CBG MEB

Public Assessment Report

Scientific discussion

Imatinib Denk 100 mg and 400 mg film-coated tablets

(imatinib mesilate)

NL/H/3277/001-002/DC

Date: 18 July 2016

This module reflects the scientific discussion for the approval of Imatinib Denk 100 mg and 400 mg film-coated tablets. The procedure was finalised on 12 August 2015. 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 Imatinib Denk 100 mg and 400 mg film-coated tablets from Denk Pharma GmbH.

The product is indicated for the treatment of:

- Paediatric patients with newly diagnosed Philadelphia chromosome (Bcr-Abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Adult patients with Ph+ CML in blast crisis.
- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

The effect of imatinib on the outcome of bone marrow transplantation has not been determined.

Imatinib is indicated for the treatment of:

- Adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, the effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with imatinib in patients with MDS/MPD associated with PDGFR gene rearrangements is very limited (see section 5.1 of the SmPC). There are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

The following indications which are covered by orphan designation for the product Tasigna (nilotinib) were not applied for:

Tasigna
150 mg
- *Treatment of adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase.*

200 mg
Treatment of adult patients with:
- *Newly diagnosed Philadelphia-chromosome-positive CML in the chronic phase;*
- *Chronic phase and accelerated phase Philadelphia-chromosome-positive CML with resistance or intolerance to prior therapy including imatinib.*

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Glivec 100 mg film-coated tablets which has been registered by Novartis Europharm

Limited in the EEA (EU product number: EMEA/H/C/000406) since 7 November 2001 by the centralised procedure EU/1/01/198/002-006.

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

Imatinib Denk are film-coated tablets in the strengths of 100 mg and 400 mg imatinib, as 119.5 mg and 478 mg imatinib mesilate respectively.

Imatinib Denk 100 mg film-coated tablets are round tablets with light brown film coating and a diameter of 8 mm, score on one side, debossed with “IM” on the same side and with “100” on the other side.

Imatinib Denk 400 mg film-coated tablets are oval tablets with light brown film coating, 17 mm long and 8 mm wide, score on both sides, debossed with “IM” on one side and with “400” on the other side.

The tablets of both strengths can be divided into equal doses along the score line.

The film-coated tablets are packed in PVC/PE/PVDC-Alu blisters.

The excipients are:
Tablet core
- Povidone
- Crospovidone
- Colloidal anhydrous silica
- Magnesium stearate

Film coating
- Hypromellose
- Macrogol
- Talc (E553b)
- Iron oxide yellow (E172)
- Iron oxide red (E172)

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is imatinib mesilate, an established substance described in the European Pharmacopoeia (Ph.Eur.). Imatinib mesilate is a white to pale yellow powder and it is freely soluble in water, slightly soluble in methanol and 2-propanol, and insoluble in noctanol, acetone and acetonitrile. It neither has asymmetric carbons, nor centres of chirality. The drug substance exhibits polymorphism. Form α is produced. Imatinib mesilate is not hygroscopic under conditions applied during production and storage.

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
A multiple stage synthesis was used to form intermediates which are then combined to form the imatinib base. Subsequently the final active substance is formed. No metal catalysts or class 1 organic solvents are involved. The proposed starting materials are acceptable as they are sufficiently simple. The active substance was sufficiently characterised with regard to chemical structure and stereochemistry. Control and stability of the polymorphic form is sufficiently discussed.

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

Stability of drug substance
Stability data on the active substance have been provided for nine batches stored at 30°C/65% RH (12-48 months) and 40°C/75% RH (6 months). No significant changes were observed in the currently available stability data. The claimed re-test period of 24 months is justified. No temperature storage conditions are needed. The drug substance is considered photostable.

II.3 Medicinal Product

Pharmaceutical development
The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The qualitative composition of the generic product differs from that of the reference product and a slower dissolution of the generic product at initial time points was observed. Both strengths of the generic product have score lines, and the tablets have been shown to comply with the Ph.Eur. requirements for subdivision of tablets. Manufacturing process development was adequately explained.

Bioequivalence studies were carried out with the 100 mg and 400 mg strength. No objection is made regarding the dissimilar dissolution profiles as bioequivalence was shown *in vivo* and the latter prevails (see section IV.2 'Pharmacokinetics').

Manufacturing process
The description of the manufacturing process is in sufficient detail. It includes dry blending, roller compaction, final blending, compression, and film-coating. The manufacturing process is regarded as a standard process.
Process evaluation data were presented for two batches of each strength of the full scale batch size. All batches complied with the predefined acceptance criteria.

Control of excipients
All individual excipients comply with the Ph.Eur. or relevant directives. The specifications of the excipients 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, dissolution, uniformity of dosage units, assay, degradation products, and microbial limits. 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 two full scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product was provided for two full scale batches of each strength stored at 25°C/60% RH (48 months), 30°C/65% RH (48 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in

PVC/PE/PVDC-Alu blisters. The photostability testing demonstrates that light exposure does not result in any unacceptable change of the medicinal product. Furthermore no significant changes were observed in the currently available stability data. Based on the provided stability data, the proposed shelf life of 48 months can be approved. The proposed storage conditions (none) are acceptable as well.

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. The magnesium stearate used for the manufacture of the drug product is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Imatinib Denk 100 mg and 400 mg film-coated tablets 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 Imatinib Denk 100 mg and 400 mg film-coated tablets are 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

These products are generic formulations of Glivec film-coated tablets which are 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

Imatinib mesilate 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 first conducted a pilot study in order to estimate the number of patients needed in the bioequivalence studies. Subsequently two bioequivalence studies were performed, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Imatinib Denk 400 mg film-coated tablets (Denk Pharma GmbH & Co. KG, Germany) is compared with

the pharmacokinetic profile of the reference product Glivec 400 mg (Novartis Europharm Ltd, UK, marketed in France).
The MAH conducted a second bioequivalence study in which the pharmacokinetic profile of the test product Imatinib Denk 100 mg film-coated tablets (Denk Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Glivec 100 mg (Novartis Europharm Ltd, UK, marketed in Germany).

Dissolution profiles of the test product 100 mg strength are slightly faster than the 400 mg strength. Therefore, no biowaiver is requested and both the 100 mg and the 400 mg strength have been used in the bioequivalence studies. This is an acceptable procedure.

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

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.

Since Imatinib Denk is an immediate release formulation and can be given safely to healthy subjects, a single dose study in healthy subjects is the preferred design. Both studies were conducted under fed conditions. It is recommended to administer Imatinib Denk with a meal in order to avoid gastrointestinal irritation. Administration with food has minimal effect on the absorption of imatinib mesilate and is accepted.

Bioequivalence study II – 100 mg tablet
Design
An open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 24 healthy adult male subjects. Each subject received a single dose (100 mg) of one of the 2 imatinib mesilate formulations. The drug was administered 30 minutes after the start of a high fat and high calorie vegetarian breakfast. Study subjects had to completely consume this meal in 30 minutes or less. There were 2 dosing periods, separated by a washout period of at least 10 days.

Blood samples were collected pre-dose and at 1:00, 1:30, 1:45, 2:00, 2:15, 2:30, 2:45, 3:00, 3.15, 3:30, 3:45, 4:00, 4:20, 4:40, 5:00, 5:30, 6:00, 8:00, 10:00, 12:00, 24:00, 48:00 and 72:00 hours post-dose in each period after administration of the products.

The design of the study is acceptable. The dosing schedule is adequate. The washout period is considered sufficient.

Results
Two subjects were withdrawn from the study on medical grounds in Period-II due to fever and leukopenia. 22 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 100 mg imatinib mesilate under fed conditions.

Treatment N=22	AUC_{0-t} ng/ml/h	C_{max} ng/ml	t_{max} h
Test	8678 ± 2831	537 ± 174	3.25 (1.00-5.50)
Reference	9456 ± 3686	544 ± 188	3.25 (1.50-6.00)
***Ratio (90% CI)**	0.92 (0.86-1.00)	0.98 (0.90-1.07)	--
CV (%)	14.4	16.5	--

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*

Bioequivalence study I – 400 mg tablet

Design

An open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 49 healthy adult male subjects. Each subject received a single dose (400 mg) of one of the 2 imatinib mesilate formulations. A standard non high-fat breakfast (total calorific value of approximately 650 kcal with about 30% of calories derived from fat) was provided approximately 30 minutes before dosing on day 1 in both study periods. There were 2 dosing periods, separated by a washout period of at least 10 days.

Blood samples were collected pre-dose and at 1:00, 1:30, 1:45, 2:00, 2:15, 2:30, 2:45, 3:00, 3.15, 3:30, 3:45, 4:00, 4:20, 4:40, 5:00, 5:30, 6:00, 8:00, 10:00, 12:00, 24:00, 48:00 and 72:00 hours post-dose in each period.

The design of the study is acceptable.
The dosing schedule is adequate, blood samples were taken pre-dose and until 72 h after drug-ingestion. AUC truncated at 72 h (AUC_{0-72h}) is used as an alternative to $AUC_{(0-t)}$ for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations. The washout period is considered sufficient.

Results

There was one drop-out because of vomiting within the first 3 hours post dose. 48 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 400 mg imatinib mesilate under fed conditions.

Treatment N=48	AUC_{0-72} ng/ml/h	C_{max} ng/ml	t_{max} h
Test	38814 ± 10134	2241 ± 594	4.00 (1.75-8.00)
Reference	39549 ± 10345	2300 ± 545	2.75 (1.50-6.00)
***Ratio (90% CI)**	0.98 (0.96-1.00)	0.97 (0.94-1.00)	--

CV (%)	6.2	8.9	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} (100 mg), AUC_{0-72} (400 mg) and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Imatinib Denk 100 mg and 400 mg film-coated tablets are considered bioequivalent with Glivec 100 mg and 400 mg film-coated tablets.

The MEB has been assured that the bioequivalence studies have 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 Imatinib Denk.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myelosuppression • Oedema and fluid retention • GI and CNS haemorrhage • GI ulceration, perforation and obstruction • Hepatotoxicity • Skin Rashes and severe cutaneous reactions • Hypothyroidism • Hypophosphatemia • Cardiac failure • Acute renal failure • Severe respiratory adverse reactions • Rhabdomyolysis and myopathy • Ovarian haemorrhage and haemorrhagic ovarian cyst • Tumour lysis syndrome • Growth retardation in children *Important identified interactions* • Interaction with strong CYP3A4 inhibitors • Interaction with strong CYP3A4 inducers • Interaction with drugs eliminated by CYP3A4
Important potential risks	• Second Malignancies in Survivors • Disseminated intravascular coagulation • Hypoglycaemia • Suicidality • Tolerability during Pregnancy and Pregnancy outcomes *Important potential interactions* • Interaction with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6 • Interaction with acetaminophen/ paracetamol
Missing information	• Paediatric population • Paediatric patients below

	• 2 years of age • Renal impairment • Hepatic impairment • Elderly patients

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 Glivec film-coated tablets. 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 Glivec, EU/1/01/198/002-006. The MAH has successfully tested the in-house leaflet design and layout. The results demonstrated that the in-house style allows for information to be easily located by potential users. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Imatinib Denk 100 mg and 400 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Glivec 100 mg and 400 mg film-coated tablets. Glivec 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 Imatinib Denk with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 August 2015.

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