IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Bonasol Once Weekly 70 mg Oral Solution
Alendronic acid
PA1572/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This module reflects the scientific discussion for the approval of Bonasol Once Weekly 70 mg Oral solution. The procedure was finalised at 30th August 2010. For information on changes after this date please refer to the module 'Update'.

II. QUALITY ASPECTS

II.1 Introduction

The application is for Alendronic Acid (Bonasol) Once weekly 70 mg Oral Solution submitted as a decentralised application in accordance with article 28(3) of Directive 2001/83/EC, as amended and the legal basis is an Article 10(3) hybrid application. The drug product is formulated as an oral solution and is indicated for treatment of postmenopausal osteoporosis. The recommended dosage is 70 mg (the contents of one single-dose container) once weekly.

II.2 2.2 Drug Substance

The drug substance, alendronate sodium, is well established active substance and it is described in the European Pharmacopoeia (Ph.Eur.), monograph 1564. The Active Substance Master File (ASMF) procedure is followed for the drug substance.

Synthesis of the drug substance has been satisfactorily described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient.

The active substance specification is considered adequate to control the quality and meets the current requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

II.3 Medicinal Product

II.3.1 Composition

Alendronic Acid (Bonasol) Once weekly 70 mg Oral Solution is an orange flavoured opalescent solution presented in a single-dose 100 ml container. Each 100 ml single-dose container contains 70 mg alendronic acid present as sodium alendronate. The excipients are Xanthan Gum, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Sodium cyclamate, Sucralose, Sunset Yellow (E110), Orange flavour (containing ethanol and butylated hydroxyanisole)and Purified Water.

II.3.2 Pharmaceutical Development

The primary objective of the development programme was to develop an alternative dosage form of Alendronic Acid/Sodium Alendronate to the reference product, Fosamax 70mg tablets, that would be suitable for patients that are unable to take tablets or would prefer a liquid dosage form. The applicant has submitted a very detailed formulation development and the development of Alendronic Acid 70mg Oral Solution was informed by pharmacokinetic/biopharmaceutical, pharmaceutical and pharmacological/safety considerations.

The pharmaceutical development is adequately described in accordance with the relevant European guidelines. The manufacturing process has been scaled-up to production scale and bioavailability testing has confirmed that the product is bioequivalent to the reference tablet product. Use of the excipients is justified.

II.3.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) using conventional manufacturing techniques. A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for the manufacture of the product. In-process controls are appropriate considering the nature of the product and the method of manufacture. The manufacturing process is considered adequately validated.

II.3.4 Control of Excipients

The excipients are well known pharmaceutical excipients and their specifications are satisfactory. There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product.

II.3.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form.
The release specifications for the drug product are based on the Ph. Eur. monograph for Alendronate
Sodium and the standard requirements associated with solutions for oral use. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory description and validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

The product is packaged in polyethylene terephthalate (PET) bottle fitted with a Low Density Polyethylene (LDPE) lined tamper-proof closure.
Satisfactory specifications and certificates of analysis have been provided for all packaging
Components confirming compliance with directives 2002/72/EC (bottle) and 2007/19/EC (liners and caps) concerning food safety and migration limits and European Pharmacopoeia monographs on
polyolefines (3.1.3) and polyethylenes with additives (3.1.5).

II.3.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC).

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality ofBonasol Once Weekly 70 mg Oral Solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Alendronic acid (Alendronate) is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption. Alendronic acid has been approved and marketed as a medicinal product in the EU since 1993. Alendronate is an established active substance and the non-clinical pharmacodynamic, pharmacokinetic and toxicology aspects have been extensively evaluated and are supported by the widespread and long-term clinical experience. Thus, the non-clinical evaluation for this product was based on the literature data and data from the Summary of Product Characteristics of the originator, Fosavance® 70mg Tablets, approved in Europe and the 2005 EMEA review of Alendronic Acid as a component of Fosavance® .
As the product relates to a new galenical form of an active substance that has been shown to have a potential to cause local irritation to the upper gastrointestinal mucosa, a six-month local tolerance study in rabbits was performed relevant to the liquid oral solution formulation.

III.2 Pharmacology

The pharmacology of Alendronic Acid has been well established and is extensively reviewed in the literature. No additional pharmacology studies with Alendronic Acid 70 mg Oral Solution were performed by the applicant.

III.3 Pharmacokinetics

The pharmacokentics of Alendronic Acid has been well established and is extensively reviewed int eh literature. No additional pharmacokinetic studies with Alendronic Acid 70 mg Oral Solution were performed by the applicant.

III.4 Toxicology

In animal studies, alendronate has been reported to cause local irritation to the upper gastrointestinal mucosa at high concentrations, high dosages and/or frequent administration. It is considered that these irritations arise due to the disintegration characteristics of oral solid dosage forms that have the potential to adhere to oesophageal or gastric mucosal surfaces thereby potentiating oesophageal reflux of a tablet or tablet fragment. These studies have led to a change in oral dosing frequency from daily to once weekly for the reference tablet product.

By ensuring that alendronate is only ever present as a 100% solution at dilute concentration, with a once weekly dosing frequency, the nonclinical data suggests that the oral solution formulation can be expected to eliminate the potential for certain adverse effects relating to focalized high local concentrations.
In support of this rationale, the applicant has performed a six-month local tolerance study in rabbits relevant to the new galenical form (liquid oral solution) of an active substance. At the doses and administration schedules used in this study, no clinical signs were observed that were indicative of any systemic or local toxicity in the gastrointestinal mucosa and that could be attributed to the treatment with either bisphosphonate at doses corresponding to 1X and 3X the equivalent human alendronic acid dose.

III.5 Ecotoxicity/environmental risk assessment
No separate environmental risk assessment has been performed by the applicant with Alendronic Acid 70 mg Oral Solution as it is a generic product whose introduction on the market will not cause any significant increase in environmental exposure to the drug substance.

III.6 Discussion on the non-clinical aspects
The applicant is claiming that Alendronic Acid oral solution is bioequivalent to Fosamax 70mg reference tablets, and has provided a bioequivalence study to demonstrate this.
Overall, the non-clinical studies which includes a specific long-term tolerability study supports the rationale that Alendronic Acid 70 mg Oral Solution will be well tolerated and will potentially have a similar safety profile to that of the reference tablet product.

IV. CLINICAL ASPECTS

IV.1 Introduction
Alendronate is a well known bisphosphonate used in the treatment of post menopausal osteoporosis.
This application is a generic application in which the applicant has demonstrated that their product is bioequivalent (produces similar levels of the drug in the body) and so, a full dossier is not required.

IV.2 Pharmacokinetics
The applicant commissioned "A Randomised, Two-way Crossover, Single Dose, Bioequivalence Study of Alendronic Acid 70mg Oral Solution and Alendronic Acid 70mg (Fosamax®) Tablets in Healthy Male Subjects under Fasted Conditions".
This was a single site, single dose, oral administration, fasting condition, open, randomised, two-period, two-way cross-over design with a washout period of 14 days between the two administrations of the study products (Period 1 and Period 2) with urine collection up to 36 hours post dose. The main purpose of the study was to confirm that the formulation ingredients of the new dosage form did not affect the bioavailability of the active substance.
Bioequivalence in relation to the extent of alendronate absorption was concluded based on the results were within the acceptance limits of 80% to 125%.

IV.3 Pharmacodynamics
N/A

IV.4 Clinical efficacy
This product should have efficacy which is similar to the reference product.

IV.5 Clinical safety
This product should be as safe as the reference product.

IV.6 Discussion on the clinical aspects
As an "abridged application", this application avoids the need for repetitive tests on animals and humans by showing that administration of this product is associated with similar levels in the body as those seen after administration of the product it is being compared to, the reference medicinal product. For these applications the demonstration of similar levels through bioequivalence studies is essential.

IV.7 Pharmacovigilance System
The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

IV.8 Risk Management Plan

The Applicant submitted a risk management plan in 2014 under the renewal procedure IE/H/213/001/R/001, 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 Bonasol. The RMP (version 3.0, date of final sign-off, 17/10/2016) is acceptable. Routine pharmacovigilance and routine risk minimisation are considered sufficient. The Applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity • Oesophageal reactions • Osteonecrosis of the jaw • Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Important potential risks	• Use in patients with renal impairment (GFR less than 35ml/min) • Alcohol content (0.15% volume ethanol) may potentially present a trigger effect to alcoholics and in very rare cases may be a risk to those with liver disease or epilepsy • Patients with untreated hypocalcaemia or other untreated disorders affecting mineral metabolism may be adversely affected. • Gastrointestinal irritation due to concomitant NSAID use. • Oesophageal irritation following overdose • Risk of atypical femur fracture with long term use
Missing information	• Use in children and adolescents • Pregnancy and lactation

IV.9 Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

V. OVERALL CONCLUSIONS

As bioequivalence has been shown, benefit risk for this product is considered to be the same as the reference product, and therefore positive.

VI. REVISION DATE

March 2019

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
Update section 4.2, 4.4 and 4.8 of the SPC	IE/H/213/001/1A/006	SmPC/PL update	06/12/2011	06/01/2012
Renewal	IE/H/213/001/R/001	Risk Management Plan submitted	23/04/2014	09/04/2015
Update section 4.2, 4.4, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 & 6.6 of the SPC	IE/H/213/1/1B/014	SmPC/PL update	11/05/2015	23/09/2015
Changes to the SPC sections 4.4 & 4.8	IE/H/0213/001/1A/018	SmPC/PL update	17/05/2016	21/06/2016