CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Atenolol Accord 25 mg, 50 mg and 100 mg tablets
Accord Healthcare Ltd, United Kingdom

atenolol

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/1845/001-003/MR
Registration number in the Netherlands: RVG 23281, 25366-25367

24 June 2010

Pharmacotherapeutic group:	beta blocking agents, selective
ATC code:	C07AB03
Route of administration:	oral
Therapeutic indication:	hypertension; chronic stable angina pectoris; secondary prevention after acute myocardial infarction; supraventricular arrhythmias; ventricular arrhytmias
Prescription status:	prescription only
Date of first authorisation in NL:	25 mg – 12 July 1999 50 mg/100 mg - 21 March 2000
Concerned Member States:	Mutual recognition procedure with BE, DE, EL, FR, IT, LT, LV, PL, SE, SK; only 50 and 100 mg - ES
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 Atenolol Accord 25 mg, 50 mg and 100 mg tablets, from Accord Healthcare Ltd. The date of authorisation in the Netherlands was on 12 July 1999 for 25 mg and on 21 March 2000 for the 50 and 100 mg tablets.

The product is indicated for:
- Hypertension
- Chronic stable angina pectoris
- Secondary prevention after acute myocardial infarction: early intervention within 12 hours.
- Supraventricular arrhythmias:
  - paroxysmal supraventricular tachycardia (in therapeutic or prophylactic treatment)
  - atrial fibrillation and atrial flutter: in case of inadequate response to maximum dosages of cardiac glycosides; in cases where cardiac glycosides may be contra-indicated or may be associated with an unfavorable risk/benefit ratio.
- Ventricular arrhythmias:
  - ventricular extrasystoles (prophylactic or therapeutic treatment), if the extrasystoles are the result of increased sympathetic activity
  - ventricular tachycardias and ventricular fibrillation (prophylactic treatment), especially when the ventricular abnormality is the result of elevated sympathetic activity.

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

Atenolol is a selective beta-1-adrenergic blocking agent, without intrinsic sympathomimetic of membrane stabilising characteristics. Clinical effects are reached fast and will maintain at least 24 hours after the intake of atenolol. Therefore both Atenolol 50 and Atenolol 100 can be taken once daily, which simplifies the therapy. Atenolol is a very hydrophylic compound which passes the blood-brain barrier only in very limited amounts. This causes a relatively low incidence of CNS-side effects. Atenolol mainly acts on the beta receptors of the heart and can therefore, contrary to non-selective beta adrenergic blocking agents, be administered, under carefull surveillance and check-up of the lung function, to patients with chronic obstructive pulmonal diseases, who can not bear a non-selective beta adrenergic blocking agent.
The beta-1-selectivity is reduced with increased dose. Beta-adrenergic blocking agents have a negative inotropic and chronotropic effect and inhibit the effect of catecholamines resulting in reduced heart rate and blood pressure.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Tenormin 25 mg, 50 mg and 100 mg tablets (NL License RVG 14374, 07294-07295) which were first registered in the Netherlands in 1977 (50/100 mg) and 1990 (25 mg). Currently, Tenormin is not registered in the Netherlands anymore. Various generic products of atenolol are however authorised in the Netherlands. In addition, reference is made to Tenormin 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 Tenormin 100 mg tablets, registered in the UK. 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 their reference products.

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 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 atenolol, a well-known active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder, which is sparingly soluble in water, soluble in anhydrous ethanol and slightly soluble in methylene chloride. A declaration has been provided that atenolol 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 in the dossier.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the additional CEP requirements. The active substance batch will be tested on compliance with the approved drug substance specification prior to each drug product batch manufacture.

Stability of drug substance
Stability data on the active substance have been provided. A retest period of 1 year has been granted.

* 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
Atenolol Accord 25 mg is a white, round, flat, bevelled tablet with the inscription ‘AA’ on one side and a scoreline on the other side.
Atenolol Accord 50 mg is a white, round, flat, bevelled tablet with the inscription ‘AB’ on one side and a scoreline on the other side.

Atenolol Accord 100 mg is a white, round, flat, bevelled tablet with the inscription 'AC' on one side and a scoreline on the other side.

The uncoated tablets have a score line on one side and an inscription on the other site. All tablets can be divided into equal halves.
The three strengths are dose-proportional and are all manufactured from the same blend.

The tablets are packed in PVC/PVDC/aluminium blisters and in an HDPE tablet container with a PP screw cap.

The excipients are: heavy magnesium carbonate, maize starch, sodium lauryl sulphate, gelatine, magnesium stearate (E572), microcrystalline cellulose, talc.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The products are presented as a revised formulation of an already approved formulation. Details on the development of the former formulation are summarised. The products used in the bioequivalence study are acceptable. The choice for the dissolution method has been justified. Comparison of the dissolution profiles of test and reference product demonstrate that both product dissolve very fast. As the dissolution is very fast, a problem with bio-inequivalence is not expected.

Manufacturing process
The tablets are manufactured by a standard wet-granulation process. Adequate in-process controls have been set. Validation data have been provided for two full-scale granulation batches. The validation comprises the in-process controls with additional results of tests for sifting yields, blend uniformity and particle size distribution and content uniformity of the compressed tablets. Results of a third batch will be kept available for the authorities.

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, uniformity of dosage units (by content uniformity), disintegration time, identification of atenolol and magnesium and lauryl sulphate, resistance to crushing, friability, water content, subdivision of tablets, dissolution, assay, magnesium oxide content, related substances and microbial quality. Adequate description and validations have been provided. The limits for related substances are acceptable in view of the Ph Eur and British Pharmacopoeia monographs on atenolol tablets. Results of batch analysis have been provided on two batches of all three strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two batches of all three strengths manufactured from three full-scale granulation batches stored at 25°C/60% RH (24 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 HDPE bottles and blister packs. No changes were observed at both conditions. Photostability studies have demonstrated that the tablets are photostable.
In view of these results, the proposed shelf life of 3 years is acceptable. A storage condition is not required. Additional stability data covering the whole shelf life will be provided, and long term stability data for Atenolol in biological matrix for minimum 65 days will be established and submitted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A TSE Certificate of Suitability for gelatine has been provided. The magnesium stearate used is from vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Tenormin, 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 atenolol 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

Atenolol 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 Atenolol Accord 100 mg (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Tenormin 100 mg tablets (AstraZeneca, UK).

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, open label, randomised, two-period, two-treatment, two-way crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-45 years. All subjects were of the Indian Asian race. Each subject received a single dose (100 mg) of one of the 2 atenolol 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 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, and 36 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
All 28 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atenolol 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	6376 +/- 2142	6600 +/- 2144	697 +/- 262	3 (1-5)	6.23 +/-0.81
Reference	6087 +/- 2324	6300 +/- 2322	694 +/- 305	3 (1.5-5)	6.44 +/- 1.35
***Ratio (90%**	1.06	1.06	1.03		

CI)	(0.97-1.15)	(0.98-1.16)	(0.94-1.13)		
CV (%)	19	18	20		

$AUC_{0-\infty}$ 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 atenolol under fasted conditions, it can be concluded that Atenolol Accord 100 mg and Tenormin 100 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.

Food interaction
The oral bioavailability of atenolol is about 50 to 60%. The bioavailability is decreased by 20% when taken with food. Atenolol should be swallowed with a sufficient amount of fluid and before food intake. As this is adequately addressed in the SPC, 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 different strengths
The use of a biowaiver for the 25 and 50 mg tablets according the current guidelines has been sufficiently justified. The contents of the tablets are dose proportional. The results of the bioequivalence study performed with the 100 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
Atenolol was first approved in 1976, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of atenolol 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

SPC
The SPC is in accordance with the approved Dutch text for procedure NL/H/160-161/MR, concerning Atenolol Sandoz 50 mg and 100 mg tablets.

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. They were spread on age, sex and education quotas. Participants who had undertaken similar studies in the last six months were excluded as were healthcare professionals and other staff who routinely work with medicine information to avoid bias. Where possible participants who had previously taken the medication were also excluded except in the case of commonly prescribed medication such as antibiotics or analgesics.

There were 14 questions about the content and they address the key safety issues. Each question consisted of two parts: the first part investigates the ability to find and the second part investigates the ability to understand. For assessment of the layout and the content, seven assessment criteria focusing on clarity, fonts and paper, readability, language, completeness and appearance were lay down to the subjects. The respondents found the layout to be acceptable in general. For all items at least 70% scored acceptable or good. The use of a larger font was suggested by some subjects to make the patient information leaflet more patient friendly.

Results of the first round of testing were good. For all items at least 90% scored well on the diagnostic questions. Therefore no changes were made to the leaflet for the second test round. Results of the second round of testing confirmed the results of the first round. At least 90% of the participants scored well on the diagnostic questions. The results have shown that the information most relevant to the patient can be found (99.6%) and understood (98.9%) in a good way. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Atenolol Accord 25 mg, 50 mg and 100 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Tenormin 25 mg, 50 mg and 100 mg tablets. Tenormin 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 atenolol containing products.

The Board followed the advice of the assessors. Atenolol Accord 25 mg tablets were authorised in the Netherlands on 12 July 1999, and Atenolol Accord 50 and 100 mg tablets on 21 March 2000.

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 Atenolol Accord 25 mg, 50 mg and 100 mg tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 11 February 2010.

A European harmonised birth date has been allocated (19 February 1976) and subsequently the first data lock point for atenolol is February 2010. The first PSUR will cover the period to February 2010, after which the PSUR submission cycle is 3 years.

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

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

Quality - medicinal product

- The MAH committed to keep validation data of a third full-scale batch available for the authorities.
- The MAH committed to continue the stability studies at least up to the approved shelf life of 36 months, and data will be submitted upon completion of the stability studies.
- The MAH committed to establish and submit long term stability data for atenolol in biological matrix for minimum 65 days (total storage period of study samples).

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