COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(dasatinib)

NL/H/4002/001-006/DC

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Updated 16 October 2019

This module reflects the scientific discussion for the approval of Dasatinib Sandoz film-coated tablets. The procedure was finalised at 25 July 2018. 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
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 Sandoz 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg, film-coated tablets from Sandoz B.V.

The product 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 mesilate.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

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 Belgium, Bulgaria, Cyprus, Germany, Finland, France, Hungary, Italy, Lithuania, Latvia, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia and the United Kingdom.
Through a repeat use procedure the product is registered in Austria, Czech Republic, Denmark, Estonia, Croatia and Norway.

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 Xaluprine (mercaptopurine), Blincyto (blinatumomab), Iclusig (ponatinib), Atriance (nelarabine), Bosulif (bosutinib), or Tasigna (nilotinib), and therefore, the existence of any market exclusivity for any of these products will not prevent the granting of the marketing authorisation of Dasatinib Sandoz.

<u>Scientific advice</u>
The MAH received two scientific advices from CHMP; on 26 May 2016 (EMEA/H/SA/3312/1/2016/SME/I) and on 10 November 2016 (EMEA/H/SA/3312/1/FU/1/2016/SME/I):

- The rationale and study design of bioequivalence study 1955 was discussed in one of those advices and it was not supported. Therefore, termination of this study is understood.

- One single dose pivotal bioequivalence study (2048) with the highest strength is considered acceptable to investigate bioequivalence for immediate release product with linear pharmacokinetics. In addition, fasting conditions are also considered appropriate since dasatinib can be taken regardless of the food intake.
- Also, the MAH received an advice regarding a possibility of widening the acceptance criteria for C_{max}, which was eventually not applied in the bioequivalence study 2048. Furthermore, CHMP also stressed that exclusion of subjects for pharmacokinetic reasons could be accepted only exceptionally after critical evaluation.

II. QUALITY ASPECTS

II.1 Introduction

Dasatinib Sandoz is a film-coated tablet:

- Dasatinib Sandoz 20 mg film-coated tablets are white to off-white, biconvex, round film-coated tablets with "20" debossed on one side and plain on the other.
- Dasatinib Sandoz 50 mg film-coated tablets are white to off-white, biconvex, oval film-coated tablet with "50" debossed on one side and plain on the other.
- Dasatinib Sandoz 70 mg film-coated tablets are white to off-white, biconvex, round film-coated tablet with "70" debossed on one side and plain on the other.
- Dasatinib Sandoz 80 mg film-coated tablets are white to off-white, biconvex, triangular film-coated tablet with "80" debossed on one side and plain on the other.
- Dasatinib Sandoz 100 mg film-coated tablets are white to off-white, biconvex, oval film-coated tablet with "100" debossed on one side and plain on the other.
- Dasatinib Sandoz 140 mg film-coated tablets are white to off-white, biconvex, round film-coated tablet with "140" debossed on one side and plain on the other.

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 Aluminium-OPA/Alu/PVC blisters (perforated unit dose blisters) or high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure and a plastic (HDPE) canister containing silica gel.

The excipients are:
Tablet core

- Cellulose, microcrystalline (E460)
- Lactose monohydrate
- Croscarmellose sodium
- Hydroxypropylcellulose (E463)
- Magnesium stearate (E470b)

Film-coating

- Poly(vinyl alcohol) (E1203)
- Titanium dioxide (E171)
- Talc (E553b)
- Glyceryl monostearate (E471)
- Sodium laurilsulfate

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

II.2 Drug Substance

The active substance is dasatinib, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.) or any other pharmacopoeia. It is a white to off-white crystalline powder, freely soluble in dimethylsulphoxide, slightly soluble in methanol and 0.1N hydrochloric acid solution, very slightly soluble in ethanol, and practically insoluble in water. The crystalline N-6 form is used. The stability of polymorphic form has been sufficiently demonstrated.

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

There are two manufacturers. The active substance is manufactured by five full chemical steps and a purification step. The manufacturing steps are adequately described. All starting materials are accepted, and all specifications involved are considered acceptable.

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 sufficient batches.

Stability of drug substance

Three batches from manufacturer-I have been stored for 24 months at 25°C/60% RH and six months at 40°C/75% RH. All stability results meet the set specification requirements. Three batches from manufacturer-II have been put on stability, twelve months long-term and six months accelerated stability data are available. Additionally, two batches from manufacturer-I and three batches from manufacturer-II, manufactured according to the modified manufacturing process (additional purification steps) have been put on stability, and six months long-term data of batches manufactured by manufacturer-I and nine months

long term data of batches manufactured by manufacturer-II and six months accelerated data of batches manufactured by both manufacturers are available.
The forced degradation study performed demonstrates that the drug substance is not stable when exposed to light and air. Based on the data submitted, a retest period could be granted of 36 months when stored in a well closed container, protected from light and stored at controlled temperature.

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 pharmaceutical development focused on dissolution aspects, such as development of the dissolution methods, comparative dissolution studies of the test and reference biobatches, and all dissolution studies as support for the biowaivers of the 20 mg, 50 mg, 70 mg, 80 mg and 100 mg strengths. Information about formulation development is sufficiently provided. A pilot bioequivalence study has been adequately dealt with leading to the final composition of the pivotal biobatch. Also polymorph stability, particle size evaluation and the effect of hardness of the tablet cores has been adequately shown. Testing of the reference and test biobatches shows that the relative standard deviations at the early time-points are acceptably low.

The MAH submitted the results of five bioequivalence studies using the 140 mg strength (three studies under fasted conditions; two studies under fed conditions). For the additional strengths a biowaiver has been requested. Dissolution testing against the biobatch was done including an additional sampling point at five minutes. At pH 1.2, dissolution was >85% in 15 minutes. At pH 4.5, due to solubility limitations, the MAH used 2x 70 mg tablet, 3x 50 mg tablet and 7x 20 mg tablet. Similarity was shown based on f2. For 3x 50 mg, RSD at ten minutes was just above the acceptance criteria, but the similarity was confirmed by bootstrapping. At pH 6.8, similar approach was performed, i.e. testing at similar dose. Similarity was shown by f2.

Manufacturing process
The manufacturing process is a standard process comprising steps of weighing, sieving, mixing, wet granulation, drying, sieving, pre-lubrication blending, lubrication, compression, film-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 two batches of each of the 20 mg, 70 mg and 140 mg strengths and three batches of each of the 50 mg, 80 mg and 100 mg strengths in accordance with the relevant European guidelines.

Control of excipients
All excipients, except glyceryl monostearate (meets requirements of United States Pharmacopoeia-National Formulary) and the film-coat mixture, comply with Ph.Eur. standards. The film-coat mixture complies with in-house specifications. 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, identification of titanium dioxide, tablet dimensions, assay, related substances, dissolution, uniformity of dosage units, water content, uniformity of mass, and microbiological examination. The MAH restricted the shelf-life specification on total impurities and release specification. 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 sufficient batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Four batches of 20, and 140 mg, three batches of 70 mg have been stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH for six months. Moreover, two batches of 50, 80 and 100 mg strengths have been stored at 25°C/60% RH (up to 9 months) and 40°C/75% RH for six months. All stability results meet the set specifications. No significant changes were observed. Based on this data and on extrapolation, the claimed shelf-life of 36 months is accepted. In view of the fact that all batches have the same composition, the data from the seven stability batches are considered to be sufficient. The storage condition 'This medicinal product does not require any special storage conditions' is considered acceptable. According to the stability protocol for all strengths ultimately three batches will be put on stability.

Considering that no relevant changes have been seen in the two months in-use stability testing, and taking into account the stable nature of the tablets in the stability studies, forced degradation studies and bulk stability studies, there is no need to include an in-use shelf-life claim in the SmPC (for HDPE bottles having 60 tablets or 30 tablets).

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

Lactose monohydrate is the only material of animal origin included in the drug product. BSE statements from the suppliers have been provided and are considered acceptable. For all excipients, except for water, statements have been provided declaring absence of TSE/BSE components.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dasatinib Sandoz 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 Dasatinib Sandoz 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

To support the application, the MAH initially submitted one single-dose, randomised, open-label, crossover, bioequivalence study 2048 in healthy male volunteers under fasting conditions, as the innovator product can be taken regardless of the food intake.
The initial bioequivalence study was conducted for the 140 mg dasatinib film-coated tablets (Sandoz Ltd., Greece) compared with Sprycel 140 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG, UK). The study was carried out in 130 healthy male subjects. Each subject received a single dose (140 mg) of one of the two dasatinib formulations. The tablet was orally administered. There were two dosing periods, separated by a washout period of five days.

In addition, the MAH submitted four bioequivalence studies:

- Four-way replicate pivotal study 2119 with 140 mg strength (fasting conditions)
- Two-way cross over pilot study 1955 with 140 mg strength (fasting conditions)
- A fully replicate pilot study 2176 under fed conditions in order to evaluate intra-subject variability of the reference product Sprycel 140 mg tablet
- A pivotal bioequivalence fully replicate study under fed conditions 2207 with 140 mg tablet

Discussion

During the procedure, an issue has been raised regarding exclusion of the subjects identified as a statistical outliers (with AUC>5% of the mean AUC of the reference treatment, which is not an acceptable exclusion reason according to the guideline) and consequently the MAH was requested to perform statistical analysis including all subjects enrolled in the above mentioned initial study as no justification was provided for the exclusion. In the responses, the MAH argued that subjects were excluded due to the very low plasma concentrations, which are identified as statistical outliers, of dasatinib following administration of the reference product (Sprycel).

Considering the current guideline recommendations, exclusion of subjects due to pharmacokinetic reasons is only possible in case where a very low exposure (AUC<5% of the mean reference AUC) is observed after administration of the reference product. The exclusion of "low-liers" was therefore not considered acceptable (since the AUC was >5% of the mean reference AUC). In addition, when a reference product must be taken regardless of food, a bioequivalence study under fasting conditions is considered the most sensitive. Therefore, it was concluded that Dasatinib Sandoz did not demonstrate to be bioequivalent with Sprycel regarding both C_{max} and AUC under fasting conditions.

The MAH was subsequently asked to perform sensitivity analyses by excluding either the 1% lowest values or the 1% highest values, in order to evaluate if the results from the fasting studies are driven by the atypical low values encountered with the reference product or by higher values that would be observed with the test. This proposal was endorsed by the Medical Evaluation Board at the Board meeting on 3 July 2018, which concluded that it would find the product approvable based on the totality of data for both modes of administration (fed/fasted) when the requested sensitivity analyses turn out positive.

In response the MAH provided two sensitivity analyses; one based on data from all eligible subjects, including subjects with AUC<5% of reference medicinal product geometric mean AUC (full data set), and one excluding those subjects. The latter one is considered more appropriate in this case as exclusion of those subjects is in line with EMA Guideline on Investigation of Bioequivalence and this data set was used in evaluation of bioequivalence earlier during the procedure. In addition, analysis after exclusion of those subjects as per the guideline is regarded as more conservative and thus more sensitive.

Sensitivity analysis following exclusion of subjects with AUC<5% of reference medicinal product geometric mean AUC from all eligible population (both studies) showed that the 1%

highest values are equally distributed between the Test and the Reference product and that Test/Reference ratio of both AUC and C_{max} together with their 90% CI for both AUC and C_{max} were not impacted.
The lowest 1% values are all corresponding either to the Reference product (study 2119) or in majority to the Reference product (study 2048) for both AUC and C_{max}. Exclusion of the 1% lowest values resulted in Test/Reference Ratio of both AUC and C_{max} being decreased by 6.01% and 7.25%, respectively, in study 2119, and by 4.56% and 4.24%,respectively, in study 2048. Consequently, 90% CI become tighter with a greater impact observed in study 2119. In addition, the intra-subject variability decreased as well. This indicates that failure to demonstrate bioequivalence in both pivotal fasting studies is driven by the atypically low values corresponding to the reference product and not by the higher values observed, the latter corresponding to both test and reference products.
In addition, sensitivity analysis performed on a full data set (including subjects with AUC<5% of reference medicinal product geometric mean AUC), supported the outcome of the former sensitivity analysis.

Study 2048	% Test/Reference Ratio of Geometric Means	Intra-Subject CV (%)
AUC	120.27 (108.88-132.86)	48.07
Cmax	107.28 (94.70-121.54)	62.17

Table 27. Study 2048 bioequivalence results of all eligible data following the exclusion of subjects 008, 037 and 122.

Study 2048	% Test/Reference Ratio of Geometric Means	Intra-Subject CV (%)
AUC	117.72 (107.47 – 128.95)	43.21
Cmax	108.02 (95.17 – 122.60)	62.59

Table 28. Study 2048 bioequivalence study results of plasma dasatinib excluding subjects with AUC <5% of reference medicinal product geometric mean AUC (subjects 008, 037 and 122) and Highest 1%.

Study 2048	% Test/Reference Ratio of Geometric Means	Intra-Subject CV (%)
AUC	115.71 (107.96 – 124.02)	32.16
Cmax	103.04 (94.35 – 112.54)	41.56

Table 29. Study 2048 bioequivalence study results excluding subjects with AUC <5% of reference medicinal product geometric mean AUC (subjects 008, 037 and 122) and Lowest 1%.

In conclusion, bioequivalence under fasting conditions in the two pivotal studies 2048 and 2119 was not demonstrated either for AUC (study 2048) or for both C_{max} and AUC. However, the sensitivity analysis conducted for both studies indicates that failure to demonstrate bioequivalence is driven by the atypically low values corresponding to the Reference product and not by the higher exposure to the Test product, meaning that the variability of the Test product is not greater than that of the Reference product. This conclusion is also in line with the CHMP opinion issued to the company during Scientific Advice in May 2018. Based on the totality of the data provided by the MAH, it was concluded that Dasatinib Sandoz is considered approvable under both methods of administration, i.e. with or without food, in

line with the SmPC of the reference product Sprycel, considering that this is a generic application according to Art. 10.1.

Biowaiver

All the conditions for a biowaiver of Dasatinib Sandoz 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 of the test product are manufactured with the same manufacturing process followed.
- The qualitative composition of the six strengths is the same and their composition is quantitatively proportional.
- Similarity of *in vitro* dissolution has been demonstrated at all conditions within the applied product series, i.e. between additional strength and the strength (i.e. 140 mg) used for bioequivalence testing.

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 Sandoz.

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

Important identified risks	• Myelosuppression • Fluid retention • Bleeding related events • QT prolongation • Pregnancy related malformative or foetal/ neonatal toxicity • Pulmonary arterial hypertension
Important potential risks	• Severe hepatotoxicities • Direct cardio toxic effects (e.g., cardiomyopathy) • Growth and development disorders and bone mineral metabolism disorders in paediatric patients • Toxic skin reactions • CYP3A4 drug interactions • Hepatitis B reactivation
Missing information	• Carcinogenicity • Paediatric data • Lactation data • Data in ethnic groups

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 sensitivity analysis 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 two bridging reports. The first makes reference to Sprycel film-coated tablets (content). The parent PL in regards to the layout is Darunavir (general PL without product name and MAH); which has been approved for all Darunavir procedures that have run for a multitude of MAHs.
The bridging reports submitted by the MAH have been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dasatinib Sandoz 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.

Based on the totality of the data provided by the MAH, it was concluded that Dasatinib Sandoz is considered approvable under both methods of administration, e.g. with or without food, in line with the SmPC of the Sprycel.

In the Board meeting of 3 July 2018, the following was discussed: The proposal to perform sensitivity analyses was endorsed by the Medical Evaluation Board which concluded that it would find the product approvable based on the totality of data for both modes of administration (fed/fasted) when the requested sensitivity analyses turn out positive.

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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 July 2018.

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
NL/H/4002/IB/001/G	Change in the name of the medicinal product in NL, BE, DE, FR, IT, PL, SK, due to the upcoming transfer of ownership. Introduction of the summary of Pharmacovigilance System Master File (sPSMF) of the new MAH in all countries.	--	21-10-2018	Approval	--
NL/H/4002/IB/002	Change the product name in BG, HU, LV, SI and the UK from Dasatinib PharOS to Dasatinib Sandoz.	--	22-2-2019	Approval	--
NL/H/4002/E/001	Repeat use procedure to register the product in Austria, Czech Republic, Denmark, Estonia, Croatia and Norway.	--	7-5-2019	Approval	--
NL/H/4002/IA/003	Addition of secondary packaging site.	--	3-6-2019	Approval	--