CBG MEB

Public Assessment Report

Scientific discussion

Bosenwel 62.5 mg and 125 mg, film-coated tablets

(bosentan monohydrate)

NL/H/3422/001-002/DC

Date: 24 January 2017

This module reflects the scientific discussion for the approval of Bosenwel 62.5 mg and 125 mg, film-coated tablets. The procedure was finalised on 13 March 2016. 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
BP	British Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bosenwel 62.5 mg and 125 mg, film-coated tablets from Welding GmbH & Co. KG.

The product is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:

- Primary (idiopathic and heritable) pulmonary arterial hypertension (PAH)
- PAH secondary to scleroderma without significant interstitial pulmonary disease
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology

Some improvements have also been shown in patients with pulmonary arterial hypertension WHO functional class II.
Bosenwel is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

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 Tracleer 62.5 mg and 125 mg, film-coated tablets which has been registered in Europe by Actelion Registration Limited since 15 May 2002 through a centralised procedure (EU/1/02/220/001-005).

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Bosenwel 62.5 mg is a light orange, round, biconvex film-coated containing 62.5 mg bosentan, as 64.541 mg bosentan monohydrate.
Bosenwel 125 mg is a light orange, oval, biconvex film-coated containing 125 mg bosentan, as 129.082 mg bosentan monohydrate.

The film-coated tablet is packed in Opaque PVC/PVDC–Aluminium foil blister packs.

The excipients are:
Tablet core - maize starch, pregelatinised maize starch, sodium starch glycollate (Type A), povidone K 30, poloxamer 188, colloidal anhydrous silica, glycerol dibehenate and magnesium stearate.
Film coating - Opadry Orange 21K23007 (containing hypromellose, titanium dioxide (E171), ethylcellulose, triacetin, talc, yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172)).

The composition of the two strengths is dose proportional.

II.2 Drug Substance

The active substance is bosentan monohydrate, an established active substance not described in any pharmacopoeia. The active substance is a white to yellowish coloured powder, which is practically insoluble in water in the pH range 1.2 – 8.0. Bosentan exhibits polymorphism and both manufacturers deliver the material as the monohydrate crystalline form. Bosentan does not contain any chiral centre and hence does not exhibit optical isomerism.

For both manufacturers, 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 manufacturers 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
The manufacturing process consists of 3 or 4 steps and a final purification by crystallisation. No class I or heavy metal catalysts are used in both manufacturing processes. Acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 6 (manufacturer-I) and 5 batches (manufacturer-II).

Stability of drug substance
Stability data on the active substance from manufacturer-I have been provided for 4 full scaled batches, stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The stability data support a 3 year retest period when stored in a well-closed container below 30°C; excursions permitted up to 40°C (up to 6 months).

Stability data on the active substance from manufacturer-II have been provided for 6 pilot and full scaled batches, stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months), and 40°C/75% RH (6 months). Storage under long-term and accelerated conditions did not show any up or downward trends throughout the test period. Therefore, the claimed retest period of 3 years (manufacturer-II) is considered acceptable.

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. Due to high drug content it was decided to select wet granulation process as the primary manufacturing process of choice. Several development batches were prepared where the composition was changed. Based on the development batch with the optimal properties the formula for the registration batches was selected. The two strengths are directly proportional.

A bioequivalence study has been conducted with the higher strength only. Comparative dissolution studies with and without sodium dodecyl sulphate (SLS) have been performed for the test and reference bio-batches. The generic and originator products behave in a similar way. The 62.5 mg generic batch and the 125 mg test bio-batch have similar dissolution profiles in the pH buffer media (pH 1.0, 4.5 and 6.8 with and without SLS).

Manufacturing process
The main steps of the manufacturing process are wet granulation, drying, blending compression and coating. The process has been adequately validated according to relevant European guidelines and uses conventional manufacturing techniques. Process validation has been provided on 3 pilot scale batches of each strength.

Control of excipients
The excipients, except for the coating system, comply with various Pharmacopoeia. These specifications and the in-house specification of the coating system 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, mean tablet weight, water, hardness,

disintegration, dissolution, assay, impurity assay, and microbiological purity tested at release and shelf-life. In addition, identity, weight uniformity, dimensions, uniformity of dosage units, and ethyl alcohol are tested at release and blister leakage at shelf-life. 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 from 4 batches per strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for 3 full scaled batches for each strength, stored at 25°C/60% RH (24 months), 30°C/65% RH (12 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 the proposed packaging. A slight increase in water content was observed at all conditions. All other parameters tested remained relatively stable throughout the test periods at all test conditions and within specification limits. The tablets are not sensitive to light. Based on the stability data provided a shelf life of 36 months can be granted. The medicinal product does not require any special storage conditions.

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 Bosenwel 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 Bosenwel 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 Tracleer 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

Bosentan is a well-known active substance 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.

For this generic application, the MAH has submitted two bioequivalence studies with the bosentan 125 mg tablet, and for the 62.5 mg strength a biowaiver was claimed.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Bosenwel 125 mg, film-coated tablets (Welding GmbH & Co. KG., Germany) is compared with the pharmacokinetic profile of the reference product Tracleer 125 mg, film-coated tablets (Actelion Registration Ltd., UK).

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver was granted for the 62.5 mg product, based on the bioequivalence study conducted on the 125 mg strength. Both batches comply with the general biowaiver criteria:

- the pharmaceutical products are manufactured by the same manufacturing process
- the qualitative composition of the different strengths is the same
- the composition of the Bosenwel 62.5 and 125 mg film-coated tablets are quantitatively proportional, the ratio between the amount of each excipient to the amount of active substance is the same for both strengths
- comparable dissolution between Bosenwel 62.5 mg and 125 mg film-coated tablets has been shown in appropriate media (pH 1.2, 4.5 and 6.8)

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.

Bioequivalence studies

Pivotal bioequivalence study I – Bosenwel 125 mg, film-coated tablets vs Tracleer 125 mg, film-coated tablets
Design
A randomised, single-dose, four-period, two-sequence, replicate, crossover comparative bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-55 years. Each subject received a single dose (125 mg) of one of the 2 bosentan formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 4 dosing periods, separated by a washout period of 7 days. The order of investigational product administration was sequentially assigned from a computer-generated randomisation list.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 8, 10, 12, 24 hours after administration of the products.

The design of the study is acceptable. Bosentan may be taken regardless of food. Thus, studies using fasting conditions are appropriate as this is considered to be the most sensitive condition to detect a potential difference between formulations. The study was performed using a full replicate design, which allows the bioequivalence acceptance interval for C_{max}, to be widened.

Results
Four subjects discontinued the study; two due to a positive urine drug screen test result, one for personal reasons related to clinical events and the other for personal reasons not related to clinical events. 37 subjects had sufficient evaluable data to be included in the pharmacokinetic analysis.

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

Treatment N=37	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	6692.99	1332.59	3.75
Reference	7114.25	1448.64	3.75
***Ratio (90% CI)**	0.94 (0.89 – 1.00)	0.92 (0.84 – 1.01)	--
CV (%)	21.5	34.4	--

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
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
Widening of the acceptance intervals, based on the study results, was proved not to be necessary. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Bosenwel 125 mg, film-coated tablets is considered bioequivalent with Tracleer 125 mg, film-coated tablets.

The MEB has been assured that study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC).

Bioequivalence study II – Bosenwel 125 mg, film-coated tablets vs Tracleer 125 mg, film-coated tablets
The second bioequivalence study is regarded supportive, as it was not (completely) assessed due to the GCP-non-compliance problems of the Clinical Research Organisation (CRO).
It was a randomised, open label, balanced, two-treatment, two-sequence, four-period, single-dose, crossover, replicate bioequivalence study, carried out under fasted conditions in 40 healthy adult subjects. 38 subjects completed the study. The results of this supportive study are in agreement with the results of the first bioequivalence study. Hence the 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25.

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 Bosenwel.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Teratogenicity • Hepatotoxicity • Decrease in haemoglobin concentration • Decrease of sperm count
Important potential risks	• Pulmonary oedema associated with PVOD • Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals) • Testicular disorders and male infertility • Respiratory tract infection in children
Missing information	• Use in children with renal impairment • Use of bosentan with addition of sildenafil

Additional risk minimisation measures are required as the conditions required for the reference product Tracleer also apply for the present generic product. All health care professionals who intend to prescribe and/or dispense Bosenwel are provided with a Prescriber Kit containing the following:

- Information about Bosenwel
- Patient Information Booklet
- Patient Alert Card

The information provided about the product and the Patient Information Booklet/Patient Alert Card shall contain the key elements as described for the reference product, which provide detailed information about the identified significant risks.

The MAH will agree the details of a controlled distribution system with the National Competent Authorities to ensure health care professionals obtain the kit. The implementation of the additional measures will be agreed at a national level in each of the member states.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tracleer. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the content of the PL of Tracleer. The bridging report submitted by the MAH has been found acceptable.

A user consultation study was done for Bosenwel 62.5 mg film-coated tablets, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC to evaluate the design of the PL of Bosenwel. Hence the PL of Bosenwel 62.5 mg, film-coated tablets is equal in design to the PL of Bosenwel 62.5 mg film-coated tablets. The test consisted of a pilot test with 2 participants, followed by 2 rounds with 10 participants each. The 15 questions covered key safety issues and additionally 4 questions were asked concerning lay out/design. No weaknesses of the PL were identified. The success criteria are met and the test is acceptable regarding the contents of the PL. 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

Bosenwel 62.5 mg and 125 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Tracleer 62.5 mg and 125 mg, film-coated tablets. Tracleer 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 Bosenwel with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 March 2016.

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
Implementation of wording agreed by the competent authority	NL/H/3422/ 001-002/IA/001	IA	8-12-2016	7-1-2017	Approval	No
Name change	NL/H/3422/ 001-002/IB/002/ G	IB	15-12-2016	19-12-2016	Approval	No
Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient	NL/H/3422/ 001-002/IB/003	IB	20-12-2016	19-1-2017	Approval	No