

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

**Atenolol ESP Pharma 25 mg, 50 mg, 100 mg, film-coated tablets  
ESP Pharma Limited, 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/1733/001-003/DC  
Registration number in the Netherlands: RVG 105214, 105225-105226**

**15 November 2010**

Pharmacotherapeutic group:	beta blocking agents, selective
ATC code:	C07AB03
Route of administration:	oral
Therapeutic indication:	hypertension; chronic stable angina pectoris; supraventricular arrhythmias; ventricular arrhythmias; secondary prevention after acute myocardial infarction
Prescription status:	prescription only
Date of authorisation in NL:	4 November 2010
Concerned Member States:	Decentralised procedure with AT, CY, IE, IS, MT, NO, SE; 25 and 50 mg only – BG, LT; 50 and 100 mg only - IT
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 ESP Pharma 25 mg, 50 mg and 100 mg, film-coated tablets from ESP Pharma Limited. The date of authorisation was on 4 November 2010 in the Netherlands.

The product is indicated for:

- Hypertension
- Chronic stable angina pectoris
- 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.
- Secondary prevention after acute myocardial infarction.

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 or 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 hydrophilic 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 careful surveillance and check-up of the lung function, to patients with chronic obstructive pulmonary 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 decentralised 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). In IS, IT and LT one or more strengths of the innovator product are not authorised. Therefore, reference is made to the NL innovator as a European 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, an established active substance described in the European Pharmacopoeia (Ph.Eur.\*). Atenolol 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 drug substance specification is in line with the requirement of the CEP. The methods of the Ph.Eur. are applied. Additional requirements have been set for particle size, which are acceptable in view of the particle size distribution of the biobatch. Certificates of analysis have been provided that demonstrate compliance with the Ph.Eur. and the additional requirements.

#### Stability of drug substance

A retest period of 5 years is applicable 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

Atenolol ESP Pharma 25 mg is a white, round, biconvex film-coated tablet scored and with AI engraved on one side.

Atenolol ESP Pharma 50 mg is a white, round, biconvex film-coated tablet scored and with AH engraved on one side.

Atenolol ESP Pharma 100 mg is a white, round, biconvex film-coated tablet scored and with AJ engraved on one side.

The tablets can be divided into equal halves.

The film-coated tablets are packed in PVC/Aluminium blisters with push-through foil or HDPE tablet containers with HDPE cap or PP screw cap.

The excipients are:

*Tablet core* – microcrystalline cellulose Type 101 (E460), maize starch, crospovidone Type A (E1202), calcium hydrogen phosphate dehydrate (E341), colloidal anhydrous silica, magnesium stearate (E572), hydrogenated vegetable oil, sodium laurilsulfate.

*Film-coat* – titanium dioxide (E171), hypromellose 5cP, propylene glycol (E1520), talc (E553b).

The three strengths are dose-proportional and are all manufactured from the same blend.

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. A dose-proportional approach was used for the different strengths from 25 mg up to 100 mg. It was substantiated that polymorphism is not known for atenolol. A requirement has been set for particle size, which is acceptable in view of the particle size distribution of the biobatch. Subdivision of tablets is tested in accordance with the Ph.Eur.

The dissolution profile of the UK innovator product used in the bioequivalence study was compared to the NL innovator and innovator products from other member states, and deemed acceptable. Also, the dissolution profiles of the three strengths of the proposed products have been compared. These profiles are similar.

The pharmaceutical development has been sufficiently performed.

#### Manufacturing process

The product is manufactured through dry compression. The process is simple: all ingredients are sieved and blended together, followed by coating. The following in-process controls are performed: appearance, average weight, resistance to crushing, friability, uniformity of mass and disintegration. Validation data have been submitted of semi-full scale batches. This is sufficient because the manufacturing process concerns a standard process.

#### Control of excipients

All excipients are specified and controlled according to the European Pharmacopoeia, except for hydrogenated vegetable oil and industrial methylated spirit (component of Opaspray) which are specified and controlled according to the British Pharmacopoeia. These specifications are acceptable.

#### Quality control of drug product

The product specification includes tests for description identification, average mass, uniformity of dosage units, assay, dissolution, related substances (individual known) and microbiological quality.

Release and shelf-life specifications are the same for all parameters, except for assay content which is widened during shelf-life. This limit has been set in accordance with the BP monograph for Atenolol tablets and is considered acceptable. The analytical methods have been adequately described and validated. Analysis results have been included in tabulated form for one optimisation and two validation batches for each of the three strengths. The same parameters as proposed in the drug product specification have been tested for, with the exception of microbial testing. All results were found to be within limit. Results of batch analysis of the first industrial-scale batches will be provided when available.

#### Stability of drug product

A bracketing approach was followed whereby three batches of each of the 25 mg and 100 mg strengths have been subjected to stability studies. Twenty-four months results at 25°C/60%RH and six months results at 40°C/75%RH are available for two batches of each strength. The tablets were stored in PVC-Al blisters and polyethylene containers. No changes were observed. Photostability studies demonstrated that

the tablets are not sensitive to light. In view of these results, the proposed shelf life of 36 months is acceptable, without specific storage condition on temperature.

The MAH committed to complete the ongoing studies and to perform stability studies on the first three industrial batches per strength.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is produced from vegetable fatty acids.

## 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 ESP Pharma 100 mg (ESP Pharma Limited, 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, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-36 years. Each subject received a single dose (100 mg) of one of the 2 atenolol formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected within 1 hour before dosing and at 0.5, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.3, 3.7, 4, 4.5, 5, 6, 8, 12, 16, 24, 30 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*

Two subjects dropped out of the study: 1 subject was withdrawn due to vomiting during Period I, and 1 subject did not check in in Period II. Thirty-eight subjects completed the study and were included in the pharmacokinetic analysis.

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

Treatment N=38	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
Test	5983 $\pm$ 1807	6160 $\pm$ 1806	621 $\pm$ 213	3 (1.3-5)	6.4 $\pm$ 1.1
Reference	6144 $\pm$ 1750	6294 $\pm$ 1763	637 $\pm$ 201	3 (1.3-5)	7.0 $\pm$ 1.7
*Ratio (90% CI)	1.03 (0.95-1.11)	1.02 (0.95-1.10)	1.03 (0.95-1.13)	-	-
CV (%)	20	20	23	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> 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 ESP Pharma 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*

Atenolol kinetics were reported to be linear over the dose range. The results of the 100 mg study can thus be extrapolated to the 25 mg and the 50 mg strengths based on the following criteria:

- the products are manufactured by the same manufacturer and process;
- the qualitative composition of the different strengths is the same;
- the ratio between amounts of active substance and excipients is the same;
- the dissolution profiles are similar under identical conditions for the additional 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 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 SPC is in accordance with the approved text for procedures NL/H/160-161/MR and NL/H/1845/MR, concerning other atenolol generics.

#### 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 a pilot test carried out by three professionals, followed by two rounds with 10 participants each. The composition of the subject population is acceptable as far as age, gender and education are concerned. The range of subjects chosen was representative of the population that could imagine their need to use or supervise the use of this medication. Nineteen questions were prepared to test for findability, understandability and applicability. Seventeen questions related to the safe and effective use of atenolol.

A satisfactory test outcome is when 90% of the participants are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants. The results of testing met the study objectives. Therefore, the test was deemed to be successful and no amendments to the package leaflet were considered necessary. In addition to the questionnaire, there were seven questions at the end of the test in order to gain an opinion/feedback of the subject's interpretation of the full PIL. From the subject's answers to these questions and general comments, no adaptation of the package leaflet was deemed necessary.

The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections and the conclusions are clear, concise and clearly presented.

The readability test has been sufficiently performed.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Atenolol ESP Pharma 25 mg, 50 mg and 100 mg, film-coated 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.

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 Atenolol ESP Pharma 25 mg, 50 mg and 100 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 August 2010. Atenolol ESP Pharma 25 mg, 50 mg and 100 mg, film-coated tablets were authorised in the Netherlands on 4 November 2010.

A European harmonised birth date has been allocated (19 February 1976) and subsequently the first data lock point for atenolol is February 2013. The first PSUR will cover the period from August 2010 to February 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 October 2010.

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

#### Quality - medicinal product

- The MAH committed to perform validation on the first three production batches of each strength.
- The MAH committed to continue and complete the ongoing stability studies in support of the proposed shelf-life.
- The MAH committed to perform stability studies on the first three industrial batches per strength.



## 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 <sub>max</sub>	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 <sub>1/2</sub>	Half-life
t <sub>max</sub>	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