COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atenolol Xiromed 25 mg, 50 mg and 100 mg film-coated tablets (atenolol)

NL/H/5724/001-003/DC

Date: 13 February 2026

This module reflects the scientific discussion for the approval of Atenolol Xiromed 25 mg, 50 mg and 100 mg film-coated tablets. The procedure was finalised on 21 May 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atenolol Xiromed 25 mg, 50 mg and 100 mg film-coated tablets, from Medical Valley Invest AB.

The product is indicated for treatment of:

- Hypertension
- Chronic stable angina pectoris
- Secondary prevention after acute myocardial infarction.
- 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 unfavourable 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Tenormin 25, 50 and 100 mg filmomhulde tabletten (NL RVG 14374, 07294-07295) which has been registered in the Netherlands by AstraZeneca BV since 1977 (50/100 mg) and 1990 (25 mg). Since 31 December 2007, Tenormin is not registered anymore in the Netherlands.

The concerned member states (CMS) involved in this procedure were Denmark, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Atenolol Xiromed is a film-coated tablet. The three different strengths can be distinguished by their appearance, based on their size and debossing as follows:

Atenolol Xiromed 25 mg film-coated tablets
White to off white, circular 7.0 mm biconvex, film coated tablets with "25" debossed on one side and plain on the other side.
Each film-coated tablet contains as active substance 25 mg atenolol.

Atenolol Xiromed 50 mg film-coated tablets
White to off white, circular 8.5 mm, biconvex, film coated tablets with "50" debossed on one side and a breakline on the other side.
Each film-coated tablet contains as active substance 50 mg atenolol.

Atenolol Xiromed 100 mg film-coated tablets
White to off white, circular 11.0 mm, biconvex, film coated tablets with "100" debossed on one side and a breakline on the other side.
Each film-coated tablet contains as active substance 100 mg atenolol.

The excipients are:
Tablet core - heavy magnesium carbonate (E504), maize starch (E1403), sodium starch glycolate, colloidal anhydrous silica (E551), sodium laurilsulfate and magnesium stearate (E572).
Tablet coating - hypromellose (E464), macrogol, titanium dioxide (E171) and talc (E553b).

The three tablet strengths are dose proportional.

The film-coated tablets are packed in high-density polyethylene (HDPE) bottle covered with a screw caps consisting of Aluminum induction seal liner and screw cap with Rayon fibre.

II.2 Drug Substance

The active substance is atenolol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder sparingly soluble in water, soluble in anhydrous ethanol and slightly soluble in methylene chloride. Atenolol shows polymorphism. For this product, the same polymorphic form is consistently produced which remains stable in the drug product during shelf life.

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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

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 additional requirements of the respective CEP, with an additional in-house requirement for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for seven batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The choice of excipients is justified and their functions explained. The objective of the development programme was to formulate a generic formulation for atenolol tablets to match the physical parameters and in-vitro dissolution profile with the reference product Tenormin.

Manufacturing process
The main steps of the manufacturing process are dispensing of raw materials, sifting, dry mixing, granulation, drying, sifting and sizing, lubrication, compression, coating and packaging. There are two manufacturing sites. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 34 batches in total (three batches at minimum batch size for each strength, three or four batches at full scale per strength for both manufacturing sites and three batches for two additional batch sizes at site II) in accordance with the relevant European guidelines.

Control of excipients
The compendial excipients comply with Ph.Eur. requirements. These specifications are acceptable. The additional specification for in-house excipient dried maize starch is acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of atenolol and titanium dioxide, diameter, average weight, uniformity of dosage units, dissolution, related

substances, assay, water content and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three pilot scaled batches per strength and three full scaled batches of both manufacturing sites per strength have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for 9-11 production batches per strength from both manufacturing sites stored at 25°C/60% RH (24-48 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Results of a photostability study in accordance with ICHQ1B have been provided and demonstrate that the drug product is not sensitive to light. On basis of the data submitted, a shelf life was granted of three years. No specific storage conditions needed to be included in the SmPC or on the label.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atenolol Xiromed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Atenolol Xiromed is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Tenormin which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atenolol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one biowaiver and bioequivalence study, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atenolol Xiromed 25 mg, 50 mg and 100 mg film-coated tablets (Medical Valley Invest AB, Sweden) was compared with the pharmacokinetic profile of the reference product Tenormin 25, 50 and 100 mg filmomhulde tabletten (AstraZeneca GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. In support of the biowaiver for the 25 mg and 50 mg strengths, comparative dissolution data have been provided in 3 pHs (0.1N HCl, pH 4.6 (QC medium) and pH 6.8) versus the 100 mg bioequivalence study test batch. Conditions of the in vitro dissolution test were in line with the guideline and in all media >85% dissolution in 15 minutes was reached and therefore the dissolution profiles are considered similar. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The MAH requested a waiver for bioequivalence studies with the additional 50 mg and 25 mg strengths. The following justification has been provided:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths,
d. appropriate *in vitro* dissolution data is generated to confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Design

A single-dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-44 years. Each subject received a single dose (100 mg) of one of the two atenolol formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of seven 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, 7, 8, 10, 12, 24 and 36 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject was dropped-out from the study in period II due to a personal reason. Of the 28 subjects enrolled in the study, 27 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atenolol, 100 mg under fasted conditions.

Treatment N=27	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	6822 ± 2008	7002 ± 1995	769 ± 215	3.0 (1.0 - 4.5)
Reference	7190 ± 1824	7362 ± 1837	825 ± 187	3.5 (1.5 - 5.5)
***Ratio (90% CI)**	0.94 (0.85 – 1.03)	0.94 (0.86 – 1.03)	0.92 (0.83 – 1.02)	-

$AUC_{0-\infty}$	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 t = 36 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Atenolol Xiromed 100 mg is considered bioequivalent with Tenormin, 100 mg.

The results of the bioequivalence study with the 100 mg formulation can be extrapolated to the lower strengths of 25 mg and 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Atenolol Xiromed. At the time of approval, the most recent version of the RMP was version 0.2 dated 14 Augustus 2023.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tenormin. The MAH demonstrated through a biowaiver and a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atenolol Xiromed 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Tenormin 25, 50 and 100 mg filmomhulde tabletten. 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 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 Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 May 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5724/001-003/IB/001	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan - Other variation.	No	17-10-2024	Approved	N.A.
NL/H/5724/IB/002/G	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation	Yes	9-1-2025	Approved	N.A.