

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Terazosine Accord 1 mg, 2 mg and 5 mg tablets
Accord Healthcare Ltd., United Kingdom

terazosin (as monohydrochloride dihydrate)

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/1161/001-003/DC
Registration number in the Netherlands: RVG 100579, 100581, 100582

6 April 2010

Pharmacotherapeutic group:	alpha-adrenoreceptor antagonists
ATC code:	G04CA03
Route of administration:	oral
Therapeutic indication:	mild to moderate hypertension; urinary obstruction by benign prostatic hyperplasia (BPH)
Prescription status:	prescription only
Date of authorisation in NL:	21 September 2009
Concerned Member States:	Decentralised procedure with BG, CZ, DE, DK, EE, EL, ES, HU, IE, LT, LV, MT, PL, PT, RO, 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 Terazosine Accord 1 mg, 2 mg and 5 mg tablets, from Accord Healthcare Ltd. The date of authorisation was on 21 September 2009 in the Netherlands.

The product is indicated for:

- the treatment of mild to moderate hypertension
- symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH).

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

Although the exact mechanism of the hypotensive action is not established, the relaxation of peripheral blood vessels appears to be produced mainly by competitive antagonism of post-synaptic alpha-1-adrenoceptor. Terazosin usually produces an initial gradual decrease in blood pressure followed by a sustained anti hypertensive action.

Clinical experience indicates that a 2-5% decrease in total cholesterol plasma concentration and a 3-7% decrease in the combined LDLc + VLDLc fraction plasma concentration from pretreatment values are associated with the administration of therapeutic doses of terazosin.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Hytrin 1, 2 and 5 mg tablets by Abbott Laboratories Limited. In the Netherlands, Hytrin 1, 2 and 5 mg (NL License RVG 14558-14560) have been registered since 1991 by Amdipharm Limited. In addition, reference is made to Hytrin 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 Hytrin 2 mg tablets, registered in the UK and Ireland. 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 generic medicinal products.

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 these product types 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 terazosine monohydrochloride dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is slightly soluble in water (pH 1.3 and pH 12.6), ethanol (95%) and chloroform, soluble in methanol, and sparingly soluble in water pH 6.0. The drug substance is manufactured as one polymorphic form only.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Terazosin HCl dihydrate is manufactured in a three step synthesis process. A reaction scheme is provided in the dossier that includes molecular formulae, weights, yield ranges and chemical structures of starting materials, intermediates, reagents and solvents. The manufacturing process is adequately described. Elemental analysis, NMR, MS, DSC, X-ray powder diffraction and optical rotation provide proof that terazosine HCl dihydrate is formed.

Quality control of the drug substance

The drug substance specifications are in line with the Ph.Eur. monograph, with additional requirements for particle size, microbial quality and residual solvents. The analytical methods have been adequately described and validated. Batch analysis was performed on three production-scale batches, demonstrating compliance with the specification.

Stability of the drug substance

Data on two pilot-scale, six lab-scale and nine industrial-scale batches have been provided. At long term conditions (25°C/60% RH) data up to 60 months was available and for accelerated conditions data (40°C/75% RH) up to 12 months was available. All batches were packaged stored. No trends were observed; all parameters stayed well within the specifications. A retest period could be granted of 5 years without further storage conditions.

* *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

Terazosin Accord 1 mg is a white, round, flat tablet with bevelled edges and a score line on one side of the tablet.

Terazosin Accord 2 mg is a yellow coloured, round, flat tablet with bevelled edges and a score line on one side of the tablet.

Terazosin Accord 5 mg is a light pink coloured, round, flat tablet with bevelled edges and score line on one side of the tablet.

The tablets are packed in PVC/PVdC/Al blisters.

The excipients are: lactose monohydrate, maize starch, talc, magnesium stearate; quinoline yellow E104 (2 mg only); iron oxide red (5 mg only).

The tablet weight of the different strength is the same, the amount of terazosin HCl differs between the various strengths, the excipients are quantitatively the same except small difference in lactose to compensate for the amount of active substance.

Pharmaceutical development

In general the development of the products is satisfactory performed and explained. The excipients used are common in the manufacture of tablets. The packing materials are usual and suitable for the products at issue. The reference product Hytrin Tablets was evaluated for dissolution profile in 3 media pH 1, pH 6.8 and in water (paddle, 50 rpm), in all three media sink conditions are achieved. All four strengths of the innovators tablets rapidly dissolve in all three media (>80% in 5 minutes). The product development was initiated with the 5 mg strength in same line as the innovator product in the UK market. A dose similar approach was initiated for the 1 mg and 2 mg strengths using the UK innovator as the reference product. The qualitative composition of the UK reference products is included in the dossier and the qualitative composition is identical to the products for registration. The dissolution profile of terazosin hydrochloride 1 mg, 2 mg and 5 mg tablets were compared with the dissolution profile of the innovator and were found to be comparable.

Manufacturing process

The product is prepared by granulating the drug substance with the excipients followed by compressing it into tablets. The production process, in process controls and process parameters have been described in sufficient detail. Validation was performed on three full-scale batches of each manufacturing site, as the manufacturing as regarded a non-standard process.

Product specifications

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for identity, uniformity of dosage units, friability, disintegration time, dissolution, moisture, impurities, microbiological quality and sub-division of tablets. The release and shelf-life requirements are acceptable. Compliance with the release parameters is demonstrated on three production-scale batches.

Stability tests on the finished product

For several of the batches tested, an increase is observed in the amount of impurity 1 and impurity 2 in long term and accelerated conditions. The maximum increase in impurity 1 observed during long term stability studies is 0.3%. The maximum increase in impurity 2 observed during long term stability studies is 0.4%. The MAH has set the release requirement for both impurities at NMT 0.2% for the drug substance as well as the drug product. Therefore, the qualified limit of NMT 0.5% can be maintained as the shelf-life requirement for impurity 1 and 2. However, the MAH made several commitments regarding these impurities, which can be found on page 7 of this report. For all tablets strengths a shelf-life of 2 years could be granted, when the tablets are stored in the original package to protect from light.

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

Appropriate TSE declarations for all excipients used have been provided. Magnesium stearate is of vegetable origin and lactose is sourced from milk from healthy cows suitable for human consumption.

II.2 Non clinical aspects

These products are generic formulations of Hytrin 1, 2 and 5 mg tablet, which are 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 products are intended as a substitute for other identical products on the market. The approval of these products will not result in an increase in the total quantity of terazosin 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

Terazosin 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 Terazosine Accord 2 mg tablets (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Hytrin 2 mg tablets (Abbot Laboratories Ltd, Ireland).

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-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 18-55 years. Each subject received a single dose (2 mg) of one of the 2 terazosin formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 48 and 72 hours after administration of the products.

Analytical/statistical methods

The analytical method is adequately validated and 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

There were no withdrawals. All 24 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=24	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	403 $\pm$ 100	423 $\pm$ 103	40.5 $\pm$ 10.1	0.75 (0.50-2.25)	13.1 $\pm$ 3.7
Reference	435 $\pm$ 129	450 $\pm$ 129	41.9 $\pm$ 13.4	0.75 (0.50-2.50)	13.0 $\pm$ 1.9
*Ratio (90% CI)	0.89-0.98	0.90-0.99	0.92-1.05	-	-

CV (%)	12.6	12.3	13.6	-	-
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 terazosin under fasted conditions, it can be concluded that Terazosine Accord 2 mg tablets and Hytrin 2 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.

Terazosin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of terazosin. 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 other strengths

The qualitative and quantitative composition of the different strengths is comparable. The tablets are manufactured by the same manufacturer and manufacturing process, and exhibit similar dissolution profiles. The pharmacokinetics of the active substance are linear in the therapeutic range. The concentration of the active substance is below 5% and the ratio between the amounts of excipients is practically similar. The results of the bioequivalence study performed with the 2 mg tablets therefore apply to the other strengths.

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

Terazosin was first approved in 1984, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of terazosin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

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 composition of the subject population is acceptable as far as age, gender and education are concerned. Potential users were asked to read the leaflet as they would usually do, for a minimum of 10 minutes.

After reading the leaflet, the patient was asked for a first impression. The actual test was then performed, using 14 standard practical questions. The questions were asked in random order. First it was determined how well and how rapidly the respondent was capable of finding the answer in the leaflet - the ability to find. Second, the interviewer recorded to what extent the respondent was capable of giving the correct answer - the ability to understand. The diagnostic test was followed by an assessment of layout and content. To this purpose the interviewers laid down 7 assessment criteria focusing on clarity, fonts and paper, readability, language, completeness and appearance.

The conclusion of the user test was that the information most relevant to the patient can be found (98.93%) and understood (97.50%) in a good way. No recommendations are suggested to the structure and presentation of the patient information leaflet. The conclusions are clear, concise and well presented.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Terazosine Accord 1 mg, 2 mg and 5 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Hytrin 1, 2 and 5 mg tablets. Hytrin 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 committed to ensure that their pharmacovigilance obligations will be fulfilled prior placing the product on the market, see also the commitment stated below.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other terazosin containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Terazosine Accord 1 mg, 2 mg and 5 mg with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 March 2009. Terazosine Accord 1 mg, 2 mg and 5 mg tablets were authorised in the Netherlands on 21 September 2009.

A European harmonised birth date has been allocated (30 November 1984) and subsequently the first data lock point for terazosin is March 2010. The first PSUR will cover the period from March 2009 to March 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 November 2013.

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

Quality – medicinal product

- The MAH committed to re-evaluate the requirements for impurities in the drug product when more stability data become available.

Pharmacovigilance system

- The MAH committed not to market the product until a description of the Pharmacovigilance System has been submitted and approved, in compliance with *Volume 9A of The Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use*.

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