CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Propranolol HCl Accord 10 mg, 40 mg and 80 mg, film-coated tablets Accord Healthcare Ltd, United Kingdom

propranolol hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2564/001-003/MR
Registration number in the Netherlands: RVG 55387, 55388, 55880

10 April 2013

Pharmacotherapeutic group:	beta blocking agents, non-selective
ATC code:	C07AA05
Route of administration:	oral
Therapeutic indication:	see next page
Prescription status:	prescription only
Date of first authorisation in NL:	9 April 1981 (40 mg), 9 July 1981 (10 mg), 12 July 1983 (80 mg)
Concerned Member States:	Mutual recognition procedure with: 10 mg - BE, CY, DE, DK, ES, FI, MT, PL, PT, SE, UK 40 mg - BE, BG, CY, DE, DK, EE, ES, FI, FR, IT, MT, PL, PT, SE, UK 80 mg - BG, DE, DK, FI, MT, PT, SE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Propranolol HCl Accord 10 mg, 40 mg and 80 mg, film-coated tablets from Accord Healthcare Ltd. The date of authorisation was on 9 April 1981 (40 mg), 9 July 1981 (10 mg) and 12 July 1983 (80 mg) in the Netherlands.

The product is indicated for:

- Angina pectoris.
- Hypertension.
- Long-term prophylaxis against myocardial reinfarction after recovery from acute myocardial infarction
- Hypertrophic obstructive cardiomyopathy.
- Essential tremor.
- Supraventricular cardiac arrhythmia.
- Ventricular cardiac arrythmias.
- Hyperthyroidism and thyrotoxicosis
- Phaeochromocytoma (with an alpha-blocker).
- Migraine.
- Prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension
- oesophageal varices.

A comprehensive description of the indications and posology is given in the SPC.

Propranolol has no β-1 receptor selectivity (cardioselectivity) and has no intrinsic sympathomimetic activity (ISA). Propranolol is a strongly lipophilic substance and has a membrane stabilising effect.
These properties are important in connection with the occurrence of undesirable effects and/or overdose.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Inderal 10 mg, 40 mg and 80 mg tablets (NL License RVG 05013, 05014, 05966) which were first registered in the Netherlands by AstraZeneca B.V. in 1965 (original product). This product is no longer available in the Netherlands. In addition, reference is made to Inderal authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Inderal 40 mg tablets, registered in Portugal. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is propranolol hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder, which is soluble in water and ethanol. Propranolol HCl is a racemic mixture. The substance exists in three different crystalline forms, denoted as forms I, II and III. Polymorphic form-II is used.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification and analytical methods are in line with the Ph.Eur. and the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Propranolol HCl Accord 10 mg is a white to off-white, round, biconvex film-coated tablet imprinted with "AI" on one side and a score line on the other side.
Propranolol HCl Accord 40 mg is a white to off-white, round, biconvex film-coated tablet imprinted with 'AL' on one side and a score line on the other side.
Propranolol HCl Accord 80 mg is a white to off-white, round, biconvex film-coated tablet imprinted with "AM" on one side and a score line on the other side.

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

The film-coated tablets are packed in PVC-PVdC/ALU blisters.

The excipients are: maize starch, lactose monohydrate, cellulose microcrystalline (E460), magnesium stearate, hypromellose (E464), acetylated monoglycerides, diglycerides titanium dioxide (E171).

The different tablet strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The tablets bear a score line. Results of uniformity of mass of halved tablets have not been provided which is acceptable as the score line is only for facilitating drug intake. The drug product specification is compliant to the Ph.Eur. The MAH has performed a bioequivalence study with the 40 mg tablets of the current formulation. The MAH has provided dissolution data comparing the biobatch in three dissolution media. The dissolution was over 85% in 15 minutes and therefore considered similar without further calculation. Dissolution data in three media of one batch of 10 mg and one batch of 80 mg compared to the 40 mg biobatch have also been provided. The results are also over 85% dissolution in 15 minutes. The biowaiver for the 10 mg and 80 mg formulations is therefore acceptable from a chemical-pharmaceutical point of view.

Manufacturing process
The manufacturing process consists of wet granulation, drying and blending. The mixture is used for compression of the core tablets. The tablets are then film-coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two consecutive full-scale batches of all three strengths. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with their Ph.Eur. monographs, except for the film-coating. An in-house specification for the film-coating is provided. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, dissolution, microbial contamination, uniformity of dosage units and uniformity of halved tablets. The proposed requirements are acceptable. The shelf life specification should be re-evaluated when the stability studies are finalized. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two full-scale batches of all three strengths.

Stability of drug product
Stability data on the product has been provided for two full-scale batches of each strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a PVC/PVdC-Al blister package.
No trends and out-of-specification can be observed at either condition. Based on the stability results, the proposed shelf-life of 3 years without specific storage condition is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only material of animal origin used in the formulation is lactose monohydrate. It is confirmed by the manufacturer of lactose that it does not have potential for TSE and is derived from milk, sourced from healthy animals in the same conditions as milk collected for human consumption and is prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev2.

II.2 Non-clinical aspects

This product is a generic formulation of Inderal, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of propranolol released into the environment. It

does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Propranolol is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Propranolol HCl Accord 40 mg (Accord Healthcare Ltd, United Kingdom) is compared with the pharmacokinetic profile of the reference product Inderal 40 mg tablets (Astra Zeneca Pharmaceuticals, Portugal).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 76 (including two extra subjects) healthy male subjects, aged 18-55 years. Each subject received a single dose (40 mg) of one of the 2 propranolol hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8,10, 12, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable and the wash-out and sampling period long enough to estimate the pharmacokinetic variables. The bioequivalence study was not carried out on the highest strength, but on propranolol hydrochloride 40 mg tablets due to non-availability of samples of the 80 mg tablets. This is in line with the advice of the MEB.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
74 subjects were randomized and were dosed in the study. 70 subjects were dosed in Period-II of the study and all of them (70 subjects) completed the clinical phase of the study. Plasma samples of all the 70 subjects were analysed. Three subjects were withdrawn from the study on the grounds of protocol deviation, one due to positive in urine drug scan and two due to a positive in alcohol breath test. One subject was also withdrawn on medical grounds, as he was suffering from conjunctivitis. The study sample of this subject was also analyzed on basis of protocol requirement (safety basis).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of S-propranolol under fasted conditions.

Treatment N=70	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h

Test	1590 ± 620	1610 ± 622	244 ± 66	2.3	4.4 ± 0.7
Reference	1517 ± 507	1537 ± 510	240 ± 60	2.3	4.4 ± 0.7
***Ratio (90% CI)**	1.03 (1.00-1.07)	1.03 (1.00-1.07)	1.00 (0.98-1.04)	--	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **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 concentration **$t_{1/2}$** half-life					

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of S-propranolol under fasted conditions, it can be concluded that Propranolol HCl Accord 40 mg and Inderal 40 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Propranolol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of propranolol. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Biowaiver
A biowaiver was granted for the 10 mg and 80 mg tablets. The following requirements are considered fulfilled:

- The tablets are manufactured at the same manufacturing site using a similar manufacturing process.
- Propranolol HCl demonstrates linear pharmacokinetics over the therapeutic dose range.
- The qualitative composition of the propranolol tablets is the same.
- The propranolol tablets are dose proportional
- The dissolution profiles of the tablets are similar under the same conditions.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Propranolol was first approved in 1965, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of propranolol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Inderal.

Readability test

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 test consisted of two rounds with 10 participants each. There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. There were no changes made to the PL based on first testing. The data show all 20 questions met the passing criteria in the first and second round.

After the readability test, the PL has been revised. Therefore, a bridging statement was provided. The bridging to the “newly” approved leaflet according to the bridging guideline (Consultation with Target Patient Groups) meets the requirements of Article 59(3) of Council Directive 2001/83/EC.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Propranolol HCl Accord 10 mg, 40 mg and 80 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Inderal 10 mg, 40 mg and 80 mg tablets. Inderal is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Propranolol HCl Accord 10 mg, 40 mg and 80 mg, film-coated tablets were authorised in the Netherlands on 9 April 1981 (40 mg), 9 July 1981 (10 mg) and 12 July 1983 (80 mg).

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 26 September 2012.

The date for the first renewal will be: 26 September 2017.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached