CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Leutipol 100 mg and 400 mg, film-coated tablets Pharmaceutical Works Polpharma S.A., Poland

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/2911/001-002/DC
Registration number in the Netherlands: RVG 113576-113577

21 August 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:	18 July 2013
Concerned Member States:	Decentralised procedure with PL
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 (SPC), 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 Leutipol 100 mg and 400 mg, film-coated tablets from Pharmaceutical Works Polpharma S.A. The date of authorisation was on 18 July 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 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.
- 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 following indications are registered for Glivec, but covered by orphan designation for the products Sprycel (dasatinib) and Tasigna (nilotinib):

Sprycel
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.*

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.*

As these indications are protected in accordance with the Orphan Regulation, the MAH has not applied for these indications.

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

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 and 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 and 400 mg film-coated tablets by Novartis Europharm Limited, which have been registered in the EEA through a centralised procedure since 7 November 2001 (100 mg) and 11 November 2003 (400 mg) (EU license number EU/1/01/198).

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 400 mg tablets, 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 and 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.*). It is a white to off-white to brownish or yellowish tinged crystalline powder, which is freely soluble in water, soluble in methanol and slightly soluble in chloroform. The drug substance is produced in one polymorph form (Alpha Form).

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 comprises 6 steps for one manufacturer, and 4 steps for the other. The synthesis steps were adequately described. Starting materials, intermediates, and reagents used have been sufficiently specified.

Quality control of drug substance
Adequate drug substance specifications have been laid down. For both suppliers, batch analysis results for 3 batches have been provided, meeting the set requirements.

Stability of drug substance
For one active substance manufacturer, three batches have been stored at 25°C/60% RH for 18 months and 6 months at 40°C/75% RH, and a more recent batch at 25°C/60% RH for 12 months and 6 months at 40°C/75% RH. No clear trends can were observed. Based on the available stability data the proposed re-test period of 2 years can be granted. Since the drug substance is stable at both long term and accelerated conditions, it does not require specific storage conditions, therefore the proposed storage condition 'store below 25°C' is considered not required.
Sufficient stability results for the process of the second manufacturer are available to support the claimed retest period of 12 months without specific storage temperature condition based on 6 months accelerated and normal stability data for 3 batches. All new stability results meet the current drug substance specification.

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

Medicinal Product

Composition
Leutipol 100 mg is a dark yellow to brownish-orange, round shaped, film-coated tablet with a break-line on one side and '100' on the other side. The tablet can be divided into equal doses.
Leutipol 400 mg is a dark yellow to brownish-orange, ovaloid shaped, film-coated tablet with a break-line on one side and '400' on the other side. The tablet can be divided into equal doses.

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

The excipients are:
Tablet core - microcrystalline cellulose (E460), low substituted hydroxypropyl cellulose (E463), povidone (E1201), crospovidone (Type A) (E1201), colloidal anhydrous silica, magnesium stearate (E572)
Coating - hypromellose (E464), macrogol 400, talc (E553b), red iron oxide (E172), yellow iron oxide (E172).

The two strengths are dose proportional.

Pharmaceutical development
The choice and functions of the various excipients have been sufficiently described. A bioequivalence study was conducted in order to compare the bioavailability between Glivec 400 mg (Novartis Pharmaceuticals UK Ltd.) and the proposed 400 mg product. The development of the dissolution and its justification by the MAH are endorsed. All dissolution results in all media are >85% at 15 min. Breakability of both tablet strengths has been demonstrated in accordance with Ph. Eur. requirements.
The manufacturing process development has been adequately described.

Manufacturing process
The manufacturing process comprises the following steps: weighing of materials, preparation of the granulation solution, granulation, drying and sieving, blending, lubrication, compression, coating and packaging. The manufacturing process – a straightforward process based on wet granulation – has been adequately described. Process validation has been performed for three batches of both the 100 mg and the 400 mg manufacturing processes.

Control of excipients
All excipients including the protective gas nitrogen comply with the respective Ph. Eur. monographs. The colourants red iron oxide (E172) and yellow iron oxide (E172) are in accordance with Directive 2008/128/EC. These specifications are acceptable.

Quality control of drug product
Drug product specifications are applied on description, identification of imatinib, identification of mesylate counter ion, identification of ferric oxides, dimensions, assay, related substances, residual ethanol, dissolution, uniformity of dosage units, water content, uniformity of mass, subdivision of tablets, and microbiological examination. All analytical methods have been adequately described. All other drug product specifications – often pharmacopoeial requirements – can be accepted. Batch results are provided for the 3 validation batches per strength as well as a smaller batch per strength. All results met the set requirements.

Stability of drug product
The stability batches (3 validation batches per strength as well as the smaller batches mentioned above) have been stored at 25°C/60% RH for 12 months and 40°C/75% RH for 6 months. All stability results met the set shelf-life requirements, and no clear trends have been observed. Photostability testing showed that the tablets are not sensitive to light.
Based on this available data a shelf-life of 24 months without specific storage condition can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.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 Leutipol 400 mg (Pharmaceutical Works Polpharma S.A., Poland) is compared with the pharmacokinetic profile of the reference product Glivec 400 mg tablets (Novartis Pharmaceuticals 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, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 30 healthy volunteers (21 males, 9 post-menopausal and/or surgically sterile females), aged 21-68 years. Each subject received a single dose (400 mg) of one of the 2 imatinib formulations. The meal consisted of 2 eggs, 2 slices of toast, 136 g of hash brown potatoes, 240 ml whole milk, 2 slices of bacon and 2 tablespoons of butter (total 910.8 Cal). There were 2 dosing periods, separated by a washout period of 14 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, 7.0, 8.0, 10, 12, 18, 24, 36, 48, 72 and 96 hours after administration of the products.

The single-dose study design is acceptable. Since imatinib has to be administered with a meal in order to avoid gastrointestinal irritation, the administration under fed conditions is agreed. The dosing schedule is adequate and 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
Three subjects dropped out prior to period 2, due to personal reasons, due to adverse events or due to out-of-range of creatinine and creatinine clearance levels. Pharmacokinetic and statistical analysis was conducted using data obtained from 27 subjects completing both study periods.

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

Treatment N=27	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h

Test	34434 ± 12177	35372 ± 12390	1900 ± 635	5.0 (2.0-8.0)	--
Reference	36231 ± 12127	37081 ± 12357	2031 ± 634	4.0 (2.0-10.0)	--
***Ratio (90% CI)**	0.95 (0.89-1.00)	0.95 (0.90-1.01)	0.93 (0.87-0.99)	--	--
CV (%)	12.81	12.33	13.56	--	--
$AUC_{0-\infty}$ 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 Leutipol 400 mg and Glivec 400 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
There were 23 adverse events (AEs) involving 13 subjects in this study No serious AEs were reported. 11 AEs were associated with 7 subjects receiving the test formulation, and 11 AEs in 9 subjects receiving the reference formulation.

Biowaiver
A biowaiver has been granted for the 100 mg strength, based on the result of the bioequivalence study conducted with the 400 mg strength, with the following justification:

- Imatinib 100 mg & 400 mg tablets are manufactured by the same manufacturer using the same manufacturing process.
- The qualitative composition of the 100 mg tablets is the same as that of the 400 mg tablets
- Imatinib 100 mg tablets are dose proportional with imatinib 400 mg tablets. Thus, the ratio between amount of each core excipient to the amount of active substance is the same for both the strengths.
- Imatinib pharmacokinetics has been shown to be linear between 25 and 1000 mg in patients with chronic-phase (CP) CML or advanced-phase CML or acute leukaemias.
- The dissolution profiles of imatinib 100 mg tablets are similar to the 400 mg 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).

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 SPC. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. The Risk management plan as described by the MAH is in line with the EU-RMP of Glivec (imatinib).

Product information

SPC

Apart from sections 4.1, 4.2 and 5.1 all the information in the proposed product information is in line with the reference product Glivec. The other sections are in line with the product information for another imatinib product that was registered through a centralized procedure.

Readability test

The package leaflet has not been evaluated via a user consultation study. A user test of another imatinib generic (Parent PIL) was approved in June 2012. Considering the essentially similar content and layout of both PILs a waiver for conducting user testing on the PIL of Leutipol film-coated tablets (daughter PILs) proposed for this DCP was requested and granted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Leutipol 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, 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 Leutipol 100 mg and 400 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 18 June 2013. Leutipol 100 mg and 400 mg film-coated tablets were authorised in the Netherlands on 18 July 2013.

The date for the first renewal will be: 18 June 2018.

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

Quality - medicinal product

- The MAH committed to compare the dissolution profiles of the first three full-scale batches of each strength to the bio-batch of the test product, prior to launch of the product. The comparative dissolution report will be submitted to the authorities upon its availability.
- The MAH committed to re-evaluate the shelf-life specification for impurities.

List of abbreviations

AE	Adverse Event
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
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
SPC	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