COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dasatinib Krka 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg, film-coated tablets

(dasatinib)

NL/H/4594/001-006/DC

Date: 30 October 2019

This module reflects the scientific discussion for the approval of Dasatinib Krka. The procedure was finalised on 7 August 2019. 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
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 Dasatinib Krka 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg, film-coated tablets from Krka d.d.

Dasatinib Krka is indicated for the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

Dasatinib Krka is indicated for the treatment of paediatric patients with:

- newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

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 Sprycel 140 mg film-coated tablets (EU/1/06/363) which has been centrally registered in EEA by Bristol-Myers Squibb Pharma EEIG since 20 November 2006.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Hungary, Iceland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden.

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

<u>Similarity assessment in view of the orphan drug legislation</u>
Dasatinib is not considered similar to Iclusig (ponatinib), Blincyto (blinatumomab), Besponsa (inotuzumab ozogamicin), Xaluprine (mercaptopurine), and Tasigna (nilotinib) and Kymriah (Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19). Therefore, the existence of any market exclusivity for any of these products does not prevent the granting of the marketing authorisation for Dasatinib Krka.

II. QUALITY ASPECTS

II.1 Introduction

Dasatinib Krka 20 mg film-coated tablets are white to off-white, biconvex, round film-coated tablets with “D7SB” debossed on one side and “20” on the other side.
Dasatinib Krka 50 mg film-coated tablets are white to off-white, biconvex, oval film-coated tablets with “D7SB” debossed on one side and “50” on the other side.
Dasatinib Krka 70 mg film-coated tablets are white to off-white, biconvex, round film-coated tablets with “D7SB” debossed on one side and “70” on the other side.
Dasatinib Krka 80 mg film-coated tablets are white to off-white, biconvex, triangular film-coated tablets with “D7SB” debossed one side and “80” on the other side.
Dasatinib Krka 100 mg film-coated tablets are white to off-white, biconvex, oval film-coated tablets with “D7SB” debossed on one side and “100” on the other side.
Dasatinib Krka 140 mg film-coated tablets are white to off-white, biconvex, round film-coated tablets with “D7SB” debossed on one side and “140” on the other side.

Each film-coated tablet contains as active substance 20 mg, 50 mg, 70 mg, 80 mg, 100 mg or 140 mg of dasatinib.

The film-coated tablets are packed in oPA/Al/PVC/Al blisters or HDPE container with a child resistant polypropylene (PP) closure.

The excipients are:
tablet core - lactose monohydrate (200), microcrystalline cellulose (101 and 102), croscarmellose sodium, hydroxypropylcellulose (MW 80,000), magnesium stearate
Film-coat - lactose monohydrate, hypromellose (15 mPas), titanium dioxide (E171), triacetin

The six strengths of Dasatinib Krka film-coated tablets (20-50-70-80-100-140 mg) have a dose weight proportional composition for the tablet cores and the same film-coat.

II.2 Drug Substance

The active substance is dasatinib, an established active substance not described in the Ph. Eur. or any other pharmacopoeia. It is a white to off-white crystalline powder, freely soluble in N,N-dimerthylformamide of 80°C, soluble in methanol of 65°C, soluble in pH 1.2 of 37°C, and practically insoluble in water of 37°C. Dasatinib exhibits polymorphism. The crystalline anhydrous form is manufactured.

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 synthesis route comprises 5 chemical steps and 3 isolated intermediates. All synthesis steps are adequately described. The four starting materials are all considered acceptable. Four critical steps have been identified, and adequate in-process controls are applied for these steps.

Quality control of drug substance

Adequate specifications have been set for the drug substance. Batch analysis results were provided for batches from both manufacturing sites, with results meeting the set specifications.

Stability of drug substance

Three batches from both manufacturers were put on stability. From both sites 6 months accelerated stability data were submitted. Batches from the first manufacturer were stored for 36 months at 25°C/60% RH, and from the second manufacturer for 12 months (1 batch) and 18 months (2 batches) at 25°C/60% RH for site. All available accelerated and long-term stability results meet the set requirements. No significant change in any of the test results could be observed. The submitted stability data support the claimed re-test period of 36 months.

II.3 Medicinal Product

Pharmaceutical development

All aspects of pharmaceutical development have been dealt with in full detail by the applicant. The formulation of the generic product is strongly based on the composition of the originator product. Specific attention received the different crystalline forms of dasatinib in proposed generic and the originator product: the anhydrous form is used in the generic product and the monohydrate form in the originator product. Consequences regarding solubility and herewith for dissolution have been discussed.
An adequate description has been given regarding the development of the dissolution method. Dissolution specification: The average result (n=12) after 45 min for the test bio-batch in the QC test medium is 84.9%. Herewith the proposed dissolution specification of ≥ 75% (Q) after 45 min is considered in line with the Reflection Paper on dissolution testing and herewith considered acceptable.

A bioequivalence study was performed with Dasatinib Krka 140 mg versus Sprycel 140 mg film-coated tablet, under fasting conditions. Comparative dissolution studies have been performed between the test and reference bio-batches in in three different pH media (HCl 0.1N pH 1.0, acetate buffer pH 4.5, phosphate buffer 6.8) and in the QC medium (acetate buffer pH 4.0+ triton 1%). For the lower strengths a biowaiver has been granted. The f2 values for comparative dissolution testing of the 5 additional strengths versus the 140 test

bio-batch in acetate buffer pH 4.5 and in phosphate buffer pH 6.8 in all cases > 50, and herewith the dissolution profiles are similar. In HCL 0.1N pH 1.0 dissolution is > 85% in 15 min, and herewith f2 calculation is not further needed.

Manufacturing process

The manufacturing process is a standard process comprising steps of wet granulation, blending, compression and coating. The manufacturing steps are clearly described. For the most pivotal steps in-process controls are applied. Validation results have been provided for 13 validation batches and are considered satisfactory.

Control of excipients

The excipients and the quantities used are usual for immediate release tablets, and the core excipients comply with Ph. Eur. requirements. The components of the film-coat mixture comply with Ph. Eur. standards. These specifications are acceptable.

Quality control of drug product

Drug product specifications are applied for appearance, identification, tablet dimensions, assay, related substances, dissolution and uniformity of dosage units (content uniformity). The proposed drug product specification comprises tests that are usual for solid oral dosage forms. All analytical methods have been sufficiently described and the quantitative methods have been adequately validated.

Batch analytical data on thirteen batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

The following batches have been put on stability: 3 batches of 20 mg and 140 mg, and 1 batch of 50 mg, 70 mg, 80 mg and 100 mg. The batches have been stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). All stability results meet the set specifications. No significant changes in assay of active substance, impurity content and all other tested parameters were observed. Based on the available stability data a shelf-life of 24 months for both the Aluminium-OPA/Alu/PVC blisters and HDPE bottles without specific storage condition has been granted.

It has been adequately demonstrated that there is no need to apply an in-use shelf-life for the HDPE container products after opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For all excipients it is stated that there is no risk on TSE/BSE. For lactose and Opadry II White 32K28000 a statement on BSE/TSE is present in the dossier. Also for lactose monohydrate as tablet core excipient an adequate BSE/TSE statement is present. Triacetin as component in the film-coat mixture is made from rapeseed oil. Regarding magnesium stearate it has been stated that the stearic acid raw material is from vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The following post-approval commitments was made:

- The MAH committed to re-evaluate the end-of-shelf life specification on total impurities at the end of shelf life, and to consider the limits on total impurities at release and at end-of-shelf life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dasatinib Krka 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 Sprycel 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

Dasatinib 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 five bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dasatinib Krka 140 mg (Krka d.d., Slovenia) is compared with the pharmacokinetic profile of the reference product Sprycel 140 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG, UK).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The choice of the reference product in the bioequivalence study is justified, as it has been authorised through a centralised procedure.

Biowaiver

All the conditions for a biowaiver of Dasatinib Krka 20 mg, 50 mg, 70 mg, 80 mg and 100 mg strengths according to the guideline on investigation of bioequivalence have been met:

- all strengths are manufactured by the same manufacturing process
- The qualitative composition of the film-coated tablets are the same and quantitatively proportional for the various strengths.
- Appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence studies for Dasatinib Krka 20, 50, 70, 80 and 100 mg film-coated tablets. Complementary *in vitro* dissolution tests were performed in three different pH media (pH 1.0, acetate buffer 4.5, phosphate buffer 6.8).

Bioequivalence study

Design

A single-dose, randomized, two treatment, four-period, two sequence, full replicate crossover bioequivalence study was carried out under fasted conditions in healthy males and post-menopausal or surgically sterile female volunteers under fasting conditions. 128 healthy male and females (aged 18-48 years) were dosed. Each subject received a single dose (140 mg) of one of the 2 dasatinib 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 at least 3 days days.

Blood samples were collected pre-dose and at 0.083, 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16 and 24 hours after administration of the products.

A single dose study with the highest strength is considered acceptable to investigate bioequivalence for immediate release product with linear pharmacokinetics. Fasting conditions are also considered appropriate since dasatinib can be taken regardless of the food intake.

The design of the study is acceptable. The sampling times and the wash-out period are considered sufficiently long considering the elimination half life of dasatanib of 5-6 hours.

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
Three subjects withdrew for personal reasons after study drug administration in period I and before study drug administration in period II and another 3 subjects withdrew for personal reasons after study drug administration in period II and before study drug administration in period III. A total of 122 subjects completed the crossover study.
In total, data from 125 subjects were included in the statistical analysis: data from the 122 subjects who completed the full replicate crossover study and the three subjects who completed the first two periods.
One subject completed all periods, however on period I (after receiving reference product), the concentration values were low (AUC is less than 5% of reference medicinal product geometric mean AUC). Therefore, period I was removed from statistical analysis while the other three periods were included. Exclusion of data from this subject from statistical analysis is in line with the guideline and therefore acceptable. In addition, it is known that there are instances of no or very low plasma concentrations after administration of Sprycel.

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

Treatment N=125	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	592.62 ± 249.66	609.45 ± 253.54	190.79 ± 98.43	1.00 (0.50-8.00)	--
Reference	583.73 ± 259.61	601.72 ± 258.14	193.04 ± 100.24	1.00 (0.50-12.00)	--
***Ratio (90% CI)**	1.07 (1.02-1.12)	--	1.05 (0.98-1.13)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
Although the intra-subject variability of C_{max} of dasatinib of the reference product in this study was 58.26%, 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 Dasatinib Krka 140 mg is considered bioequivalent with Sprycel 140 mg film-coated tablets.

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 Dasatinib Krka.

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

Important identified risks	• Bleeding-related events • Fluid retention • Myelosuppression • QT prolondagtion • Pulmonary arterial hypertension (PAH) • Pregnancy related malformative or foetal / neonatal toxicity
Important potential risks	• CYP3A4 drug interactions • Direct cardiotoxic effects (e.g. Cardiomyopathy) • Growth and development disorders and bone mineral metabolism disorders in the paediatric population • Hepatitis B virus (HBV) infection reactivation • Nephrotic syndrome • Severe hepatotoxicities • Toxic skin reactions
Missing information	• Carcinogenicity • Paediatric data for patients < 1 year of age • Reproductive and lactation data

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 Sprycel. No new clinical studies were conducted. The MAH demonstrated through 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

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 PL of the reference product Sprycel. In addition, the MAH has previously performed a successful user test of a PL for Clozapine 12.5 mg orodispersible tablets. This user test is used to support the changes made to the proposed PL compared to the parent PL (e.g. house style). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dasatinib Krka 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Sprycel 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg film-coated tablets. Sprycel 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 Dasatinib Krka with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 August 2019.

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