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MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR PUBLIC ASSESSMENT REPORT FOR GINIB 100 (IMATINIB MESYLATE EQUIVALENT TO IMATINIB 100 MG) FILM-COATED TABLETS

Version number 01, 03/01/2023

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1. Introduction

GINIB 100 is a generic medicine of Glivec 100 film coated tablets of Novartis pharma GmbH, is an antineoplastic agent of protein-tyrosine kinase inhibitor family 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. GINIB 100 is approved in Tanzania for use only in adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD), unresectable dermatofibrosarcoma protuberans (DFSP), unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), and hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).

And in adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML).

1.1 Product details

Registration number	TAN 22 HM 0009
Brand name	GINIB 100
Generic name, strength, and form	Each film-coated tablet contains 100 mg imatinib (as mesilate)
ATC classification	ATC Code-L01XE01 Antineoplastic and Immunomodulating agents, Protein Kinase Inhibitors
Distribution category	POM
Country of origin	Cyprus
Associated product	GINIB 400 film coated tablets
Marketing Authorization Holder	Eurolab (Pty) Ltd Woodmead Office Park, 3 Stirrup Lane Van Reenens, Woodmead, 2144 South Africa Email: info2eurolab.co.za
Local Technical Representative	BB Pharma Consultancy Limited EPZA, Off Mandela Road, Mabibo External P.O Box 31338, Dar es salaam Tanzania Email:info@bbpharmatz.com

1.2 Assessment procedure

The application for registration of GINIB 100 was submitted on 18 June 2019. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 10 January 2022.

1.3 Information for users

Visual description of the finished product	Dark yellow to brownish-orange, round shaped, film-coated tablets with a break-line on one side and ‘100’ on the other side. Diameter of the tablet 10.1 mm ± 5% (9.6-10.6) mm

Primary packing material	Aluminium – PVC-PE-PVDC Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Store below 30 °C. Store in the original container to protect from moisture and light.
Route of administration	Oral
Therapeutic indications	GINIB is indicated for the treatment of • adult and 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. • adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or 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 eosinophilicleukaemia (CEL) with FIP1L1-PDGFRα rearrangement. The effect of GINIB on the outcome of bone marrow transplantation has not been determined. GINIB 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 GINIB 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 GINIB in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited (see section 5.1). Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: GINIB 100

Composition: Each film coated tablet contains: 100 mg imatinib (as mesilate)

Pack size:60 tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Store below 30 °C. Store in the original container to protect from moisture and light

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: See enclosed professional information leaflet

The details of the primary pack include:

Brand name and strength: GINIB 100 (Each film-coated tablet contains imatinib mesilate equivalent to 100 mg imatinib)
Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Remedica Ltd
The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredients

Information on the quality of the API was submitted in form of DMFs.

Site No. 1: Acebright (India) Pharma Private Limited

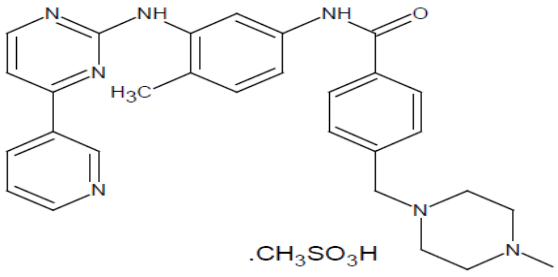
General Information

Imatinib Mesylate API is compendia in Ph.Eur./BP.

Molecular formula: $C_{29}H_{31}N_7O.\ CH_3SO_3H$

Chemical name:
4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2- pyrimidinyl] aminophenyl] benzamide methane sulfonate salt

Structure:



General properties

Imatinib mesylate has no chiral center hence no chirality. Polymorphism has been observed for imatinib mesylate. However, there is no impact on the quality and performance of drug product since the polymorphs of imatinib mesylate are highly soluble.

Manufacture

Imatinib mesylate API manufacturer is Acebright (India) Pharma Private Limited, No.77D & 116/117, KIADB Industrial Area, Jigani, Bangalore - 560 105, Karnataka, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Department of Government of Karnataka. Imatinib mesylate API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per Ph.Eur. standards and ICHQ3A. The parameters monitored during quality control are: Description (visual inspection), solubility, identity (IR), assay (HPLC), related impurities (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph. Eur), heavy metals (Ph. Eur), 174A content (GCMS), and particle size. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Imatinib mesylate API is 24 months when packed in transparent polyethylene bag followed by black polyethylene bag and triple laminated aluminum pack. It is further packed in a fibre board drum and sealed with storage condition ‘Store in airtight containers at below 25 °C. Protect from light’.

Site No. 2: Zhejiang Jiuzhou Pharmaceutical Co. Ltd

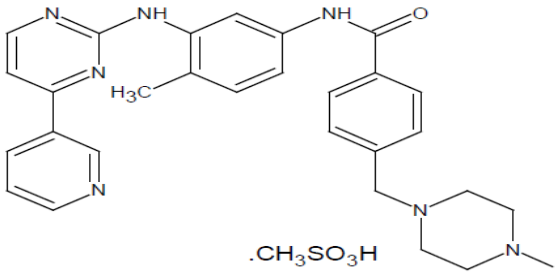
General Information

Imatinib Mesylate API is compendia in Ph.Eur./BP.

Molecular formula: $C_{29}H_{31}N_7O.\ CH_3SO_3H$

Chemical name:
4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2- pyrimidinyl] aminophenyl] benzamide methane sulfonate salt

Structure:



General properties

Imatinib mesylate has no chiral center hence no chirality. Polymorphism has been observed for imatinib mesylate. However, there is no impact on the quality and performance of drug product since the polymorphs of imatinib mesylate are highly soluble.

Manufacture

Imatinib mesylate API manufacturer is Zhejiang Jiuzhou Pharmaceutical Co. Ltd, 99 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province, 318000, China. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Zhejiang Food and Drug Administration. Imatinib mesylate API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per Ph.Eur. standards and ICHQ3A. The parameters monitored during quality control are: Description (visual inspection), solubility, identity (IR), polymorphism (XRPD), content of mesylate (titration), assay (HPLC), related impurities (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph. Eur), heavy metals (Ph. Eur), and microbiological quality. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Imatinib mesylate API is 24 months when packed in two-layer polyethylene bag; heat-seal the bag after making inside vacuum, then put the bag into aluminum foil bag, using paper fiber drum as tertiary packaging material with storage condition ‘Store in airtight containers at below 25 °C. Protect from light’.

Site No. 3: Pharmaceutical Research Institute

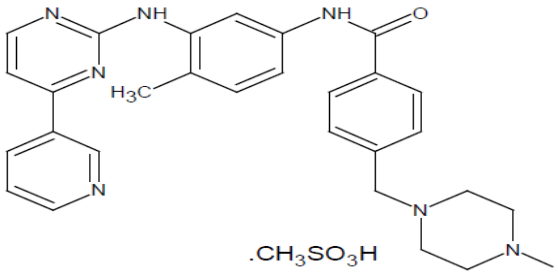
General Information

Imatinib Mesylate API is compendia in Ph.Eur./BP.

Molecular formula: $C_{29}H_{31}N_7O.\ CH_3SO_3H$

Chemical name:
4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2- pyrimidinyl] aminophenyl] benzamide methane sulfonate salt

Structure:



General properties

Imatinib mesylate has no chiral center hence no chirality. Polymorphism has been observed for

imatinib mesylate. However, there is no impact on the quality and performance of drug product since the polymorphs of imatinib mesylate are highly soluble.

Manufacture

Imatinib mesylate API manufacturer is Pharmaceutical Research Institute (PRI), 8 Rydygiera St, 01-973 Warsaw, Poland. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Chief Pharmaceutical inspectorate, Poland. Imatinib mesylate API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per Ph.Eur. standards and ICHQ3A. The parameters monitored during quality control are: Description (visual inspection), solubility, identity (IR and HPLC), melting range, polymorphism (XRPD), content of mesylate (titration), assay (HPLC), related impurities (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph. Eur), heavy metals (Ph. Eur), microbiological quality, and particle size. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Imatinib mesylate API is 24 months when packed in two polyethylene bags with a package of drying agent between them. The tightly closed bags are placed in small cardboard drums with storage condition ‘Store in airtight containers at below 25 °C. Protect from light’.

Quality of the Finished Pharmaceutical Product

Formulation

GINIB 100 is a dark yellow to brownish-orange, round shaped, film-coated tablets with a break-line on one side and ‘100’ on the other side. Diameter of the tablet 10.1 mm ± 5% (9.6-10.6) mm.

GINIB 100 contains the Imatinib mesylate and other ingredients listed here after: Microcrystalline Cellulose, Low substituted Hydroxypropyl Cellulose (E463), Povidone (E1201), Ethanol (96%), Purified water, Crospovidone (Type A) (E1202), Silica colloidal anhydrous (E551), Magnesium Stearate (E470b), Hypromellose (E464), Macrogol 400, Talc (E553b), Red Iron oxide (E172), Yellow Iron Oxide (E172). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Remedica Ltd, Aharnon Street, Limassol Industrial Estate, Limassol (Buildings 5 & 10), Cyprus. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 25 May 2018.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: visual description, dimension, identification of API (HPLC and PDA), Identification of mesylate counter ion, assay (HPLC), uniformity of dosage unit (Ph. Eur), related substances (HPLC), residual solvent (GC), subdivision of tablets (Ph. Eur), dissolution (Ph. Eur), water content (K. F), identification of colorant, uniformity of mass (Ph. Eur), and microbiological quality (Ph. Eur). Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 6 (six) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 36 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in Aluminum-PVC/PE/PVDC blisters with storage condition 'Store below 30 °C. Store in the original container to protect from moisture and light'.

Safety and efficacy information

The biowaiver was approved based on additional strength.

GINIB 100 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of lower strength - Imatinib 100 mg film-coated tablets was compared to Imatinib 400 mg film-coated tablets. At least 85% of the labelled amount of Imatinib had dissolved in all three media. Therefore, confirming similarity.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. GINIB 100 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

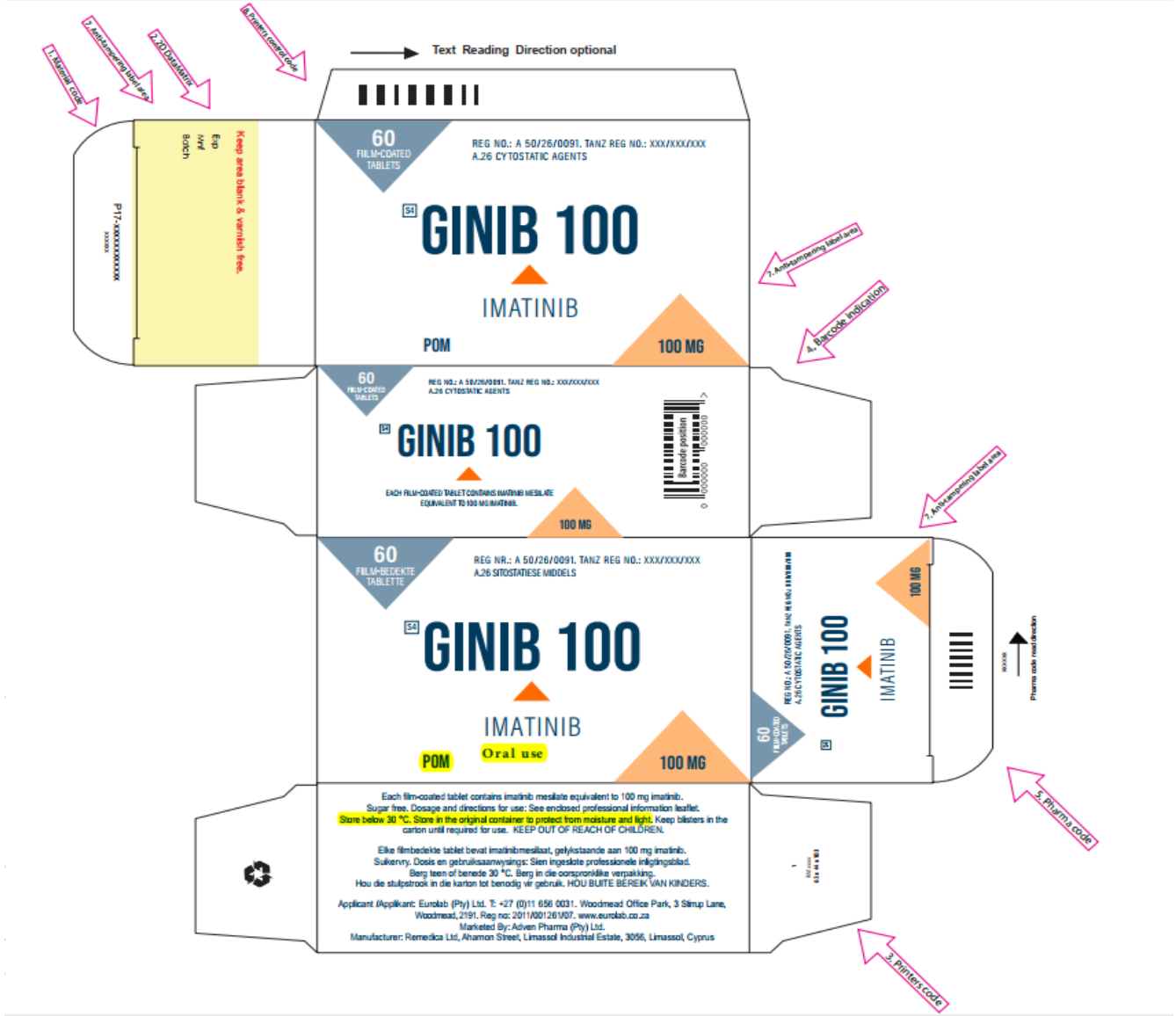
PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;

Secondary pack label;



Effective date: 03/10/2022