22 July 2021
EMA/CHMP/444756/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imatinib Koanaa

International non-proprietary name: imatinib

Procedure No. EMEA/H/C/005595/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Imatinib Koanaa
Applicant:	KOANAA Healthcare GmbH Fehrgasse 7 2401 Fischamend AUSTRIA
Active substance:	IMATINIB MESILATE
International Nonproprietary Name/Common Name:	imatinib
Pharmaco-therapeutic group (ATC Code):	OTHER ANTINEOPLASTIC AGENTS, (L01XE01)
Therapeutic indication(s):	Imatinib 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 eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement. 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 (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.
Pharmaceutical form(s):	Oral solution
Strength(s):	80 mg/mL
Route(s) of administration:	Oral use
Packaging:	bottle (PET)
Package size(s):	1 bottle + 1 oral syringe with adaptor

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List of abbreviations

AGP	Acid glycoprotein
ALL	Acute lymphoblastic leukaemia
ANOVA	Analysis of variance
AS	active substance
AUC	Area under graph
CCyR	Complete cytogenetic response
CEL	Chronic eosinophilic leukaemia
CEP	Certificate of Suitability of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum concentration
Cmin	Minimum concentration
CML	Chronic myeloid leukaemia
CP	Chronic phase
CR	Complete remission
CrCL	Creatinine clearance
CSF	Colony stimulating factor
CV	Coefficient of variation
CYP	Cytochrome
DCP	Decentralised prodecure
DFSP	Dermatofibrosarcoma protuberans
DHMA	Danish Health Medicines Agency
DLT	Dose-limiting toxicities
EC	European Commission
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERA	Environmental Risk Assessment
FP	finished product
GC	gas chromatography
GCP	Good Clinical Practice
GC-MS	gas chromatography-mass spectrometry
GIST	Gastrointestinal stromal tumours
HES	Hypereosinophilic syndrome
HPLC	high performance liquid chromatography

ICH	International Conference on Harmonisation
IECBPH	Independent Ethics Committee Brij Psychiatry Hospital
ICP-MS	inductively coupled plasma -mass spectrometry
IFN	Interferon
IMP	Investigational medicinal product
IR	infrared sprectrometry
IRIS	International Randomized Interferon Study
ISR	Incurred sample reanalysis
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LC	Liquid chromatography
LC/MS-MS	Liquid chromatography/mass spectrometry-mass spectrometry
LDPE	low density polyethylene
LLOQ	Lower limit of quantification
MAA	Marketing Application Authorisation
MDS	Myelodysplastic
MHRA	Medicines and Healthcare products Regulatory Agency
MO	major objection
MPA	Medical Products Agency (Sweden)
MPD	Myeloproliferative diseases
MRP	Mutual recognition procedure
MS	Mass spectrometry
MTD	Maximum tolerated dose
OOS	out of specifications
OS	Overall survival
PD	Pharmacodynamics
PDGFR	Platelet-derived growth factor receptor
PET	polyethylene terephthalate
PFS	Progression-free survival
Ph	Philadelphia
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
R	Reference Product
RH	relative humidity
ROC	Receiver operating curve
SAE	Serious adverse events
SCF	Stem cell factor

SCT	Stem cell transplantation
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SS	Steady state
SWOG	Southwest Oncology Group
T	Test Product
TE-EPE lined	tamper evident-expanded polyethylene foam liner
TK	Tyrosine kinase
TTP	Time to progression
UV	ultra violet spectrometry
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant KOANAA Healthcare GmbH submitted on 26 June 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Imatinib Koanaa, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 March 2020.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication.

Imatinib 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 eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

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 (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.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Glivec 400 mg film-coated tablets instead of non-clinical and clinical unless justified otherwise

The chosen reference product is Glivec 400 mg film-coated tablets, EU/1/01/198/009, EU/1/01/198/010, EU/1/01/198/013:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Glivec 400 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 07-11-2001
  - Marketing authorisation granted by: Union
- Union Marketing authorisation number: EU/1/01/198/009, EU/1/01/198/010, EU/1/01/198/013

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Glivec 400 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (dd-mm-yyyy) 07-11-2001
  - Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/01/198/009, EU/1/01/198/010, EU/1/01/198/013

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Glivec 400 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (dd-mm-yyyy) 07-11-2001
  - Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/01/198/009, EU/1/01/198/010, EU/1/01/198/013
- Bioavailability study number(s): ARL/16/343

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg Co-Rapporteur: N/A

The application was received by the EMA on	26 June 2020
The procedure started on	16 July 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	5 October 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 October 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 October 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 November 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 February 2021
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	29 March 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 April 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	26 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 June 2021
The Rapporteurs circulated the Joint Assessment Report on the	18 June 2021

responses to the List of Outstanding Issues to all CHMP members on	
The CHMP agreed on the 2nd list of outstanding issues in writing to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	29 June 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	7 July 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Imatinib Koanaa on	22 July 2021
The CHMP adopted a report on similarity of Imatinib Koanaa with Iclusig, Xaluprine, Blincyto, Besponsa, Kymriah and Ayvakit on	22 July 2021

2. Scientific discussion

2.1. Introduction

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.

This marketing authorisation application has been submitted through the Centralised Procedure for Human Medicinal Products in accordance with Regulation (EC) No.726/2004, Article 3(3)b, "Generic of a Centrally Authorised Medicinal Product".

The applicant Koanaa Healthcare GmBH, Austria has submitted a Marketing Application Authorisation (MAA) for a product named Imatinib Koanaa 80 mg/mL oral solution (EMEA/H/C/005595) as a generic of Glivec 400 mg film-coated tablets which is authorised within the EU Community through Centralised procedure and the marketing authorisation holder is Novartis Europharm Limited. The application falls under Article 10(3) (hybrid application) of Directive 2001/83/EC, as amended since there is a difference between the pharmaceutical form of the reference medicinal product (tablets) and the test product which is an oral solution.

A pivotal bioequivalence study carried out to demonstrate the bioequivalence between Test Product (T): Imatinib oral solution 400mg/5ml and Reference Product (R): Glivec tablets, 400 mg is submitted in support of this MAA. The study is considered necessary to demonstrate that generic meets relevant criteria as defined in appropriate detailed guidelines. [See Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1] due to the change in the pharmaceutical form.

The applicant of the generic has applied for all the indications of the reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an oral solution containing 80 mg/mL of imatinib (as mesylate) as active substance.

Other ingredients are: maltitol, liquid (E965), glycerol (E422), sodium benzoate (E211), acesulfame potassium (E950), citric acid monohydrate, strawberry flavour (flavouring components, glyceryl triacetate, water, triethyl citrate) and purified water.

The product is available in amber polyethylene terephthalate (PET) bottle with a child resistant tamper-evident (TE-EPE lined) closure containing 150 mL of oral solution. Each carton contains 1 bottle and one 10 ml oral polypropylene syringe (graduated in 0.25 ml increments, equivalent to 20 mg) along with low-density polyethylene adaptor

2.2.2. Active substance

The chemical name of imatinib mesylate is 4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-yl)amino]phenyl]benzamidemethanesulfonate. It corresponds to the molecular formula $C_{29}H_{31}N_7O$, CH_4O_3S. Its relative molecular mass is 589.7 and it has the chemical structure shown in

.

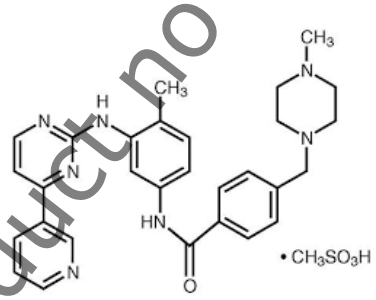

Figure 1 ***Chemical structure of imatinib mesylate***

As per the Ph. Eur. monograph 2736, imatinib mesylate appears as a white or almost white, slightly brownish or yellowish, crystalline hygroscopic powder. It is freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride. Four pK_as were reported namely 1.52, 2.56, 3.73, 8.07.

Imatinib mesylate exhibits polymorphism; it has been shown that the manufacturing process consistently yields the same form (form SA). However, the finished product is a clear solution, in which the AS is in solubilised form. Hence, the polymorphism of AS will not affect the quality of the finished product.

As there is a monograph of imatinib mesylate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for imatinib mesylate which has been provided within the current Marketing Authorisation Application.

Manufacture

The relevant information on the manufacture of imatinib mesylate has been assessed by the EDQM before issuing the CEP.

The CEP specifies that the active substance is packaged in a double polyethylene bags (LDPE) (outer black) as approved, by the European Directorate for the Quality of Medicines (EDQM) in relation to the Certificate of Suitability.

Specification

The CEP confirms that the imatinib mesilate is suitably controlled by the Ph. Eur. monograph (no. 2736).

The AS specification, is based on the Ph. Eur. Monograph and includes tests for description, solubility (Ph. Eur.), identification (IR, HPLC), water content (KF), sulphated ash (Ph. Eur.), related substances (Ph. Eur., HPLC and LC/MS-MS methods), assay (Ph. Eur., HPLC), residual solvents (GC), genotoxic impurities (GC-MS), elemental impurities (ICP-MS) and microbial limit tests (Ph. Eur.), residual solvents (GC) and elemental impurities (ICP-MS).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents and elemental impurities. All additional methods have been adequately validated and described according to ICH Q2.

Satisfactory information regarding the reference standards used in the routine analysis of the AS has been presented.

Batch analysis data from several batches of the AS are provided. The results are within the specifications and consistent from batch to batch.

Stability

No re-test period is defined in the CEP.

Stability data from several production scale batches from the proposed manufacturer stored in the proposed container closure system under long term conditions (25±2ºC / 60±5% RH) and accelerated conditions (40±2°C / 75±5% RH), according to the ICH guidelines were provided.

The applicant has provided results of the photostability study as per ICH Q1B. As the CEP includes details on container closure system, its suitability has already been assessed by the EDQM.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of with the proposed storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical development

Imatinib Koaana 80 mg/mL is an oral solution; it is clear, yellow to brownish yellow coloured solution with characteristic odour filled in 150 mL amber colour PET bottle. Qualitative composition is provided in Table 1.

Table 1 ***Qualitative composition of Imatinib Koanaa 80 mg/ml Oral Solution***

Name of ingredient
Imatinib (eq. to imatinib mesilate)
Maltitol, liquid
Glycerol
Sodium benzoate
Acesulfame potassium
Citric acid monohydrate, powder form
Strawberry flavour • Natural flavouring substances • Flavouring substances • Glyceryl triacetate (triacetin) • Water • Triethyl citrate
Purified water

The aim of pharmaceutical development was to develop the formulation of Imatinib oral solution 400 mg/5 mL in line with approved product Glivec 400 mg film-coated tablets. The oral liquid formulation would overcome swallowing problem of the tablet dosage form. Hence, the focus of the pharmaceutical development was a stable, ready to use, oral solution formulation.

The specific objectives of pharmaceutical development were to:

- achieve a clear imatinib oral solution 400 mg/5 mL.
- achieve a suitable pH range for the stability of Imatinib oral solution 400 mg/5 mL.
- mask the bitter taste and characteristic odour of Imatinib oral solution 400 mg/5 mL if any.
- achieve a presentation that is free from microbial spoilage.

The following product quality attributes were considered based on the properties of the active substance and characterisation of the reference product- description, pH, colour of the solution, identification of imatinib, identification of sodium benzoate, content of sodium benzoate, related substances, microbiological examination.

The physicochemical properties of the AS such as polymorphic form, solubility and particle size that are relevant for the performance of the product have been discussed. Solubility data is provided, whereas particle size and polymorphic form are not critical given the product formulation (solution) and high solubility of the AS. The AS has been proven to exhibit high solubility and complete absorption and is classified as a BCS class I compound.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except for the strawberry flavouring, which is controlled against in-house standard. There are no novel excipients used in the finished product formulation. The function of the excipients has also been stated. The compatibility of excipients with the active ingredient has been proven by stability studies and stated that the excipient compatibility studies will not be applicable to the current

formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Formulation development trials were carried out to assess the inclusion of each excipient and their minimal optimal levels. The finished product has been developed to comply with relevant ICH guidelines and general requirements of pharmacopoeial requirement of the oral liquid products. The suitability of the formulation for paediatric use with respect to the excipients has been justified based on references to EFSA reports for defined ADI limits. Excipients that are used in the formulation are also within the safety limits for paediatric use as per IIG and JECFA safety limits database. Adequate justification has been provided for the formulation pH and glycerine content. The formulation palatability has adequately been investigated in a palatability study including paediatric and adult subjects and was found acceptable across the tested age group (5 to 35 years). The choice and suitability of the preservative and the amount used has been justified by appropriate experimental data including preservative efficacy test study at the lower specification limit of the preservative label amount.

The initial development study was performed on a prototype formulation. Based on satisfactory stability data of the prototype formulation, a series of optimisation studies has been initiated including pH optimisation study, palatability study, preservative concentration optimisation. A satisfactory summary of development batches and the studies performed on them and composition comparison between the prototype batch and the final composition has been provided.

There are no overages.

The applicant has carried out bioequivalence with test product batch and reference product Glivec 400mg tablet. The composition of the test batch is the same as the final formulation. Comparative dissolution profiles generated for both formulations in all the dissolution media (purified water, pH 1.2, 4.5 and 6.8).

The product is a simple solution manufactured by dissolving the active substance and excipients in water for oral solution. For each process step, a risk assessment was conducted to identify potentially high-risk process variables which could impact the finished product CQAs. These variables were then investigated in order to understand the manufacturing process better and to develop a control strategy to reduce the risk of a failed batch. No high-risk process variables and material attributes were identified for the compounding of the finished product.

Adequate justification has been provided with regard to the formulation compatibility with stainless steel, polypropylene filter and tubing used during manufacture.

Imatinib oral solution is packaged in an amber polyethylene terephthalate (PET) bottle with a child resistant tamper-evident (TE-EPE lined) closure containing 150mL of oral solution. Each carton contains 1 bottle and one 10 ml oral polypropylene syringe (graduated in 0.25 ml increments, equivalent to 20 mg) along with low-density polyethylene adaptor.

A Major Objection (MO) had been raised about the rationale of the choice of the oral syringe, its graduations, and the dosing accuracy in relation to the SmPC posology recommendations. In response to the MO the applicant replaced the initially proposed 5 mL syringe with 1.25 mL graduations with a 10 mL syringe with 0.25 mL graduation and marking at 1 mL interval. It is accepted that the new proposed 10 mL syringe allows for easier dosing adjustments. The relevant sections of the dossier have been updated. In addition, the uniformity of mass of delivered dose report was provided; results are compliant with acceptance criteria of Ph. Eur. 2.9.27 for 1 mL (minimum dose) and 10 mL (maximum dose). The SmPC and the PIL have been updated accordingly. From a quality perspective the MO is considered resolved.

The finished product includes medical devices (syringe and adaptor), which have been CE-marked prior to submission of the dossier for the medicinal product, and the CE mark has been attributed for the intended use by a notified body of the European Union. The child resistance nature for the bottle and cap configuration has been confirmed to be in compliance with ISO 8317:2015 for re-closable containers.

Manufacture of the product

The manufacturing process consists of four main stages: sequential dissolving of excipients and active substance in purified water; bulk solution volume adjustment and mixing; filtration, bottle filling and capping; labelling and secondary packaging. The process is a standard manufacturing process.

The manufacturing process has been described in sufficient detail. No critical steps have been identified. The proposed in process controls are acceptable to control the process. The container of the bulk solution and the storage conditions were described. The proposed holding time for the bulk solution is acceptable based on the presented hold time study results.

The batch size range has been clearly stated. Process validation and evaluation have been performed on several industrial scale batches at the lower end of the batch size range. Based on the presented data, this standard manufacturing process is considered to be adequately validated. In addition, the applicant will perform process validation study on the first three production-scale batches of the finished product at the higher production batch size range as per the submitted protocol (section 3.2.R.1) prior to commercialisation.

Product specification

The finished product release and shelf life specifications include tests and limits for appearance (visual), identification (HPLC-UV/diode array), identification of sodium benzoate (HPLC), pH (potentiometry), colour of solution (Ph. Eur.) assay (HPLC), content of sodium benzoate (HPLC), related substances (HPLC), uniformity of mass of delivered dose (Ph. Eur.), deliverable volume (in-house), microbial examination (Ph. Eur.) and water loss (in-house).

The proposed specification test and limits are considered acceptable for an oral solution. The proposed limits have been justified based on batch data ICH guidelines and the requirements of Ph. Eur. The shelf-life limit for assay has been revised following an OOS result during the stability studies (see below Stability of the product, for details). The shelf-life limit for sodium benzoate has been tightened following a single OOS result for the content of sodium benzoate during stability. Considering also that the maximum daily dose of sodium benzoate is 0.48 mg which is much lower than the ADI, the revised proposed limit is considered acceptable. However, the CHMP requested the applicant to revisit the specification for the upper shelf-life limit of the sodium benzoate assay once the stability data of five commercial batches is available (REC).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities (Options 2b and 3). Based on the risk assessment and the presented batch data several batches it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products"

(EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. The finished product is released on the market based on the above release specifications through traditional finished product release testing.

Batch analysis data have been provided on three process validation commercial scale batches manufactured by the proposed manufacturer. All the test results remain within the proposed specification limits demonstrating consistent product quality.

Stability of the product

Stability data from several validation batches, stored for up to 36 months under long term conditions (25±2°C / 40±5% RH) and intermediate conditions (30±2°C / 65%±5%), and for up to 6 months under accelerated conditions (40±2°C / 25±5% RH), according to ICH, were provided. Samples were stored in inverted and upright position, under conditions of low relative humidity as required for semi-permeable containers. These primary stability batches are identical to those proposed for marketing and were packaged in the proposed commercial container closure system (PET bottle).

Stability samples were tested against the specifications as discussed above. The analytical methods were shown to be stability indicating. All batches met all the acceptance criteria across all stability storage conditions and timepoints. The only exception was a high OOS assay and preservative content result observed in a sample in the inverted position. It has been determined that this OOS result was an isolated case not observed in the upright position sample nor at any of the following timepoints Moreover, no other OOS result has been observed for any of the other stability batches nor in the intermediate conditions Based on all the above the shelf life assay specification limits have been revised; this is acceptable.

An in-use stability study, simulating clinical practice, has been performed on two batches of the finished product stored at 25°C. Results met the specification. The proposed in-use stability shelf-life of 30 days after first opening and storage conditions "store the bottle below 25°C" as stated in SmPC section 6.3 are acceptable.

A photostability study was conducted in accordance with ICH Q1B on a pilot batch. The test results while meeting acceptance criteria, showed some level of degradation upon light exposure of the bottles not stored in the carton. Although the proposed primary packaging provides adequate protection from light, the proposed SmPC recommendation (section 6.4) "Store in the original package in order to protect from light" is acceptable.

Based on the overall submitted stability data, the proposed shelf-life of 36 months with the storage condition "Store below 30°C. Store in the original package in order to protect from light", as stated in SmPC sections 6.3 and 6.4, is acceptable.

Adventitious agents

No materials of human or animal origin are used in the manufacture of the finished product.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and the finished has been presented in a satisfactory manner. A MO had been raised about the choice of the oral syringe, its graduations and dosing accuracy, which has been satisfactorily resolved by replacing the initially proposed syringe with a different one, which allows easier dosing adjustments. A minor issue having no impact on the benefit risk balance of the product is proposed as a Recommendation (see below), concerning reviewing the specification limit of the sodium benzoate assay based on stability data from a number of commercial batches.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to revisit the specification for the upper shelf-life limit of the sodium benzoate assay based on five commercial batch stability data.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant has submitted a non-clinical overview, dated May 2020, accompanied by the signature and the curriculum vitae of the expert. The evaluation in the submitted non-clinical overview is based on published scientific literature of the well know active substance imatinib providing a review of the pharmacology, pharmacokinetics, and toxicological profile of imatinib from 35 articles in the published literature, dating back from 1997 to 2015.

No significant new information on the pharmacology has been identified by the applicant

The proposed product, Imatinib Koanaa 80 mg/ml Oral solution, has a different pharmaceutical form compared to the reference medicinal product, Glivec 400 mg film-coated tablets, however the route of administration is unchanged, i.e. oral administration. Oral administration of imatinib is well established and therefore its general pharmacokinetics following oral administration is known. No further PK non-clinical studies are submitted

The non-clinical expert has provided a suitable evaluation on the toxicology of the well-known active substance imatinib based on examples from the published scientific literature. No significant new information has been identified with regards to the non-clinical safety profile of imatinib and no additional studies have been submitted.

Regarding excipients, the applicant has provided, in the non-clinical overview, a general review of the proposed excipients for the applied product, namely acesulfame potassium, citric acid, glycerine, liquid maltitol and sodium benzoate.

Regarding impurities, the applicant has provided a section with a general review, in the non-clinical overview. A brief presentation of the impurities included in the drug substance and product has been provided with their set limits, stating that these comply with the ICH Q3B guideline requirements. Cross reference to the quality documentation has also been provided. A comparative impurity profile has also been provided to show similarity in terms of impurity safety level limits as compared to the reference medicinal product 'Glivec'.

2.3.2. Ecotoxicity/environmental risk assessment

The applicant submitted an updated ERA report, in Module 1.6 of the dossier, for the applied Article 10(3) 'hybrid medicinal product' Imatinib Koanaa 80 mg/mL oral solution.

Summary of main study results

Substance (INN/Invented Name): Imatinib (as mesilate); Imatinib Koanaa 80 mg/mL oral solution

CAS-number: 220127-57-1

Phase I Persistence, Bioaccumulation, Toxicity (PBT) Screening:

Bioaccumulation potential - log Kow: applicant provided value from literature without study report submission;

Phase I calculation of the Predicted Environmental Concentration (PEC):

The PEC in surface water has been calculated by the applicant using the formula explained in the current environmental risk assessment EMEA/CHMP/SWP/4447/00 corr 2 guideline.

The maximum daily dose provided by the applicant for the PEC calculation is 855 mg. The posology in the proposed SmPC allows for a maximum recommended daily dose of 800 mg.

The PEC was calculated as follows:

PEC in surface water = (855,000 µg/day x 0.01) / (200 L/day x 10) = 4.275 µg/L

Phase II:

Since the resulting PEC surface water is above the 0.01 µg/L guideline action limit, Phase II environmental fate and effects studies and analysis should be performed unless adequately justified by the applicant.

The applicant provided the following justifications for not submitting Phase II studies and assessment.

Imatinib is one of the commonly used anti-cancer product with the innovator and different generic products of imatinib already available on the European market. It has been in use for more than 10 years and its safety and efficacy are well-established. The proposed product has the same dose strength, indication and dosage regimen as the reference medicinal product. Therefore an increased environmental exposure is not expected as approval of the proposed product will only lead to a redistribution of market shares of all the available imatinib containing products. Moreover, since the proposed product is subject to medical prescription, consumption will depend exclusively on medical

need and clinical consideration, with no other patient influence of branding or pricing. The proposed product information will also have the standard text to instruct patients to avoid disposal via wastewater or household waste.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. Compared to the reference medicinal product, the applied product has a different pharmaceutical form, however, the therapeutic indication, the route of administration and the quantitative imatinib administration in the posology are unchanged. The excipients and the impurity profile have been discussed and was considered acceptable. Therefore, no new tests or further data are required to be submitted from a non-clinical point of view.

The non-clinical sections of the proposed SmPC are aligned to the latest approved SmPC of the reference medicinal product 'Glivec'. No new significant concerns were identified through the provided non-clinical overview with respect to the pre-clinical safety profile of the proposed product. The non-clinical data in the proposed SmPC is therefore acceptable.

The applicant has submitted an updated ERA report providing a log Kow value for imatinib and the Phase I estimation of environmental imatinib exposure. However, the provided log Kow value is not acceptable since no study report with a proper evaluation has been submitted by the applicant.

The applicant provided an adequate PEC calculation. Since the resulting PEC estimate is above the action limit, Phase II environmental fate and effects studies and analysis should be performed unless adequately justified by the applicant with suitable data. However, the claims provided by the applicant in the updated ERA report have not been substantiated with actual data to demonstrate that an increase in environmental exposure of imatinib is not to be expected. The provided justification is not acceptable, and the applicant is therefore requested to provide:

- A suitable study report on an experimentally derived n-octanol/water partition coefficient (log Kow) for imatinib to assess its PBT potential.
- A full Phase II assessment since the resulting PEC value exceeds the action limit of 0.01 µg/l.

The applicant has provided a signed commitment letter to submit a variation application by October 2022, to provide these required ERA studies. Refer to section 7.1 'list of post-authorisation measures' of this report.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to the approval of Imatinib Koanaa 80 mg/ml Oral solution from a non-clinical point of view. A post-authorisation measure regarding the commitment to submit ERA studies is listed in section 7.1 of this report.

2.4. Clinical aspects

2.4.1. Introduction

This is a hybrid application for an oral solution containing imatinib. To support the marketing authorisation application the applicant conducted one bioequivalence study with a cross-over design

under fasting conditions to compare the test product and the reference medicinal product Glivec which is marketed as tablets. This study was the pivotal study for the application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 2 ***Tabular overview of clinical studies***

Type of Study	Bioequivalence Study
Study Identifier	ARL/16/343
Objective(s) of the Study	Primary objective was to demonstrate the bioequivalence between Test Product (T): Imatinib oral solution 400mg/5ml and Reference Product (R): Glivec tablets, 400 mg in normal, healthy, adult, male human subjects, under fasting conditions. Secondary objective was to monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).
Study Design and Type of Control	A randomised, open label, balanced, two treatment, two period, two sequence, single dose, crossover design.
Test product(s): Dosage regimen, Route of Administration	Test Product (T) IMATINIB oral solution 80 mg/1 ml, 1 x 400 mg (5 ml oral solution), Oral [Batch No.: VAL/17/0044] Reference Product (R) Glivec 00 mg film-coated tablets imatinib, 1 x 400 mg tablet, Oral
Number of Subjects	32 subjects enrolled, 32 analysed, and

	30 subjects considered for bioequivalence
Healthy Subjects or Diagnosis of Patients	Normal, healthy, adult, male human subjects
Duration of treatment	Single Dose
Study Status	Complete

2.4.1. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2. Pharmacokinetics

Methods

Study design

The study was designed as a randomised, open-label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study under fasting conditions, to establish comparative bioequivalence of Imatinib oral solution 400/5 mL (Test: manufactured by LM Manufacturing Ltd. Ground Floor Cavendish House, 369 Burnt Oak Broadway, Edgware, Middlesex HA8 5AW) and Glivec tablet 400 mg (MAH: Novartis Pharma GmbH, Nuremberg, Alemania sourced from Germany). The primary objective of the study was to demonstrate the bioequivalence between Test Product (T): Imatinib oral solution 400mg/5ml and Reference Product (R): Glivec tablets, 400 mg in normal, healthy, adult, male human subjects, under fasting conditions. The secondary objective was to monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).

Subjects were confined within the facility for at least 10.50 hours prior to dosing until 24.00 hours post dose in each study period. Subjects were randomised to receive a single oral dose of either test product (T) [400 mg/5 ml oral solution] or reference product (R) [1 x 400 mg Tablet] in each study period with 240 mL ± 2 mL of water at ambient temperature in sitting position. Blood samples were drawn from pre-dose (collected within 01.00 hour prior to dosing) and up to 72.00 hours post dose in each study period.

Water was not accessible to the subjects from at least 01.00 hour pre-dose until at least 01.00 hour post-dose except 240 mL ± 2 mL of water given during administration of the dose in each study period. At all other times drinking water was given ad-libitum. Subjects remained upright (sitting) for the first 04.00 hours post-dose except for any procedural reason in each study period. In case of an AE, subject was given appropriate (supine/semi-supine) position in each study period.

Blood samples were collected in Sodium Heparin vacutainers at pre-dose (collected within 01.00 hour prior to dosing) and at 00.16, 00.25, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.33, 03.67, 04.00, 04.50, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post-dose. A total of 26 blood samples (5 mL per sample) were collected in each study period.

Centrifugation of the samples was done within 60 minutes after the last blood sample collection of respective time point. Following centrifugation at 3500 RPM for 10 minutes at 5°C ± 3°C, the plasma

were transferred to appropriate size polypropylene screw top (previously labelled with study code and sample code) biological sample storage vials, in duplicate (one aliquot as control samples and one aliquot for analysis; the aliquot for analysis contained approximately 1.0 ml of plasma).

The vials containing plasma samples were kept in the vial-holding racks. The vial holding racks were stored in a deep freezer maintained at -20°C ± 5°C. Both sets of analytical samples and control samples were transferred to the sample storage area in Zip lock bag by placing in a thermocol box containing dry ice (as per in-house SOP) and were stored in the deep freezer maintained at -20°C ± 5°C.

The analytical method provides for the determination of imatinib concentrations in human plasma samples employing imatinib D4 as the internal standard. The extraction was done by Solid phase extraction method. The plasma samples of subjects were analysed by validated LC-MS/MS method.

Test and reference products

In the clinical study report, the applicant submitted the table below, which includes details of the test and reference product.

Table 3 ***Identity of investigational medicinal products***

Product Characteristics	**Test product**	**Reference Product**
Name	IMATINIB oral solution 80 mg/1 ml (Name of IMP)	Glivec ® 400 mg film-coated tablets Imatinib (Brand Name)
Strength	80 mg/ml	400 mg
Dosage form	Oral solution	Tablet
Manufacturer	**Manufactured By:** LM Manufacturing Ltd., Ground Floor Cavendish House, 369 Burnt Oak Broadway, Edgware, Middlesex HA8 5AW.	**Marketing Authorization Holder:** Novartis Europharm Limited frimley business park camberley GU167SR United Kingdom **Manufacturer:** Novartis Pharma GmbH, Roonstrasse 25 D-90429 Nuremberg Germany

Population(s) studied

A total of 32 subjects were planned and enrolled in this study. All subjects (32) were dosed in period-I. Subject no. 08 was withdrawn from the study after dosing of study period-I due to adverse event (Vomiting). A total of 31 subjects were dosed in study period-II. Subject no. 17 was withdrawn from the study after dosing of study period-II due to adverse event (Vomiting).

A total of 30 subjects completed the clinical phase of study successfully. Hence plasma samples of 32 subjects were analysed and data of 30 subjects were considered for concluding bioequivalence.

Subjects who met all the inclusion and none of the exclusion criteria were enrolled into the study.

The inclusion criteria were as follows:

1. Male human subjects, age in the range of 18 – 45 years both inclusive.
2. Body Mass Index between 18.5-30 Kg / m2 extremes included.

3. Subjects with normal findings as determined by baseline history, physical examination and vital sign examination (blood pressure, pulse rate, respiration rate and body temperature).

4. Subjects with clinically acceptable findings as determined by haemogram, biochemistry, urinalysis, 12 lead ECG and chest X-ray (if done).

5. Willingness to follow the protocol requirements especially abstaining from xanthine containing food or beverages (chocolates, tea, coffee or cola drinks) or grapefruit juice, any alcoholic products, the use of cigarettes and the use of tobacco products for 48.00 hours prior to dosing until after the last blood sample collection in each study period and adherence to food, fluid and posture restrictions.

6. No history of significant alcoholism.

7. No history of drug abuse (benzodiazepines and barbiturates) for the last one month and other illegal drugs for the last 06 months.

8. Non smokers as evident from the history obtained were included.

Protocol deviations

The table below gives details of the protocol deviations identified during the study.

Table 4 ***Protocol deviations***

Nature of deviation	Details	Reason and Action taken	Impact of deviation
Blood Sample Time Point Deviation	Period-I Subject no. 01, 02, 05, 06, 07, 10, 12, 13, 14, 15, 16, 20, 21, 22, 23, 24, 25, 26, 27, 29, 30, 31 and 32	Samples were not collected as per scheduled time, subject arrived late. Time Point deviation for any subject at any time point was taken into account for the calculation of pharmacokinetic parameter using statistical package SAS® 9.2 or higher version.	Nil
	Period-II Subject no. 01, 03, 05, 06, 07, 09, 10, 11, 12, 13, 14, 15, 16, 20, 21, 23, 24, 25, 26, 27, 29, 30, 31 and 32		
Missing Sample Deviation	Period-I Subject no. 01	Subjects did not report for ambulatory sample visit. Pharmacokinetic and statistical results were reported without missing sample.	Missing samples were not considered for calculation of pharmacokinetic and statistical analysis.
	Period-II Subject no. 01 and 06		

Concomitant medications

None of the subjects used any prescription and over the counter medications including vitamins and minerals for 14 days prior to study and during the course of the study.

Analytical methods

Analysis was conducted using a validated high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (ARL/MET/AD/188IMA). The method was validated at Accutest Research Laboratories (I) PVT. Ltd. Unit–II prior to sample analysis.

The applicant provided a full bioanalytical report, including the analysis results for calibration standards, quality control samples, study samples, and incurred sample reanalysis, in compliance with the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

This LC/MS/MS method involved the extraction of imatinib, together with the respective internal standard from human plasma.

Study samples: Receipt, Storage and Analysis

A total of 1596 human plasma samples from Sponsor Study Number ARL/174/343 were received in a frozen condition on dated 20 December 2017 in cold storage area at Bio-Analytical site Ahmedabad and were stored at -20ºC ± 5ºC. The vials of subject samples were labelled with details of the study code, subject number, period and sample number. Sample analysis was performed from 01 February 2018 to 13 February 2018. There were 68 missing samples related to subjects that withdrew from the study or subjects who did not turn up for blood sampling.

The date of the first sample collection was 30 November 2017. The date of the last sample extraction was 13 February 2018. Based on the number of days from the first sample collection date and last sample extraction date, samples were stored at a nominal temperature of -20°C for a maximum of 76 days.

All samples were analysed within the determined storage stability period of 117 days for imatinib at a nominal temperature of -20°C ± 5°C and -70°C ± 10°C.

Bioanalytical report

The bioanalytical report was submitted (Study code ARL/17/343 report version 00 dated 03 May 2018) with 20% of the subject chromatograms as well as the method SOPs. Imatinib d4 (sourced from Clearsynth Labs Ltd., Canada) was used as the internal standard for the determination of imatinib concentrations in human plasma samples. Certificates of analysis for the reference and internal standards of imatinib and imatinib d4 have been provided and are deemed acceptable.

Table 5 ***Details of reference and internal standards***

Details	Analyte	Internal Standard
Name	Imatinib Mesilate	Imatinib D4
Working standard No.	ARL-A/WS/1896	ARL-A/WS/1885
Manufacturer / Supplier	Shilpa Medicare Limited	Clearsynth Labs Ltd.
Purity for calculation	99.82 %	99.48 %
Storage condition	20°C - 25°C	2°C - 8°C

Method Validation: The method has been validated (ARL/REP/AHD/1881MA/00) in October 2013 and partial revalidation of the method was performed as appropriate. The following parameters were addressed for imatinib:

Selectivity, linearity including calibration curve, limit of quantification including accuracy and precision, precision (within-run and between-run), accuracy (within-run and between-run)), recovery of the analyte and internal standard, matrix effect (accuracy and precision in human plasma), reinjection reproducibility, hemolysis and lipaemic effect accuracy and precision, dilution integrity including accuracy and precision, carry over effect, auto sampler stability, whole blood stability, post-preparative stability at room temperature, freeze and thaw stability at -20°C (five cycles), short term (at room temperature) and long term (at 2-8°C) stock solution stability, Short term (at room temperature) and long term (at 2-8°C) working solution stability and long term stability in plasma at -20°C ± 5°C and -70°C ± 10°C. Each parameter has been assessed and the limits were justified (results not shown in this report).

For the bioanalytical study: Calibration standards (at 9 different concentrations 25-5000 ng/ml) and quality controls samples (4 levels 70-20000 ng/ml) were prepared in spiked plasma according to the sample analysis plan. The LLOQ for the method was calculated at 25 ng/ml.

Repeat Analysis: Calculated concentrations and reasons for all repeat analysis were provided.
Incurred Sample Reanalysis (ISR): A total of 164 human plasma samples were identified for incurred sample reanalysis. ISR was performed at two stages during sample analysis, post completion of 50 % of subject analysis and after completion of sample analysis. Two samples per period of accepted batches of analysed subjects were selected as incurred samples. Out of these, one sample per period which had a concentration near the Cmax of that period and one sample which had a concentration roughly about three times of the LLOQ (generally towards the end of the elimination phase) were selected as per SOP for INCURRED SAMPLE REANALYSIS (BAL/043/00/N).

Pharmacokinetic variables

Primary parameters: AUC_{0-t} and C_{max}

Bioequivalence criteria:

The 90% confidence interval of the relative mean AUC_{0-t} of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

The pharmacokinetic methods and variables are adequate for the purpose of this study

Statistical methods

Pharmacokinetic data of 30 subjects, who completed the study, were included for statistical analysis.

All the statistical analyses were performed using SAS 9.2. The concentrations at each sampling time point were planned to be tabulated for each subject and product combination, together with descriptive statistics at each scheduled sampling time point for each product.

Analysis of variance (ANOVA) was performed on the ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf at α level of 0.05 for imatinib.

The analysis of variance model included sequence, subjects nested within sequence, period and treatment as fixed factors. A separate ANOVA model was used to analyse each of the parameters.

The significance of the sequence effect was tested using the subject nested within sequences as the error term. All other main effects were tested against the residual error (mean square error) from the ANOVA model as the error term. Each analysis of variance also included calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences.

The geometric least square mean ratios of the test and reference product and its 90% confidence interval on the ln transformed pharmacokinetic parameters Cmax and AUC0-t were computed and bioequivalence was concluded as the confidence interval fall within the acceptable range of 80.00%-125.00% for ln transformed Cmax and AUC0-t for Imatinib.

Results

The applicant presented a full report on the results of the study, including imatinib concentrations for each sampling time, phase and subjects. Tables and figures were included.

Table 6 ***Summary pharmacokinetic parameters estimated for both the test and reference products (N=30)***

Descriptive Statistics for Untransformed parameters				
Measures	**C_{max} (ng/mL)**	**AUC_{0-t} (ng*hr/mL)**	**AUC_{0-inf} (ng*hr/mL)**	**T_{max} (hr)**
Test Product- T				
N	30	30	30	30
Mean	2255.802	35775.631	37306.623	2.264
SD	742.872	13263.316	13770.471	0.806
CV (%)	32.932	37.074	36.912	35.592
Reference Product- R				
N	30	30	30	30
Mean	2170.344	34606.170	36080.230	2.806
SD	800.159	13623.778	14321.335	0.983
CV (%)	36.868	39.368	39.693	35.038

Table 7 ***Statistical analysis for imatinib (ln-transformed values)***

Parameters	***Geometric mean**		**% Ratio**	**90% Confidence Interval for ln-transformed data**	
	Test (T)	**Reference (R)**	**T/R**	**Lower Limit**	**Upper Limit**
AUC_{0-t}	33573.2729	32255.6822	104.0848	98.0258	110.5183
C_{max}	2149.3489	2044.6595	105.1201	99.4607	111.1016

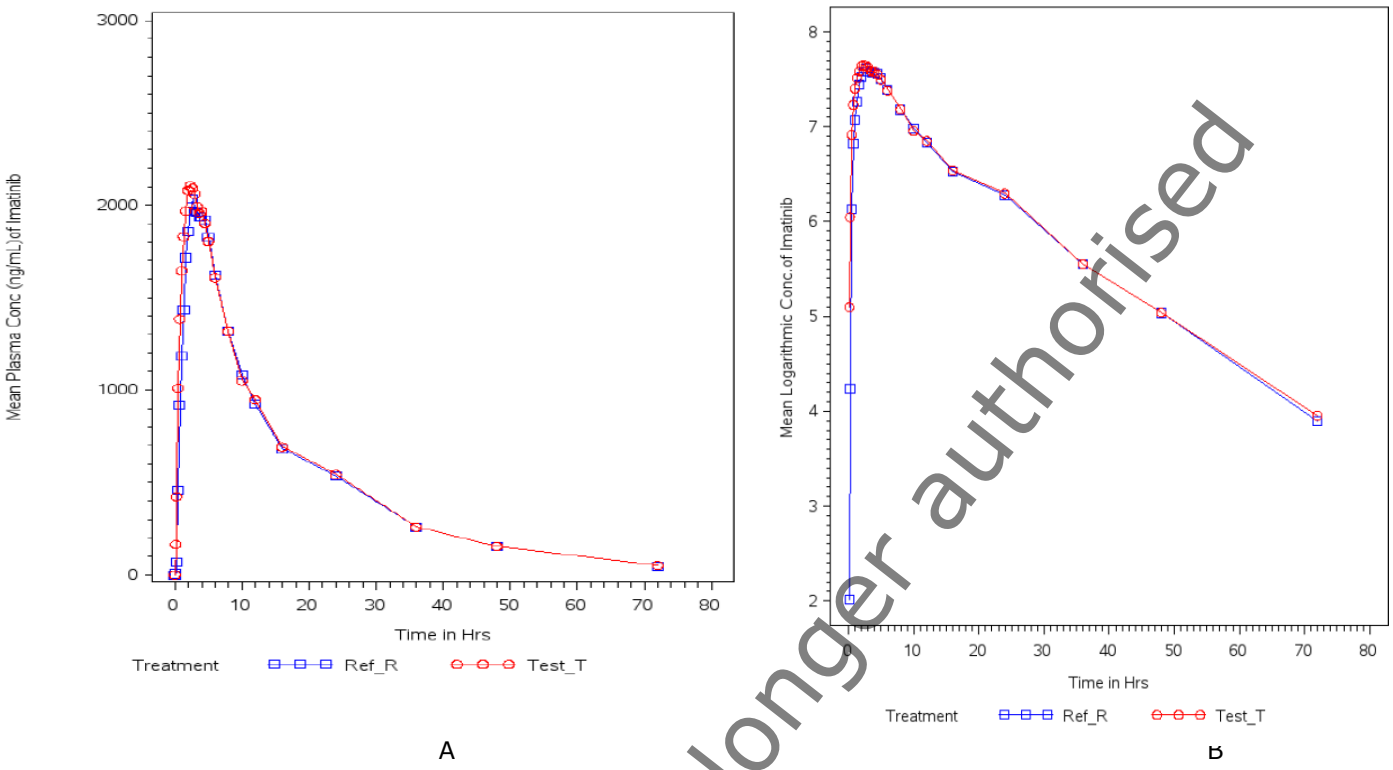

Figure 2 ***(A) Mean plasma concentration time curve of imatinib in linear scale and (B) Mean plasma concentration time curve of imatinib in semi-log scale following single oral dose of Imatinib 400 mg (n=30)***

Safety data

No serious or significant adverse event was observed during the entire course of the study.

Adverse events: Safety analysis set

Total of three (03) adverse events were observed with the test product during entire course of the study which were all mild in severity, probably related to study medication and followed up till resolution. One subject experienced vomiting during period I after taking the test product and another subject experienced vomiting twice during period II. Both subjects were discontinued from the study.

Table 8 ***Adverse event by treatment***

Adverse Event Reported	Test Product (T) N=32	Reference Product (R) N=31
Gastrointestinal System		
Vomiting	03 (09.38%)	00 (00.00%)
Total	**03 (09.38%)**	**00 (00.00%)**

Table 9 ***Adverse event by severity***

Type of Adverse Event	N=32							
	Mild		Moderate		Severe		Total	
Relation with drug	Related	Not Related	Related	Not Related	Related	Not Related	Related	Not Related
Vomiting	03 (09.38 %)	00 (00.00%)	00 (00.00%)	00 (00.00%)	00 (00.00%)	00 (00.00%)	03 (09.38 %)	00 (00.00%)

There were no clinically significant haematology or biochemistry changes for any subject. There were no clinically significant findings during assessments of vital signs, physical examinations or 12-lead ECGs.

2.4.1. Discussion on Clinical aspects

Bioequivalence

The study was designed as a randomised, open-label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study under fasting conditions, to establish comparative bioequivalence of Imatinib oral solution 400/5 mL (Test: manufactured by LM Manufacturing Ltd. Ground Floor Cavendish House, 369 Burnt Oak Broadway, Edgware, Middlesex HA8 5AW) and Glivec tablet 400 mg (MAH: Novartis Pharma GmbH, Nuremberg, Alemania sourced from Germany).

The product information of the reference and test product recommends that imatinib should be taken with a meal. Studies showed that differences in pharmacokinetic parameters between fasting and fed states were not statistically significant and were not considered to be clinically relevant (Peng et al, 2004; Levêque et al, 2005). In line with the product specific guideline for imatinib 50 mg and 100 mg hard capsules and 100 mg and 400 mg film-coated tablets, both a fasting and a fed bioequivalence study are acceptable. Although the SmPC recommends intake in fed state to minimise the risk of gastrointestinal irritation, a fasting study is considered feasible and preferred to increase the sensitivity to detect differences between products. Hence, the bioequivalence study design and sampling periods are acceptable, with an adequate wash-out period at greater than 5 times the t½ (approximately 18 hours). The sampling frequency enabled an adequate estimation of Cmax.

Certificates of analysis for both the test and reference products have been provided. Assay values of test: 100.31% and reference 97.7%. The batch control results appear satisfactory and the batch size (10% of the proposed commercial batch) and manufacturing date of the test product (June 2017) have been declared and are acceptable. The assay ranges are well within the 5% limit of each other in accordance with the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 Corr**).

The dissolution values for the test and reference products are discussed in the quality assessment report.

The population studied is appropriate and the main inclusion and exclusion criteria are in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01).

The number of subjects not completing the study will not have an effect on the results as 22 patients are enough to power the study.

Protocol deviations listed in the report are considered minor and will not have a negative effect on the study results.

Both analytical methods used are acceptable and appropriate. The chromatograms presented are acceptable and the re-analysed samples have been adequately justified. The calibration curves are appropriate (9 points) and the stability testing supports the conditions the samples were exposed to during collection and testing. The applicant has also provided all the validation reports and relevant supportive data together with certificates of analysis for the analytes and internal standards used in the analytical method validation. The relevant SOPs have been named or provided and deemed valid. 20% of the chromatograms have been provided in line with the Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 rev. 1 corr.2**).

The Incurred Sample Reanalysis was provided provided (and found to be within the limits set in the Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 rev. 1 corr.2**) as well as information on the partial revalidations of the methods. These are deemed acceptable.

The analytical methods were audited and a signed statement was provided. A statement of compliance with GLP was also provided.

The lack of testing of ruggedness (different analyst and different column) in the bioanalytical method validation should be justified. At D120, the applicant addressed the question and evidence that ruggedness has been addressed in the analytical validations was provided.

The appropriate variables were measured, and statistical methodology is accepted.

The sampling schedule provides adequate estimation of Cmax. Statistical data and a graphical representation to cover the plasma concentration time curve long enough to provide an estimate of the extent of absorption, has been provided.

The 90% confidence intervals calculated for the primary parameters Cmax, and AUC0-t for Imatinib fall within the 80.00 – 125.00% acceptance range after single dose administration under fasting conditions.

No significant sequence, period and treatment effects were observed for ln transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf.

Bioequivalence of Imatinib 80mg/mL with the reference product Imatinib 400mg tablets has been shown in the fasting state.

Clinical safety

Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study. As seen in the bioequivalence study and in line with published literature, nausea and vomiting are the most frequent adverse events. There were no new safety findings during the bioequivalence study. The conclusions of the applicant can be endorsed.

With regards to dosage administration, the applicant initially proposed a 5 ml oral syringe with adaptor (graduated at every 1.25 ml equivalent to 100 mg). The applicant was requested to discuss how a 5 ml oral syringe with adaptor (graduated at every 1.25 ml equivalent to 100 mg) will ensure that there is accurate dosing in children as per posology in the SmPC. This was also raised in the quality assessment report.

At D120 the applicant proposed a change in the dosing syringe, proposing a 10 mL oral syringe with 0.25 mL graduation which would meet the dosing requirement up to 20 mg dose difference. The 0.25 ml graduation would meet the requirement of dosing at the level of 20 mg differences during dose

administration. A summary of the Paediatric Daily Dose (all indications including reduced dose) along with dose in ml was also provided. It is accepted that the new syringe volume and grading can provide more accurate dosing in children as per posology in the SmPC. This will in turn reduce further to risk of medication errors.

However, the applicant was requested to further clarify the tables provided for the calculation of dosing in paediatrics, especially when an approximation to the nearest measurable volume is required. The applicant was requested to show that approximations of dosing in these cases are not clinically significant in terms of efficacy and safety. The applicant was also asked to provide additional information in the SPC in order to aid the healthcare professional to calculate the required dose in mg and the corresponding volume in ml. Adequate information and instructions should also be included in the PIL clearly explaining how the dosing is to be measured to the nearest mL.

At D180, the applicant discussed the calculation of dosing in paediatrics and provided the proposed nearest dosing which is not clinically significant in terms of efficacy and safety. The SmPC and PIL were updated with clear instructions and dosing tables which provide the dose given by every grading mark of the syringe. This provides adequate information for the healthcare professional to calculate the required dose in mg and the corresponding volume in mL.

2.4.2. Conclusions

Based on the presented bioequivalence study, Imatinib oral solution 400/5 mL (Test: manufactured by LM Manufacturing Ltd. Ground Floor Cavendish House, 369 Burnt Oak Broadway, Edgware, Middlesex HA8 5AW) is considered bioequivalent with Glivec® tablet 400 mg (MAH: Novartis Pharma GmbH, Nuremberg, Alemania sourced from Germany). No new safety concerns were raised.

2.5. Risk Management Plan

Safety concerns

Table 10 ***Summary of safety concerns***

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Second primary Malignancy • Tolerability during Pregnancy and Pregnancy Outcomes
Missing information	• Paediatric patients: Long term follow up • Paediatric patients below 2 years of age

Pharmacovigilance plan

The safety concerns of Imatinib can be considered to be well established. Routine Pharmacovigilance (PhV) activities that are deemed sufficient.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

Additionally, as a part of the routine pharmacovigilance activities a targeted follow-up questionnaire is planned to obtain further clinical details to aid causality assessment for the following safety concern

• Tolerability during Pregnancy and Pregnancy Outcomes

Risk minimisation measures

Table 11 ***Summary table of pharmacovigilance activities and risk minimisation activities by safety concern***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
There are no important identified risks for imatinib		
Important Potential Risks		
Second primary malignancy	Routine risk minimisation measures: Risk has been listed in the SmPC section of 5.3 SmPC: No specific measures for prevention are known. However, Section 5.3 of the SmPC provides details about the pre-clinical data on this safety concern Pack size: None Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Tolerability during Pregnancy and Pregnancy Outcomes	Routine risk minimisation measures: Risk has been listed in the SmPC sections of 4.6 and 5.3 and PL Section 2. SmPC: SmPC Section 4.6 and PL Section 2 recommend that imatinib should not be used in pregnancy unless there is a clear necessity. Pack size: None Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None
Missing information		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Paediatric patients: Long term follow up	Routine risk minimisation measures: Risk has been communicated in the SmPC sections of 4.4 and 4.9 and PL Section 2. SmPC: No specific measures for prevention are known. Pack size: None Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Paediatric patients below 2 years of age	Routine risk minimisation measures: Risk has been communicated in the SmPC sections of 4.2 SmPC: No specific measures for prevention are known. Pack size: None Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Glivec 400mg film coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a hybrid version of imatinib oral solution. The reference product Glivec 400mg film coated tablets 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 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 (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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a randomised, open-label, balanced, two-treatment, two-period, two-sequence, single dose, crossover under fasting conditions design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of imatinib oral solution met the protocol-defined criteria for bioequivalence when compared with Glivec 400mg film coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Imatinib Koanaa is favourable in the following indication:

Imatinib Koanaa 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 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 (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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.