forms of cardiac dysrhythmias
- the prophylaxis of migraine
- the management of essential tremor
- relief of situational anxiety and generalised anxiety symptoms, particularly those of somatic type
- prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices
- the adjunctive management of thyrotoxicosis and thyrotoxic crisis
- management of hypertrophic obstructive cardiomyopathy
- management of phaeochromocytoma peri-operatively (with an alpha-blocker).

Propranolol is a competitive antagonist at both the $beta_1$- and $beta_2$ adrenoceptors. It has no agonist activity at the beta adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1 to 3 mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta-blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta agonists such as isoprenaline.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Inderal 10 mg, 40 mg and 80 mg film-coated tablets that has been licensed for suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 24 August 2023 on grounds relating to quality, safety and efficacy. Following provision of additional data the CHM were reassured on the quality of the product.

Marketing Authorisations for Propranolol tablets were granted in the United Kingdom (UK) on 2 July 2024.

II QUALITY ASPECTS

II.1 Introduction

The active ingredient is propranolol hydrochloride.
Each film-coated tablet contains 10, 40 or 80 mg propranolol hydrochloride respectively.

The other ingredients are:
Core: Maize starch, lactose monohydrate, cellulose microcrystalline (E460) and magnesium stearate.
Coating: Hypromellose 6cPs (E464), glycerine (E422) and titanium dioxide (E171).

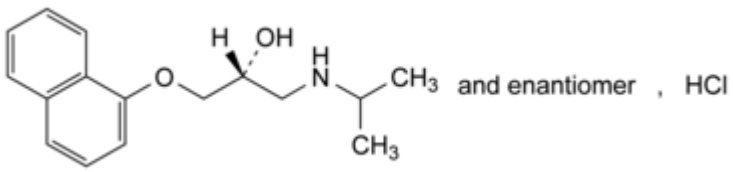
The finished products are packaged in a PVC/PVDC-Alu blister pack containing 28 and 56 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: propranolol hydrochloride
Chemical Name: (2*RS*)-1-[(Propan-2-yl)amino]-3-[(naphthalen-1-yl)oxy]propan-2-ol hydrochloride.
Molecular Formula: $C_{16}H_{22}ClNO_2$



Chemical Structure:
Molecular Weight: 295.8
Appearance: White or almost white powder.
Solubility: Soluble in water and in ethanol (96 per cent), practically insoluble in heptane.

Propranolol hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development
A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of propranolol hydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of propranolol hydrochloride are well-known. With the exception of data from a single bioequivalence study undertaken (BE/21/325), no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

Study 1: BE/21/325

This study was an open-label, balanced, randomised, two treatment, two sequence, two period, two way cross-over, single oral dose bioequivalence study comparing Propranolol 40 mg Film-coated tablets (test product) with Inderal (Propranolol) 40 mg Film-Coated tablets (reference product) in healthy, adult, human subjects under fasting conditions.

A single dose of either the test or reference product was administered after an overnight fast of at least 10 hours, in each study period. Blood samples were taken pre-dose and up to 30 hours post dose, with a washout period of 6 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Bioequivalence Assessment of S-Propranolol (N=49)

Parameter (Units)	Geometric Least-Squares Means[1]		Test-to-Reference Ratio%[2]	ISCV%[3]	90% Confidence Interval Limits[4]		Power (%)
	Test Product (A)	Reference Product (B)			Lower	Upper	
LnC_{max} (ng/mL)	50.81	47.97	105.93	25.34	97.34	115.27	99.02
$LnAUC_{0-t}$ (hr.ng/mL)	319.18	308.82	103.36	23.55	95.53	111.83	99.57

1. For $\log_e$-transformed results (Ln), value is the least-squares geometric mean.
2. Ratio% of geometric least-squares means for $\log_e$-transformed results.
3. ISCV%= %Intra-subject coefficient of variation calculated from the mean square term of the ANOVA.
4. Confidence interval on ratio.

Bioequivalence Assessment of R-Propranolol (for supportive information) (N=49)

Parameter (Units)	Geometric Least-Squares Means[1]		Test-to-Reference Ratio%[2]	ISCV%[3]	90% Confidence Interval Limits[4]		Power (%)
	Test Product (A)	Reference Product (B)			Lower	Upper	
LnC_{max} (ng/mL)	25.08	23.68	105.91	27.81	96.54	116.17	97.62
$LnAUC_{0-t}$ (hr.ng/mL)	146.86	142.66	102.95	26.95	94.11	112.62	98.20

1. For log_e-transformed results (Ln), value is the least-squares geometric mean.
2. Ratio% of geometric least-squares means for log_e-transformed results.
3. ISCV%= %Intra-subject coefficient of variation calculated from the mean square term of the ANOVA.
4. Confidence interval on ratio.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional (10 and 80 mg) strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with propranolol hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**