COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Bosutinib Newbury 100 mg, 400 mg and 500 mg film-coated tablets (bosutinib monohydrate)

## NL/H/6001/001-003/DC

## Date: 15 August 2025

**This module reflects the scientific discussion for the approval of Bosutinib Newbury 100 mg, 400 mg and 500 mg film-coated tablets. The procedure was finalised on 14 January 2025. 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 |
| CP | Chronic Phase |
| 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 |
| Ph+CML | Philadelphia chromosome-positive chronic myelogenous leukaemia |
| 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 Bosutinib Newbury 100 mg, 400 mg and 500 mg film-coated tablets, from Newbury Pharmaceuticals AB.

The product is indicated for the treatment of adult patients with:

- newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+CML).
- CP, accelerated phase (AP), and blast phase (BP) Ph+CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

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 Bosulif 100 mg, 400 mg and 500 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/13/818/001-007) since 27 March 2013 by Pfizer Europe MA EEIG, Belgium.

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

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Bosulif and Scemblix from Novartis Europharm Limited, which obtained orphan market exclusivity on 25 August 2022, based on designation EU/3/20/2261 The assessment included the comparison of the therapeutic indication, mechanism of action and principal (molecular) structure. The similarity assessment report was completed in March 2024, concluding that the two products were not similar on the three aspects mentioned above and that the existence of any market exclusivity for Scemblix (asciminib) in the treatment of chronic myeloid leukaemia, does not prevent the granting of the marketing authorisation of Bosutinib film-coated tablets. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

# II. QUALITY ASPECTS

## II.1 Introduction

Bosutinib Newbury is available in three strengths. The different strengths can be distinguish by debossing, colour and size as follow:

Bosutinib Newbury 100 mg is a light orange to orange, oval (width: approximately 6 mm; length: approximately 11 mm) biconvex, film-coated tablet debossed with "721" on one side and plain on the other side. The tablet contains as active substance bosutinib monohydrate equivalent to 100 mg bosutinib.

Bosutinib Newbury 400 mg is a light orange to orange, oval (width: approximately 9 mm; length: approximately 17 mm) biconvex, film-coated tablet debossed with "722" on one side and plain on the other side. The tablet contains as active substance bosutinib monohydrate equivalent to 400 mg bosutinib.

Bosutinib Newbury 500 mg is a light red to red, oval (width: approximately 9 mm; length: approximately 18 mm) biconvex, film-coated tablet debossed with "723" on one side and plain on the other side. The tablet contains as active substance bosutinib monohydrate equivalent to 500 mg bosutinib.

The excipients are:
*Tablet core:* microcrystalline cellulose (E460), croscarmellose sodium (E468), poloxamer 188, povidone K25 (E1201), colloidal anhydrous silica (E551), talc (E553b) and magnesium stearate (E470b).
*Film-coating:* poly (vinyl alcohol) (E1203), macrogol 3350, titanium dioxide (E171), talc (E553b), iron oxide yellow (E172) and iron oxide red (E172).

The three different strengths are fully dose proportional.

The film-coated tablets are packed in polyvinylchloride/polychlorotrifluoroethylene (PVC/PCTFE) (ACLAR)– aluminium blisters.

## II.2 Drug Substance

The active substance is bosutinib monohydrate, an established active substance not described in the European Pharmacopoeia (Eur.Ph.). The active substance is a white to yellowish tan powder and is freely soluble in dimethyl sulfoxide (DMSO), practically insoluble in water. Bosutinib monohydrate is consistently manufactured as one polymorphic form and does not have any chiral centre, hence does not exhibit stereoisomerism. The polymorphic form is controlled in the active substance specification.

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

manufacturer 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 is described in two parts. There are four starting material and five intermediates. No class 1 organic solvents are used in the process. Specifications adopted for the starting materials, solvents and reagents are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of in-house specifications by the MAH and is largely in line with the specification from the active substance manufacturer, with additional requirements for particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. The test for solubility is removed from the specification by the drug product manufacturer. Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 18 months when stored under the stated conditions.

## 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. During development the reference product was characterised. Impact of particle size distribution of the active substance on dissolution of the drug product was studied. Wet granulation was chosen for the manufacturing of the drug product, based on the high percentage of the BCS class IV active substance. Four formulation studies were conducted to optimize the formulation. Comparative *in-vitro* dissolution profiles complementary to the BE studies have been performed. The discriminatory power of the QC dissolution method has been demonstrated. Overall, the pharmaceutical development of the drug product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are pre-blending, wet granulation, drying, milling, (final) blending, compression, coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three minimum commercial scale batches for each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients, except for the in-house coating mixtures, comply with Ph.Eur. requirements. These specifications are acceptable. Acceptable in-house specifications are provided for the ready-to-use coating mixtures. The colourants comply with EU) No. 231/2012.

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 description, identification, water content, assay, uniformity of dosage units, degradation products, dissolution and microbial limits. The release and shelf-life requirements are identical, except for water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamine risk assessment has been performed to justify absence of nitrosamine control in the drug product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three production scale batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from three production scaled batches per strength stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months) in accordance with applicable ICH/European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product stable when exposed to light. A small increase in water content was observed for the drug product in blister packaging under long term and accelerated conditions. No trends or changes were seen in any of the other tested parameters and all results were in compliance with the shelf-life specification. On basis of the data submitted, a shelf life was granted of 30 months. 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 Bosutinib Newbury 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 Bosutinib Newbury 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 Bosulif 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

Bosutinib Newbury 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 two bioequivalence studies, which are discussed below.

## IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Bosutinib 100 mg and 500 mg film-coated tablets (Newbury Pharmaceuticals AB, Malta) was compared with the pharmacokinetic profile of the reference product Bosulif 100 mg and 500 mg film-coated tablets (Pfizer Europe MA EEIG, Belgium) respectively. For the 400 mg tablets, a biowaiver of strengths is claimed.

Biowaiver

For the 400 mg tablets, a biowaiver of strengths is claimed. The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

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(s) is the same for all

strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study (pH 1.2, 4.6 and 6.8) results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. The dissolution was investigated according to the EMA Bioequivalence guideline. *In-vitro* dissolution similarity could not be demonstrated in all tested media. However, as the guideline states, since bioequivalence has been demonstrated *in-vivo* for both the 500 mg and 100 mg strength, these results prevail and test and reference product are considered bioequivalent. Regarding the biowaiver, the 500 mg and 400 mg test products are qualitatively the same and quantitatively proportional and are manufactured according to the same manufacturing process and thus fulfil the respective general biowaiver criteria for an additional strength. Since bioequivalence with the 500 mg reference has been demonstrated *in-vivo*, these results prevail over the *in-vitro* data and the biowaiver for the lower 400 mg strength is granted.

Bioequivalence studies

**Study 1: bosutinib 500 mg under fed conditions**

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fed conditions in healthy male (135) and female (21) subjects, aged 18-55 years. Each subject received a single dose (500 mg) of one of the two bosutinib formulations. In each period, following an overnight fast of at least 10 hours subjects were provided a high calorie and high fat breakfast of ≥ 800 Kcal at exactly 30 minutes prior to drug administration. The subjects consumed the high calorie and high fat breakfast within 30 minutes. The tablet was orally administered with 240 mL water. Food was restricted until at least 04 hours post-dose. There were two dosing periods, separated by a washout period of 15 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 7.5, 8, 10, 12, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

*Results*

156 subjects enrolled in the study. Two subjects withdrew before period I due to personal reasons. One subject withdrew in period I before dossing due to a medical event (not related to the study). One subject was withdrawn during period I because the subject did not consume the high calorie high fat breakfast. All withdrawn subjects were replaced with additional subjects. 156 subjects completed the study and were eligible for pharmacokinetic analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of bosutinib, 500 mg under fed conditions.**

| Treatment N=156 | $AUC_{0-t}$ (ng.h/mL) | $AUC_{0-\infty}$ (ng.h/mL) | $C_{max}$ (ng/mL) | $t_{max}$ (h) |
|---|---|---|---|---|
| **Test** | 5691 ± 1746 | 6364 ± 1998 | 223 ± 69.0 | 6.0 (3.00-12.00) |
| **Reference** | 5592 ± 1709 | 6248 ± 1936 | 220 ± 63.7 | 5.5 (1.50-10.00) |
| ***Ratio (90% CI)** | 1.02 (0.98 – 1.07) | - | 1.01 (0.95 – 1.07) | - |

| | |
|---|---|
| $AUC_{0-\infty}$ | 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 to t = 120 hours |
| $C_{max}$ | Maximum plasma concentration |
| $t_{max}$ | Time after administration when maximum plasma concentration occurs |
| CI | Confidence interval |

**ln-transformed values*

**Study 2: bosutinib 100 mg under fed conditions**

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fed conditions in healthy male (45) and female (7) subjects, aged 18-55 years. Each subject received a single dose (100 mg) of one of the two bosutinib formulations. In each period, following an overnight fast of at least 10 hours subjects were provided a high calorie and high fat breakfast of ≥ 800 Kcal at exactly 30 minutes prior to drug administration. The subjects consumed the high calorie and high fat breakfast within 30 minutes. The tablet was orally administered with 240 mL water. Food was restricted until at least 04 hours post-dose. There were two dosing periods, separated by a washout period of 15 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 7.5, 8, 10, 12, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

*Results*

52 subjects enrolled in the study. 52 subjects were eligible for pharmacokinetic analysis.

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

| Treatment N=52 | $AUC_{0-t}$ (ng.h/mL) | $AUC_{0-\infty}$ (ng.h/mL) | $C_{max}$ (ng/mL) | $t_{max}$ (h) |
|---|---|---|---|---|
| **Test** | 703 ± 165 | 848 ± 207 | 23 ± 6.15 | 6.0 (1.5 - 10.0) |
| **Reference** | 711 ± 171 | 859 ± 231 | 23 ± 6.06 | 5.7 (2.5 - 12.0) |
| ***Ratio (90% CI)** | 0.98 (0.95 – 1.02) | - | 1.00 (0.94 - 1.06) | - |

| | |
|---|---|
| **$AUC_{0-\infty}$** | 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 to t = 120 hours |
| **$C_{max}$** | Maximum plasma concentration |
| $t_{max}$ | Time after administration when maximum plasma concentration occurs |
| CI | Confidence interval |

**ln-transformed values*

The design of the studies is acceptable. From the literature it is known that food interacts with the absorption of bosutinib. Therefore, a food interaction study was necessary. According to the SmPC and PL, the product should be taken orally once daily with food. Study results about the bioavailability of bosutinib and possible interactions with food are included in the SmPC.

*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.

Conclusion on bioequivalence studies:
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 studies, Bosutinib Newbury 500 mg (study 1) and 100 mg (study 2) film-coated tablets are considered bioequivalent with Bosulif 500 mg and 100 mg film-coated tablets respectively.

The results of the study with the 500 mg formulation can be extrapolated to strength 400 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 (version 0.1, 5 July 2023), 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 Bosutinib Newbury.

**Table 3. Summary table of safety concerns as approved in RMP**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | • Use in Paediatric Patients (age: ≤17 years). |

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 Bosulif. No new clinical studies were conducted. The MAH demonstrated through two 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

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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a (multiple) bridging report making reference to Bosulif 100 mg, 400 mg and 500 mg film-coated tablets, EMEA/H/C/002373 for key safety messages and to Ticagrelor 60 mg and 90 mg film-coated tablets, EE/H/0338/001-002/DC for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for content, design and layout of the leaflet.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bosutinib Newbury 100 mg, 400 mg and 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Bosulif 100 mg, 400 mg and 500 mg film-coated tablets. Bosulif 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 Bosutinib Newbury with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 January 2025.

## 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 |
|---|---|---|---|---|---|
| N.A. | N.A. | N.A. | N.A. | N.A. | N.A. |