Public Assessment Report
Scientific discussion

Imatinib Siegfried
(imatinib mesilate)

SE/H/1331/01-02/DC

This module reflects the scientific discussion for the approval of Imatinib Siegfried. The procedure was finalised at 2014-04-28. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Imatinib Siegfried, 100 mg and 400 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Siegfried GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and MT as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Glivec 50 mg and 100 mg capsule, hard authorised in the Community since 2001, with Novartis Europharm Ltd. as marketing authorisation holder.

The reference products used in the bioequivalence studies are Glivec 100 mg; film-coated tablets (Country of source: pivotal study: Germany, pilot study: France) and Glivec 400 mg film-coated tablets (Country of source: pivotal study: France) with Novartis Europharm Ltd. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Imatinib Siegfried is presented in the form of film-coated tablets containing 100 mg or 400 mg of imatinib in the form of imatinib mesilate. The excipients are crospovidone, magnesium stearate, povidone, colloidal anhydrous silica, hypromellose, macrogol, talc, iron oxide red and iron oxide yellow. The film-coated tablets are packed in blisters.

II.2 Drug Substance

Imatinib mesilate has a recently adopted monograph in the Ph. Eur. (#2736).

Imatinib mesilate is a white, or almost white to slightly brownish or yellowish powder, which is freely soluble in water and slightly soluble in ethanol. The structure of imatinib mesilate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Imatinib Siegfried film-coated tablets 100 mg and 400 are formulated using excipients described in the current Ph Eur, except for the iron oxides which are controlled according to
acceptable in house specifications. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as polymorphism.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the application, the applicant has submitted 3 single-dose bioequivalence studies, one pilot study with the 100 mg tablet performed in the fasted state and two pivotal studies in the fed state with the 100 mg and 400 mg tablets, respectively.

Pilot study (100 mg tablet, fasted state)
This was a single-dose, two-way crossover study conducted in 14 healthy volunteers, comparing Imatinib, 100 mg, film-coated tablets with Glivec, 100 mg, film-coated tablets under fasting conditions. The study design is considered acceptable. Plasma concentrations of imatinib were determined with an LC-MS/MS method. For $AUC_{0-t}$ and $C_{\text{max}}$, the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. Since the bioanalytical report and the validation report have not been submitted it is not possible to assess the validity of the results, but the results from the pilot study are considered supportive. An additional pivotal study has been submitted for this strength.

Pivotal study (100 mg strength, fed state)
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Imatinib Siegfried, 100 mg, film-coated tablets, with Glivec, 100 mg, film-coated tablets under fed conditions. Blood samples were collected pre-dose and
up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of imatinib were determined with an adequately validated LC-MS/MS method. For AUC$_{0-t}$ and C$_{max}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Pivotal study (400 mg strength, fed state)
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 49 healthy volunteers, comparing Imatinib Siegfried, 400 mg, film-coated tablets, with Glivec, 400 mg, film-coated tablets under fed conditions. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of imatinib were determined with an adequately validated LC-MS/MS method. For AUC$_{0-t}$ and C$_{max}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Based on the submitted bioequivalence studies, Imatinib Siegfried is considered bioequivalent with Glivec.

IV.2 Discussion on the clinical aspects
Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Glivec EMEA/H/C/406 (for content) and Soley NL/H/1382/01/DC (for layout). The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Imatinib Siegfried, 100 mg and 400 mg, film-coated tablet, is recommended for approval.

VI. APPROVAL
The Decentralised procedure for Imatinib Siegfried, 100 mg and 400 mg, film-coated tablet was successfully finalised on 2014-04-28.
Public Assessment Report – Update

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
<th>Y/N (version)</th>
</tr>
</thead>
</table>

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN  
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala  
Telefon/Phone: +46 (0)18 17 46 00  Fax: +46 (0)18 54 85 66  
Internet: www.mpa.se  E-mail: registrator@mpa.se