

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Isosorbide-5-mononitrat Accord 20 mg and 40 mg, tablets
Accord Healthcare Ltd, United Kingdom**

isosorbide mononitrate

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/2157/001-002/MR
Registration number in the Netherlands: RVG 56948-56949**

18 August 2011

Pharmacotherapeutic group:	vasodilators used in cardiac diseases, organic nitrates
ATC code:	C01DA14
Route of administration:	oral
Therapeutic indication:	prophylactic treatment of angina pectoris
Prescription status:	prescription only
Date of first authorisation in NL:	20 June 1988
Concerned Member States:	Mutual recognition procedure with CZ, DE, ES, IT, LT, PL, 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 Isosorbide-5-mononitrat Accord 20 mg and 40 mg, tablets from Accord Healthcare Ltd. The date of authorisation was on 20 June 1988 in the Netherlands. The product is indicated for prophylactic treatment of angina pectoris.

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

This preparation is an immediate-release formulation of isosorbide mononitrate, an active metabolite of isosorbide dinitrate. Nitro-compounds cause a dose-dependent relaxation of smooth muscle. The therapeutic effect is dependent on dose and individual sensitivity.

Low doses cause dilatation of the veins and a decreased venous return to the heart (reduced preload). High doses also cause arterial dilatation and decreased vascular resistance (reduced afterload). Isosorbide mononitrate reduces the load on the heart by venous and arterial dilatation and can have a direct vasodilatory effect on the coronary arteries. By reducing end-diastolic pressure and volume, it lowers the pressure inside the ventricle and thus improves the subendocardial blood flow. The net effect of isosorbide mononitrate is a reduced load on the heart and better oxygen supply to the myocardium.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Elantan 20 mg and 40 mg tablets Schwarz Pharma GmbH. In the Netherlands, the innovator product Mono-Cedocard 20, tabletten 20 mg registered by Cedona Pharmaceuticals B.V. on 25 November 1982. In addition, reference is made to innovator 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 Elantan 40 mg tablets, registered in Germany. 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. These generic products 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 isosorbide mononitrate, diluted, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Isosorbide mononitrate, diluted is defined by the Ph.Eur. as a dry mixture of isosorbide mononitrate and lactose monohydrate or mannitol. The drug substance used is diluted with lactose monohydrate. The active substance is a white to almost white, crystalline powder which is freely soluble in water. The drug substance does not exhibit polymorphism.

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 new 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 is in line with the CEP, with additional requirements for sulphated ash, sulphates, heavy metals, isosorbide, total impurities, and microbiological purity. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for one production-scale batch.

Stability of drug substance

Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (six months). In the provided stability data, no specific trends or significant changes were observed at both storage conditions. The claimed re-test period of 60 months is justified. The drug substance does not need specific storage conditions and was shown to be photostable.

* *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

Isosorbide-5-mononitrat Accord 20 mg is a white to off white, round, flat, bevelled edge uncoated tablet, debossed with 'AS' on one side and break line on the other side.

Isosorbide-5-mononitrat Accord 40 mg is a white to off white, round, flat, bevelled edge uncoated tablets, debossed with 'AT' on one side and break line on the other side.

Both tablets can be divided in to equal halves.

The tablets are packed in Al/PVC and Al/PVC-PVDC blisters.

The excipients for both formulations are: lactose monohydrate, microcrystalline cellulose (PH 102) (E460), sodium starch glycolate (type-A), colloidal anhydrous silica (E551), magnesium stearate (E470b). The two strengths are not dose-proportional. The weight of both tablets is the same; the amount of microcrystalline cellulose, sodium starch glycolate differs slightly to compensate for the difference in active substance.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation of the drug product was adjusted with regard to the amounts of two excipients and the manufacturing process was optimised. The new formulation was compared *in vivo* and *in vitro* to a German reference product. Dissolution profiles of the test and reference product were similar. The choice of the manufacturing process and package is justified. The tablets of both strengths have a break line. Subdivision of tablets is tested according to the test described in the Ph.Eur. general monograph on tablets. The pharmaceutical development of the product was adequately performed.

Manufacturing process

The manufacturing process consists of dry mixing of the components of the drug product followed by compression. The manufacturing process was adequately validated according to relevant European guidelines. Due to the content of drug substance in the formulation and the conventional manufacturing techniques, the manufacturing process is regarded to be standard. Process validation data on the product has been presented for two full-scale batches of each strength.

Control of excipients

All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, average weight of tablets, identification of the drug substance, resistance to crushing, friability, disintegration time, loss on drying, dissolution, uniformity of dosage units, inorganic nitrates, related substances, assay, microbial contamination, and subdivision of tablets. Except for the limit for unknown impurities, the release and shelf life requirements are identical. The specifications are acceptable. The analytical methods were adequately described and validated. Batch analytical data from the proposed production site were provided on two full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product was provided on two full-scale batches of each strength packed in both Al/PVC blisters and Al/PVC-PVdC blisters and stored at 25°C/60% RH (12 months), 30°C/65% RH (12 months), and 40°C/75% RH (1 to 2 months). The conditions used in the stability studies are according to the ICH stability guideline.

Out-of-specification results were observed at accelerated conditions. No significant changes were observed at intermediate and long-term conditions. A slight trend in loss on drying was observed, especially in Al/PVC-PVdC blisters. The proposed shelf life of two years is justified. The drug product should be stored below 30°C. Photostability was demonstrated under ICH conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose is the only excipient of human or animal origin. Magnesium stearate is of vegetable origin. TSE/BSE certificates were provided.

II.2 Non-clinical aspects

This product is a generic formulation of Elantan tablets, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 isosorbide mononitrate 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

Isosorbide mononitrate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Isosorbide-5-mononitrat Accord 40 mg tablets (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Elantan 40 mg tablets (Schwarz Pharma GmbH, DE).

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 in different member states. 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 26 healthy male subjects, aged 19-42 years. Each subject received a single dose (40 mg) of one of the 2 isosorbide mononitrate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. A meal was provided 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.66, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24 and 30 hours after administration of the products.

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

One subject was withdrawn from the study in period I due to an adverse event (vomiting and headache). The data of 25 subjects were used for pharmacokinetic/statistical evaluation.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of isosorbide mononitrate under fasted conditions.

Treatment N=25	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	8709 \pm 1335	9018 \pm 1448	1175 \pm 298	0.50 (0.16-2.50)	5.9 \pm 0.7
Reference	8416 \pm 1158	8733 \pm 1236	1154 \pm 189	0.50 (0.33-1.33)	5.9 \pm 0.7
*Ratio (90% CI)	1.03 (1.01-1.05)	1.03 (1.01-1.05)	1.01 (0.93-1.09)	--	--
CV (%)	4.2	4.3	16.6	--	--

AUC_{0-∞}	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

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 isosorbide mononitrate under fasted conditions, it can be concluded that Isosorbide-5-mononitrate Accord 40 mg and Elantan 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.

Isosorbide mononitrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of isosorbide mononitrate. 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.

Extrapolation to 20 mg tablet

The MAH provided a justification for a biowaiver for the 20 mg strength. In this justification, one point does not comply with the guideline: the tablet formulations are not dose-proportional. However, this deviation of the guideline is not expected to have any implications for bioequivalence of the 20 mg tablet. Both strengths of Isosorbide-5-mononitrate Accord tablets dissolve very fast, being almost completely (>95%) dissolved after 5 minutes in three different dissolution media. Moreover, isosorbide 5-mononitrate is rapidly and completely absorbed. Therefore, the results of the bioequivalence study with the 40 mg formulation can be extrapolated to the 20 mg strength.

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

Isosorbide mononitrate was first approved in 1980, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of isosorbide mononitrate 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. However, one of the member states argued that another indication should be included in accordance with their national innovator: the indication 'adjunctive therapy in congestive heart failure not responding to cardiac glycosides or diuretics'. Within the context of this MRP, this indication was not added. The MAH committed to submit a type II variation to include this indication.

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. The test included 14 questions related to the content of the PL. Seven questions were related to the structure/appearance of the PIL. A satisfactory outcome was achieved when 18 out of 20 participants

were able to find information and answer each question correctly and act appropriately. In round 1, on average 99% of the time the correct section was located to answer the question. Each question was answered correctly 99% of the time. In the second round 98% of the participants were able to locate the section and to answer the question correctly. Therefore no further changes were considered to be required. The readability test has been satisfactory performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Isosorbide-5-mononitrat Accord 20 mg and 40 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Elantan 20 mg and 40 mg tablets. Elantan 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. Isosorbide-5-mononitrat Accord 20 mg and 40 mg, tablets were authorised in the Netherlands on 20 June 1988.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Isosorbide-5-mononitrat Accord 20 mg and 40 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 1 March 2011.

The date for the first renewal will be: 31 October 2015.

The following post-approval commitments have been made during the procedure:

Product information

- The MAH committed to submit a type II variation to include the indication "As adjunctive therapy in congestive heart failure not responding to cardiac glycosides or diuretics".

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 _{1/2}	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