PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Imatinib Synthon 100 mg, capsules
Synthon B.V., The Netherlands

imatinib (as mesilate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2801/001/DC
Registration number in the Netherlands: RVG 112682

5 December 2013

Pharmacotherapeutic group:	protein kinase inhibitors
ATC code:	L01XE01
Route of administration:	oral
Therapeutic indication:	see next page
Prescription status:	prescription only
Date of authorisation in NL:	20 December 2013
Concerned Member States:	Decentralised procedure with BG, PL, RO
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Imatinib Synthon 100 mg, capsules, from Synthon B.V. The date of authorisation was on 20 December 2013 in the Netherlands.

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 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 the product on the outcome of bone marrow transplantation has not been determined.

The product 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.
- the treatment of 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 re-arrangements is very limited. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

The indications are in accordance with those accepted for Glivec. Except for the indications that are covered by orphan designation for the products Sprycel (dasatinib) and Tasigna (nilotinib)

A comprehensive description of the indications and posology is given in the SmPC.

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.
Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the Bcr-Abl tyrosine kinase at the *in vitro*, cellular and *in vivo* levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive CML patients and acute lymphoblastic leukaemia (ALL) patients.

In vivo the compound shows anti-tumour activity as a single agent in animal models using Bcr-Abl positive tumour cells.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Glivec 100 mg hard capsules which has been registered in the EEA by Novartis Europharm Limited since 7 November 2001 (EU license number EU/1/01/198).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Glivec 100 mg capsules, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is imatinib mesilate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to pale yellow powder, which is freely soluble in water. It has no asymmetric carbons. The active substance exhibits polymorphism. Form α is predominantly produced.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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 process of imatinib mesilate of both manufacturers is adequately described. No class 1 organic solvents are involved in the synthetic route. Adequate information was provided on the specifications for solvents and reagents as well as the potential carry-over of solvents, reagents and metal catalysts. The characterization of the active substance is acceptable.

Quality control of drug substance
The drug substance specification of the MAH is in line with the drug substance specification of the two manufacturers. The proposed drug substance specification is acceptable.
Batch analysis data of two batches of each manufacturer have been submitted, demonstrating compliance with the drug substance specification.

Stability of drug substance
Stability data on the active substance have been provided for three medium scale batches from the first manufacturer stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The retest period of 36 months is considered acceptable on the basis of real-time data.
Stability data on the active substance have been provided for three medium scale batches produced by the second manufacturer stored at 25°C/60% RH (6 months) and 40°C/75% RH (6 months). The claimed retest period of 12 months without specific storage temperature condition can be accepted.

** Ph.Eur. is an official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Imatinib Synthon 100 mg is a hard gelatin capsule (15.9 mm x 5.8 mm) with brown/orange coloured body and cap. The cap is imprinted with "I9AB 100" with black ink.

The capsules are packed in PVC/PE/PVDC/Al blisters.

The excipients are:
Capsule content - Magnesium stearate (E572)

Capsule shell - Iron oxide black (E172), Iron oxide red (E172), Iron oxide yellow (E172), Titanium dioxide (E171), Gelatine

Printing ink – Shellac, Iron oxide black (E172), Propylene glycol (E1520), Ammonium hydroxide (E527)

Pharmaceutical development
Apart from granulation studies, pharmaceutical development was conducted with drug substance sourced from only one ASMF holder. The MAH provided sufficient argumentation for the exchangeability of the drug substance from both ASMF holders, i.e., based on polymorphic form and solubility, particle size distribution, route of synthesis and solvents, and stability.
The composition of the generic product differs from that of the reference product in that no other excipients than magnesium stearate are included in the capsule content.
Pharmaceutical development focussed on the development of the manufacturing process. Hard gelatin capsules were preferred over hydroxypropylmethylcellulose (HPMC) capsules due to better dissolution.
Dissolution profiles of the test and reference product used in the bioequivalence study were not similar at pH 6.8. This is not considered an issue as bioequivalence was shown *in vivo*.

Manufacturing process
The manufacturing process includes wet granulation of the drug substance with water, fluid bed drying of the granulate, blending with magnesium stearate, and encapsulation. The manufacturing process was sufficiently described. It corresponds to a standard process.
The manufacturing process was successfully validated with three batches of a lower batch size. A sufficient protocol for process validation of full scale batches was provided.

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 product specification includes tests for appearance, dissolution, identification, assay, uniformity of dosage units, and impurities. The release and shelf life specifications differ with regard to the limit for a specified impurity. The specifications are acceptable.
Analytical methods were sufficiently described and validated.
Batch analytical data were provided for three batches demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product was provided for three batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The capsules were stored in PVC/PE/PVDC-Al blisters.
Apart from a slight increase in the levels of a specified impurity, no trends were observed in the provided stability data. Photostability was demonstrated under ICH conditions. The claimed shelf life of 24 months and storage conditions “Store below 30°C” are justified as according to the Ph.Eur. capsules should be stored at a temperature not exceeding 30°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of Suitability issued by the EDQM were provided and the supplier of the hard gelatin capsules confirmed compliance with the “Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products”.

II.2 Non-clinical aspects

This product is a generic formulation of Glivec which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of imatinib released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Imatinib 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 a bioequivalence study in which the pharmacokinetic profile of the test product imatinib Synthon 100 mg capsules (Synthon B.V., NL) is compared with the pharmacokinetic profile of the reference product Glivec 100 mg capsules (Novartis Europharm UK Ltd).

The choice of the reference product
The choice of the reference product in the bioequivalence study is accepted, 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.

Design
A single-dose, randomised, two-period, crossover bioequivalence study was carried out under fed conditions in 36 healthy subjects (22 male, 14 female), aged 18-55 years. Each subject received a single dose (100 mg) of one of the 2 imatinib formulations. The capsule was administered orally, 0.5 hours after starting a high fat breakfast. Each capsule was taken concomitantly with 200 mL of water. The dosing proceeded according to the randomization scheme. The high fat breakfast consisted of 1 croissant, butter, scrambled eggs with ham, fruit salad, and 200 ml of fruit tea, 986 kcal (249 kcal from carbohydrates, 142 kcal from proteins and 579 kcal from fat).

There were 2 dosing periods, separated by a washout period of 18 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 14.0, 24.0, 32.0, 48.0, and 72.0 hours after administration of the products.

The single dose study design is acceptable. Since imatinib is to be administered with a meal in order to avoid gastrointestinal irritation, the administration under fed conditions is agreed. The composition of the high-fat meal, as well as the dosing schedule is adequate. The washout period is considered sufficient.

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
All subjects completed the study in its entirety. Consequently, imatinib plasma levels from 36 subjects were included in the pharmacokinetic/statistical analysis.

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

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5222 ± 1428	5407 ± 1437	339 ± 105	4.5 (2-10)	-
Reference	5180 ± 1268	5366 ± 1258	334 ± 90.1	4.5 (2.5-8)	-
***Ratio (90% CI)**	1.00 (0.94-1.08)	1.00 (0.94-1.07)	1.01 (0.93-1.10)	-	-
CV (%)	17.6	16.9	21.1	-	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of imatinib under fed conditions, it can be concluded that Imatinib Synthon 100 mg and Glivec 100 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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).

Risk management plan

Imatinib was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of imatinib can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks. The MAH submitted a Risk Management Plan (RMP). In the RMP all identified and potential risks have been included in line with the innovator's RMP.

Product information

SmPC

The proposed SmPC is in line with the SmPC of the reference product Glivec with exception of those indications covered by market exclusivity due to orphan designation of Sprycel and Tasigna.

Readability test

The package leaflet has not been evaluated via a user consultation study. A bridging report between the last updated Package Leaflet (PL) of the innovator Glivec (EMEA/H/C/000406) and the proposed PL for the generic Imatinib Synthon, to replace the user testing has been provided.

The MAH gives the following justification for a bridging report:

- The content and layout of the Package Leaflet (PL) from the originator product Glivec as published on the EMA website have been taken over.

- The PL for Glivec (capsules) has been user tested.
- Minor changes between the Glivec PL and Imatinib PL are due to the MAH's house style which has been subject to successful user tests for other products. A copy of the readability test for another Synthon product has been provided.

The provided bridging report is considered adequate. The package leaflet of Imatinib Synthon 100 mg capsules is considered to fulfil the requirements of readability. Separate testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Imatinib Synthon 100 mg capsules has a proven chemical-pharmaceutical quality and is a generic form of Glivec 100 mg capsules. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

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 Synthon 100 mg capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 October 2013. Imatinib Synthon 100 mg capsules was authorised in the Netherlands on 20 December 2013.

The date for the first renewal will be: 14 October 2018.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to compare the dissolution profiles of the first three maximum scale-up batches when manufactured to that of the biobatch.
- The MAH committed to carry out process validation for a full scale batch size.

List of abbreviations

ALL	Acute Lymphoblastic Leukaemia
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEL	Chronic Eosinophilic Leukaemia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CML	Chronic Myeloid Leukaemia
CV	Coefficient of Variation
DFSP	Dermatofibrosarcoma Protuberans
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GIST	Gastrointestinal Stromal Tumour
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HES	Hypereosinophilic Syndrome
HPMC	Hydroxypropylmethylcellulose
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MDS/MPD	Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PDGF	Platelet-derived Growth Factor
PDGFR	Platelet-derived Growth Factor Receptor
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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