LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Imatinib Grindeks
(imatinib mesilate)

SE/H/1295/01/DC

This module reflects the scientific discussion for the approval of Imatinib Grindeks. The procedure was finalised at 2013-09-23. For information on changes after this date please refer to the module 'Update'.

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

I. INTRODUCTION

The applicant, AS GRINDEKS has applied for a marketing authorisation for Imatinib Grindeks, capsule, hard, 100 mg. The application for Imatinib Grindeks, capsule, hard, 100 mg is a generic application made according to Article 10(1) of Directive 2001/83/EC.
The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Glivec, capsule, hard, 100 mg authorised in the community since 11 November 2011, with Novartis Europharm Ltd as marketing authorisation holder.
The reference product used in the bioequivalence study is Glivec, capsule, hard, 100 mg from the UK.

The product contains imatinib mesilate as active substance. For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Imatinib Grindeks is presented in the form of hard capsules containing 100 mg of imatinib mesilate (form-α). The excipients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, talc, magnesium stearate, gelatin, titanium dioxide (E171) as well as red and yellow iron oxide (E172). The capsules are packed in PVC/Al blister packs.

II.2 Drug Substance

The drug substance imatinib mesilate (form-α) was not monographed in the Ph Eur. at the time of assessment or approval. However, a draft Ph. Eur. monograph on imatinib mesilate has been published in Pharmeuropa 25**.**2.

Imatinib mesilate (form-α) has no chiral centers and is thus an achiral drug substance. It is described as a white to yellow or brownish powder that is freely soluble in water. 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 Grindeks hard capsules are formulated using excipients described in the current Ph. Eur., except for the colorants red and yellow iron oxide as well as for the empty gelatin capsules. The iron oxides comply with USP/NF and commission regulation EU 231/2012 concerning specifications for food additives including colours while the empty gelatin capsules are controlled according to an acceptable in-house specification.

With the exception of gelatin, none of the ingredients included in the manufacture of the drug product contain materials of animal or human origin. The gelatin used in the product is of animal origin and comply 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.

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 the 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

Bioequivalence was evaluated in one single-dose, two-treatment, two-period, two-sequence crossover study conducted in 28 healthy volunteers, comparing Imatinib, 100 mg, hard capsules with Glivec, 100 mg, hard capsules under fed conditions. The study was conducted at CEPHA s.r.o.- Phase 1 Clinic facility, Pilsen, Czech Republic between 17th December 2010 and 14th January 2011. Blood samples were collected pre-dose and up to 72 hours after drug administration. 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% and bioequivalence was demonstrated.

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
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Imatinib Grindeks, capsule, hard, 100 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Imatinib Grindeks, capsule, hard, 100 mg was successfully finalised on 2013-09-23.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

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

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