CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Metoclopramidemonohydrochloride Accord 10 mg, tablets
Accord Healthcare B.V., the Netherlands

metoclopramide 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/2418/001/MR
Registration number in the Netherlands: RVG 11811

18 June 2012

Pharmacotherapeutic group:	drugs for functional gastrointestinal disorders, propulsives
ATC code:	A03FA01
Route of administration:	oral
Therapeutic indication:	nausea and vomiting in adults, whether or not this accompanies chemotherapy
Prescription status:	prescription only
Date of first authorisation in NL:	31 July 1987
Concerned Member States:	Mutual recognition procedure with CY, ES, FR, IT, MT, RO, 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 Metoclopramidemonohydrochloride Accord 10 mg, tablets from Accord Healthcare B.V. The date of authorisation was on 31 July 1987 in the Netherlands.

The product is indicated in the adult population for nausea and vomiting, whether or not this accompanies chemotherapy.

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

Metoclopramide is a substituted benzamide. It is used among other things because of its anti-emetic properties. The anti-emetic effect is the result of two mechanisms of action involving the central nervous system:

- antagonism of the dopaminergic D2 receptors in the chemoreceptor trigger zone and in the vomiting centre of the medulla which is affected in apomorphine-induced vomiting;
- antagonism of the serotoninergic 5HT3 receptors and agonist effect on the 5HT4 receptors which are affected in chemotherapy-induced vomiting.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Primperan, 10 mg tablets (NL License RVG 05250) which has been registered in the Netherlands by Sanofi-Aventis since 18 December 1968 (original product). In addition, reference is made to Primperan 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 Primperan 10 mg tablets, registered in the Netherlands. 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 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 metoclopramide hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white, crystalline powder, which is very soluble in water, freely soluble in alcohol and sparingly soluble in methylene chloride.

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. 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 two full-scale batches.

Stability of drug substance
The active substance is stable for 5 years 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
Metoclopramidemonohydrochloride Accord 10 mg is a white to off-white, round, biconvex, uncoated tablet with the inscription 'BD' on one side and a scoreline on the other side. The tablet can be divided into equal halves. Each tablet contains metoclopramide hydrochloride equivalent to 10 mg anhydrous metoclopramide hydrochloride

The tablets are packed in PVC/PVdC/aluminium blister strips.

The excipients are: lactose monohydrate, pre-gelatinised starch, maize starch, anhydrous colloidal silica, magnesium stearate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development study concerned comparative dissolution studies with the originator product. The choices of the packaging and manufacturing process are justified. The batch used in the bioequivalence was manufactured according to the finalized formulation and manufacturing

process. The tablets bear a break line on one side. Suitability of the break line for equal division of the tablets was adequately demonstrated by the test for subdivision of tablets performed during batch analyses and during the stability studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a standard process mainly consisting of raw material sifting, (wet) granulation, drying, sizing, blending and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale batches.

Control of excipients
The excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, average weight, friability, resistance to crushing, identification, dissolution, uniformity of dosage units, related substances, assay, microbiological limit test and subdivision of tablets. Except for related substances and assay, the release and shelf-life requirements are identical. 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, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two full-scale batches stored at 25°C/60% RH (24 months), 30°/65% RH (12 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 PVC-PVdC/Al-blisters. At accelerated conditions after 6 months a significant increase of any other impurity is observed, leading to an out-of-specification. At intermediate and long-term conditions no trends or changes are seen and all parameters remain within the specified limits. A photostability study showed that the product is photostable. The proposed shelf-life of 2 years and storage condition ‘Store below 30°C’ are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. Only lactose is of animal origin.

II.2 Non-clinical aspects

This product is a generic formulation of Primperan, 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 metoclopramide hydrochloride 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

Metoclopramide hydrochloride 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 Metoclopramidemonohydrochloride Accord 10 mg (Accord Healthcare B.V., NL)

is compared with the pharmacokinetic profile of the reference product Primperan 10 mg tablets (Sanofi-Aventis, NL).

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 30 healthy male subjects, aged 18-44 years. Each subject received a single dose (10 mg) of one of the 2 metoclopramide hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast. . Fasting was continued for 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 at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 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
Two subjects dropped out: one subject was withdrawn before check in Period II, because he tested positive for benzodiazepines, and another subject because he tested positive for alcohol. Pharmacokinetic and statistical analysis were carried out on 28 subjects.

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

Treatment N=28	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	273 ± 80	296 ± 91	37 ± 12	1.0 (0.25 – 2.75)	6.1 ± 1.0
Reference	274 ± 71	298 ± 82	37 ± 13	1.0 (0.50 – 3.0)	6.1 ± 1.0
***Ratio (90% CI)**	0.99 (0.95-1.04)	0.99 (0.94-1.03)	0.98 (0.92-1.05)	--	--
CV (%)	10.0	10.3	14.7	--	--

$AUC_{0-\infty}$ 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 metoclopramide under fasted conditions, it can be concluded that Metoclopramidemonohydrochloride Accord 10 mg and Primperan 10 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.

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

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

Metoclopramide was first approved in 1968, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of metoclopramide 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 the agreed text of the art. 45 Paediatric worksharing procedure for metoclopramide (DE/W/007/pdWS/001).
The MAH committed to submit a variation to amend the product information according to the outcome of the Art. 31 referral (EMEA/H/A-31/1321) immediately after completion of this procedure.

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 report details the demographic data of the volunteers, age, gender, social grade and education. These are well defined and show a good division. The inclusion and exclusion criteria were also acceptable.
The mock-up leaflet in the form intended for marketing was used for testing. Prior to the start of the test, respondents were asked to read the leaflet as they would usually do but for a minimum of 10 minutes. After reading the leaflet, the participants were asked for a first impression straight away – what is good and what is bad about the leaflet. Furthermore, a total of 14 questions were asked in random order. These questions sufficiently addressed the key safety messages. Model answers and criteria for the ability to find and understand were predefined.
Results of the first round of testing were good. For all items the participants scored well on the diagnostic questions. At least 90% of the participants were able to find the information requested and at least 90% showed that they understood and acted upon it. Therefore no changes were made to the leaflet for the second round. Results of the second round confirmed the results of the first round. At least 90% of the participants scored well on the diagnostic questions.
In conclusion, the results have shown that the information most relevant to the patient can be found (98.93%) and understood (99.29%) in a good way. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Metoclopramidemonohydrochloride Accord 10 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Primperan 10 mg tablets. Primperan 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, package leaflet and labelling are in the agreed templates and are in agreement with other metoclopramide containing products.

The Board followed the advice of the assessors. Metoclopramidemonohydrochloride Accord 10 mg, tablets was authorised in the Netherlands on 31 July 1987.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Metoclopramidemonohydrochloride Accord 10 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 26 January 2012.

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

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

Product information

- The MAH committed to submit a variation to amend the product information according to the outcome of the Art. 31 referral (procedure number EMEA/H/A-31/1321) immediately after completion of this 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