CBG MEB

Public Assessment Report

Scientific discussion

Dipperam, 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets

(amlodipine besilate/valsartan)

NL/H/3800/001-003/DC

Date: 21 December 2017

This module reflects the scientific discussion for the approval of Dipperam, 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets. The procedure was finalised on 13 July 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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
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 Dipperam, 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets, from Sandoz B.V.

The product is indicated for treatment of essential hypertension.

Dipperam is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Exforge which has been registered in the EEA by Novartis Europharm Limited since 19 January 2007 through centralised procedure EMEA/H/C/000716. The MAH included a statement of identity declaring that Dipperam film-coated tablets are qualitatively and quantitatively identical to Exforge film-coated tablets.

The concerned member states (CMS) involved in this procedure were Bulgaria, Estonia, Lithuania, Latvia, Poland, Romania and Slovenia.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dipperam is a film-coated tablet in three strengths:
5 mg/80 mg - dark yellow, round film-coated tablet with beveled edges, debossed with “NVR” on one side and “NV” on the other side.
5 mg/160 mg - dark yellow, ovaloid film-coated tablet with beveled edges, debossed with “NVR” on one side and “ECE” on the other side.
10 mg/160 mg - light yellow, ovaloid film-coated tablet with beveled edges, debossed with “NVR” on one side and “UIC” on the other side.

Each film-coated tablet contains two active substances: 5 mg or 10 mg of amlodipine, as 6.9 mg or 13.9 mg of amlodipine besilate, and 80 mg or 160 mg valsartan.

The film-coated tablets are packed in PVC/PVDC blisters or PVC/PVDC perforated unit dose blisters.

The excipients are:
Tablet core – cellulose microcrystalline, crospovidone, colloidal anhydrous silica and magnesium stearate.
Tablet coating – hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) (only for 10 mg/160 mg tablets), macrogol 4000 and talc.

The strengths are dose proportional.

II.2 Drug Substances

Amlodipine besilate
The active substance is amlodipine besilate, an established drug substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to almost white powder and is slightly soluble in water and sparingly soluble in ethanol. Amlodipine besilate exhibits pseudo polymorphism and exists as anhydrous, monohydrate and dehydrated crystalline forms. It is manufactured as the anhydrous

crystalline form. Amlodipine besilate has one chiral carbon center and exists as a racemic mixture with pKa 6.2.

Two CEP procedures are 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
CEPs have 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 is in accordance with the Ph.Eur. and the CEPs, and contains additional requirements for particle size distribution, clarity and colour of the solution, identification, alkyl benzene sulphonates, residual solvents, heavy metals, and microbial enumeration. 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 were provided for three batches of each CEP holder.

Stability of drug substance
The active substance is stable for 60 months (manufacturer-I) or 36 months (manufacturer-II) when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Valsartan
The active substance is valsartan, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to practically white powder and is practically insoluble in water.. Valsartan is produced as a predominantly amorphous form and corresponds to the (S)-enantiomer. The drug substance is hygroscopic and practically insoluble in water.

Manufacturing process
Valsartan is manufactured in seven steps. The manufacturing process was adequately described. The active substance was adequately characterised and acceptable specifications were adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and specification is in line with the Ph.Eur. with additional requirements for absorbance and clarity of the solution, particle size, residual solvents, and microbiological contamination. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with this specification have been provided for 10 commercial scale batches covering all manufacturing sites.

Stability of drug substance
Stability data on the active substance were provided for three commercial scale batches of each manufacturing site produced according to the most recent manufacturing process and of additional historical batches stored at fill in 25°C/60% RH (36 months) and 40°C/75% RH (6 months). On the basis of the provided stability data, the claimed retest period of 36 months is justified. No specific storage conditions are needed.

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 production process has been adequately described. The release specifications and in-process controls guarantee good control of the products.

The Dipperam products are identical to the Exforge reference products. The core formulations of Dipperam are weight and dose proportional. The manufacturing process for all strengths is identical, and the dissolution profiles are similar. The development of the routine dissolution method was adequately explained.

Manufacturing process
The manufacturing process involves dry blending, roller compaction, compression, and film-coating. It is considered to be a standard process. The manufacturing process was adequately described and validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial batches of each strength of the first manufacturer and three commercial batches of the 5 mg/80 mg and 5 mg/160 mg strength of the second manufacturer.

Control of excipients
Except for the iron oxides present in the film-coating premixes, the excipients and individual components of the film-coating materials comply with the Ph.Eur. The red and yellow iron oxides are in compliance with the National Formulary (NF) and EU Regulation 95/45/EC. These specifications are 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 the drug substances and colourants, mean mass, dissolution, degradation products, microbial enumeration, uniformity of dosage units, and assay. The release and shelf life specifications are identical and they are acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data on three commercial scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product was provided for three commercial scale batches per strength of each manufacturer stored at 25°C/60% RH (36 months), 30°C/65% RH (36 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 blisters. The product is photostable.
On the basis of the provided stability data, the claimed shelf life of 36 months and storage conditions “Do not store above 30°C. Store in the original package in order to protect from moisture.” are justified.

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

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Exforge which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Amlodipine besilate and valsartan are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver
The MAH of the reference product has submitted an identity statement that the products under review here, Dipperam, and the reference (innovator) product Exforge are identical. Hence Dipperam is produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance as their currently manufactured reference product.
As the member states have been ensured that Dipperam film-coated tablets are identical to the reference product Exforge, a biowaiver has been granted.

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 Dipperam.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hyperkalaemia • Hypotension • Decreased renal function • Fetotoxicity (with use in 2nd or 3rd trimester of pregnancy)
Important potential risks	• Teratogenicity (with use during 1st trimester of pregnancy)
Missing information	• Use during breast feeding

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 Exforge film-coated tablets. No new clinical studies were conducted. The MAH of the reference product demonstrated through an identity statement that the Dipperam is identical to the reference product. Therefore bioequivalence testing is not required. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH did not perform a readability test. Reference is made to the user test of the leaflet of Exforge which has been assessed and approved by respective authorities. Readability is further assured by applying the Sandoz layout for which user friendliness has been shown in several previously performed user-tests. The MAH provided a comparison of the technical specifications of the leaflet mock-up of Dipperam and the leaflet mock-up of Irbesartan/Hydrochlorothiazide Sandoz 300 mg/25 mg, film-coated tablets (NL License RVG 103788) that was subjected to user testing. This showed that the layout of both leaflets is identical.
The package leaflet (PL) meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dipperam, 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets have a proven chemical-pharmaceutical quality and is a generic form of Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets. Exforge is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH did not submit a bioequivalence study, but provided sufficient information to demonstrate that the product has the same quantitative and qualitative composition as Exforge and is produced in the same manufacturing sites.

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 Dipperam with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 July 2017.

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