27 June 2024
EMA/325502/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nilotinib Accord

International non-proprietary name: nilotinib

Procedure No. EMEA/H/C/006315/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ABEM	3-[aminoiminomethyl)amino]-4-methyl-benzoicacid ethyl ester mononitrate
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CPP	Critical process parameter
CQA	Critical Quality Attribute
DoE	Design of experiments
DPPO	(E)-3-(Dimethyl amino)-1-(pyridine-3-yl)prop-2-en-1-one
DSC	Differential Scanning Calorimetry
EC	European Commission
EP	European Pharmacopoeia
EU	European Union
3FTB	3-fluoro-5(trifluoromethyl)benzonitrile
GC-HS	Head Space Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IU	International Units
LCMS	Liquid chromatography mass spectrometry
MAH	Marketing Authorisation holder
MO	Major objection
MS	Mass Spectrometry
NMT	Not more than
Ph. Eur.	European PharmacopoeiaMO Major objection
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QTPP	Quality target product profile
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 26 June 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Nilotinib Accord, 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 30 March 2023.

The application concerns a generic medicinal product as defined in Article 10(2)(b) 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:

Nilotinib Accord is indicated for the treatment of:

- adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase,
- adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available,
- paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) 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 Tasigna instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

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: Tasigna 50, 150 and 200mg hard capsules
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 19-Nov-2007
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation numbers: EU/1/07/422/001-015

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

- Product name, strength, pharmaceutical form: Tasigna 50, 150 and 200mg hard capsules
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 19-Nov-2007
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: EU/1/07/422/001-015

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: Tasigna 200mg hard capsules
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 19-Nov-2007
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation numbers: EU/1/07/422/001, EU/1/07/422/002, EU/1/07/422/003, EU/1/07/422/004, EU/1/07/422/007, EU/1/07/422/008, EU/1/07/422/011, EU/1/07/422/012, EU/1/07/422/014
- Bioavailability study number: 09170/22-23

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	26 June 2023
The procedure started on	13 July 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	2 October 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 February 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	2 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant during the meeting on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 May 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 June 2024
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 Nilotinib Accord on	27 June 2024
The CHMP adopted a report on similarity of Nilotinib Accord with Scemblix on	27 June 2024

2. Scientific discussion

2.1. Introduction

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Nilotinib Accord 50/150/200mg hard capsules, for the treatment of chronic myelogenous leukaemia (CML). The applicant is Accord Healthcare S.L.U.

The originator product is Tasigna 50 mg, 150 mg, 200 mg hard capsules marketed by Novartis Europharm Limited and first authorised in the community on 19 November 2007 (EU/1/07/422/). The active substance is nilotinib in both products, however, this application contains a different salt (free base) of the active substance than the reference product (hydrochloride monohydrate salt form).

One bioequivalence study was conducted in support of this application using the reference Tasigna 200mg hard capsule marketed by Novartis Europharm Limited.

Nilotinib is a potent inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The substance binds with high affinity to the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from CML patients. In murine models of CML, as a single agent, nilotinib reduces tumour burden and prolongs survival following oral administration.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 50 mg, 150 mg and 200 mg of nilotinib as active substance.

Other ingredients are (as described in SmPC section 6.1):

Capsule content: lactose monohydrate, crospovidone (type A), magnesium aluminometasilicate, polysorbate 80, colloidal anhydrous silica and magnesium stearate.

Capsule shell: gelatin, titanium dioxide (E171), iron oxide red (E172) (50 mg and 150 mg capsules only), iron oxide yellow (E172)

Printing ink: shellac, black iron oxide (E172) (50 mg and 150 mg capsules only), propylene glycol, potassium hydroxide (50 mg and 150 mg capsules only). The printing ink of the 200 mg hard capsules contains also sodium hydroxide, titanium dioxide (E171), povidone and Allura red AC.

The product is available in PVC/PVDC/Alu blisters or PVC/PVDC/Alu perforated unit dose blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of nilotinib is 4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl) -5- (trifluoromethyl) phenyl] -3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide corresponding to the molecular formula $C_{28}H_{22}F3N_7O$ It has a relative molecular mass of 529.52 g/mol and the following structure:

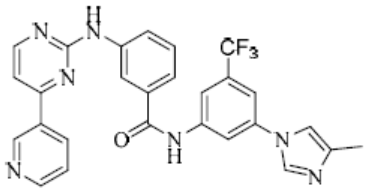

Figure 1 : Active substance structure

Nilotinib is a pharmacopoeial substance, the Ph.Eur. monograph describes nilotinib hydrochloride monohydrate.

The chemical structure of nilotinib was elucidated by using an array of spectrophotometric techniques and chemical analysis. Methods used were: elemental analysis, IR, ^{1}H and ^{13}C-NMR, MS, UV, XRD and DSC.

Nilotinib is an off-white to cream crystalline powder, sparingly soluble in DMSO and DMF, and very slightly soluble in methanol. It is insoluble in pH 6.0 and 8.0 aqueous buffers, but very slightly soluble in pH 1.2 buffer and water. Nilotinib is slightly hygroscopic, contains no chiral centres and has a LogP of 5.36.

Polymorphism has been observed for nilotinib: Form A, Form B, Form C, Form D, Form X and Form Y have been described. Nilotinib manufactured by the active substance manufacturer is crystalline Form B.

2.2.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The manufacturing process of nilotinib is described in 7 synthetic steps and one final purification step. During the procedure the CHMP noted several steps that could led to the formation on nitrosamines and raised a Major Objection (MO1). To address the concern, the ASMF holder performed additional studies which showed that all nitrosamine impurities were below the limit of quantitation established for each of those impurities (10% acceptable intake). The CHMP concluded that the proposed starting materials are acceptable and their selection has been sufficiently justified.

No critical steps are described in the process. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. The original discussion on genotoxic impurities was limited and did not follow ICH M7 and its Q&A, which led to a second Major Objection (MO2). The ASMF holder updated the dossier to include other possible genotoxic impurities beside those described in the Ph. Eur. monograph and to include further justification and supportive data to demonstrate the adequate purge of azide residuals from the process. This was considered acceptable.

The impurities and control strategy are based on the Ph. Eur. monograph for the HCl salt; the same limits are adopted for the control of the free base active substance.

The manufacturing process of nilotinib was based on literature search with process chemistry knowledge from the available scientific journals and process patents.

The active substance is packaged in double PE bags, placed in triple laminated aluminium bag placed into HDPE drum, primary packaging materials comply with EC 10/2011 as amended.

2.2.2.3. Specification

The active substance specification includes tests for description, solubility, clarity of solution, identification (IR, HPLC and XRD), loss on drying (Ph. Eur.), residue on ignition/sulphated ash (Ph. Eur.), assay (HPLC), related substances (HPLC or LC-MS/MS), residual solvents (GC-HS), microbial quality and particle size distribution (laser diffraction). A genotoxic impurity not described in the Ph. Eur. monograph was added to the active substance specification following a major objection (MO3) raised by the CHMP requesting its control.

The specification is acceptable and generally based on the Ph. Eur. Monograph for nilotinib hydrochloride monohydrate, with additional controls for microbial quality, other genotoxic impurity not described in the Ph. Eur. monograph, residual solvents, polymorphism and particle size distribution.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer, stored in in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch.

The following parameters were tested: description, identification (IR, XRD), clarity of solution, loss of drying, related substances, assay and microbial limits. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specification under both long term and accelerated conditions.

Forced degradation studies were performed demonstrating the stability indicating nature of the related substances and assay methods. Conditions tested were acidic and basic hydrolytic conditions, oxidative conditions, solution containing iron, treatment with high heat and humidity and finally, photolytic degradation.

The substance is sensitive towards degradation in acidic media, in basic media, and under oxidative conditions. The substance is stable under high heat and humidity conditions, and in heated aqueous media (water).

Photostability studies were performed following ICH Q1B. The active substance is shown to be stable as a solid under photolytic stress. In response to a query from the CHMP pointing out that the Ph. Eur. monograph

for Nilotinib HCl there is a warning statement in the related substances method to "carry out the test protected from light", asking the applicant to conduct additional studies and/or discuss the stability of the active substance in solution (under UV/VIS stress conditions), the ASMF holder confirmed that analysis are being performed through protective methods ("use amber coloured glassware to prepare all the solutions (protect from light)". This is considered acceptable.

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 36 months when stored at controlled room temperature below 25 °C in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product Nilotinib Accord consists of hard gelatin capsules containing 50 mg, 150 mg and 200 mg of nilotinib, packaged in PVC/PVdC-aluminium blisters in various pack sizes. Each filled capsule contains 50% of the active substance in the granulate.

The different capsule strengths differentiate in markings colour and size as follows:

50 mg capsules: Hard gelatin capsule (size '4') with red opaque cap and light yellow opaque body imprinted with black ink "SML" on the cap and "39" on the body containing off white to grey granular powder free from physical defect.

150 mg capsules: Hard gelatin capsule (size '1') with red opaque cap and red opaque body imprinted with black ink "SML" on the cap and "26" on the body containing off white to grey granular powder free from physical defects.

200 mg capsules: Hard gelatin capsule (size '0') with light yellow opaque cap and light yellow opaque body imprinted with red ink "SML" on the cap and "27" on the body containing off white to grey granular powder free from physical defects.

The finished product has been developed to be a generic equivalent to the reference medicinal product Tasigna. Consequently, the objective of the pharmaceutical development was to prepare oral immediate release capsules being essentially similar to the reference medicinal product, using a dose proportional approach.

The quality target product profile (QTPP) was defined as follows:

Table 1. Quality target product profile (QTPP).

QTPP element		Target	Justification
Dosage form		Capsules	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release Capsule	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration.
Dosage strength		50 mg, 150 mg and 200 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		The generic drug product should be bioequivalent with reference product in Fasting Study.	The generic drug product should be bioequivalent with Innovator drug product. Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to reference product shelf-life.
Drug Product quality attributes	Physical attributes	Pharmaceutical equivalence requirement: Must meet the same Compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Uniformity of dosage units (By weight variation)		
	Dissolution		
	Degradation Products (Related substances)		
	Water Content		
	Microbial Limits		
Container Closure system		Blister packing system qualified as suitable for this drug product.	Needed to achieve the target shelf-life and to ensure capsule integrity during shipping
Administration/ Concurrence with Labeling		Similar food effect as reference product	Reference product labeling indicates that Nilotinib capsules should not be taken with food
Alternative methods of administration		None	None are listed in the Reference product label.

From the QTPP physical and quality attributes were defined as either critical or non-critical.

The CQAs are summarised in the table below. For this product, assay, uniformity of dosage units, dissolution and degradation products are identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, were investigated and discussed in detail in subsequent formulation and process development studies.

Table 2. Critical quality attributes (CQAs).

Quality attribute (DP)	CQA?
Identification	Yes
Assay	Yes
Uniformity of dosage units (by weight)	Yes
Dissolution	Yes
Related substances	Yes
Microbial limits	Yes

Sufficient information has been provided on the formulation development.

Nilotinib is a BCS class IV compound (low solubility and low permeability). Physicochemical properties that might impact the bioequivalence and manufacturability (e.g. bulk and tapped density, compressibility, polymorphism) have been discussed. It has been confirmed that there are no changes of polymorphic form during finished product manufacture and storage.

The potential impact of nilotinib particle size distribution (PSD) on dissolution was also evaluated. Batches manufacturing using three different lots of active substance having different particle size distributions. The

study showed no considerable difference in in-vitro dissolution profile between studied particle size ranges. Hence, PSD test is incorporated in the active substance specification from the finished product manufacturer.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The three strengths originate from one common blend, and batch sizes can vary depending on the supply need for each strength.

Compatibility studies between the active substance and the excipients have been performed and no issues have been observed.

There are few differences between the reference product and the applied product.

Firstly, the salt form of the active substance. The applied product uses the free base nilotinib whereas the reference product contains nilotinib hydrochloride monohydrate (same as the Ph. Eur. monograph). Both are claimed to be as polymorph Form B, detailed information was provided clarifying that the free base and the salt form each have their own Form B.

Secondly, the surfactant/solubilizer in the reference product and Nilotinib Accord is different, being poloxamer 188 and Sepitrap 80 (mixture of polysorbate 80 and magnesium aluminiumsilicate), respectively. Due to the paediatric indication, the CHMP asked the applicant to provide a toxicological justification for the use of Sepitrap 80 in children. The levels of sepitrap 80 and its two components with respect to dosing in the paediatric population were adequately justified from a toxicological point of view and supported with reference to marketed products for paediatric population containing these two excipients in higher concentration.

The goal of the formulation development studies was to select the disintegrant (crospovidone), surfactant (polysorbate 80 and magnesium aluminometasilicate (sepitrap – 80)) and lubricant (magnesium stearate) levels and to understand if there was any interaction of these variables with assay and dissolution. A 2^3 factorial Design of Experiments (DoE) with three centre points was used to study the impact of these three formulation factors on assay and dissolution and select their levels in the formulation.

Contrary to the SmPC of the reference product (Tasigna) which states that "For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used (see section 5.2).", the originally proposed SmPC for Nilotinib Accord did not detail how patients who are unable to swallow hard capsules may take the product. The CHMP raised a multidisciplinary MO asking the applicant to justify this discrepancy. The applicant indicated that the reason for this absence was due to the existence of a patent that the innovator holds for oral administration of Nilotinib dispersed in apple sauce for patients having difficulty in swallowing. The proposed SmPC was updated to align with the existence of this patent, with the following warning under sections 4.2 and 4.4 of the SmPC and section 3 of the PIL: "For the patients with swallowing difficulties including paediatric patients that are not able to swallow the hard capsules other suitable medicinal product containing nilotinib should be used". Furthermore, to mitigate the risk for patients who are used to disperse the innovator product in applesauce and who might do the same for the proposed product, the applicant was requested by the CHMP to present *in-vitro* studies which demonstrate the compatibility of the test product with apple sauce and thus comparable pharmaceutical performance between the products. The pharmaceutical performance parameters i.e. tests assay, related substances, dissolution

study were performed and result showed that the test product is stable with apple sauce, thus the test product was found to be comparable with the reference product if consumed by any chance with applesauce.

The development of the QC dissolution method has been described, the method is based on FDAs published dissolution method and the applicant has provided justification for selection of pH, volume, apparatus and rotation speed.

The discriminatory power of the dissolution method has been demonstrated. The dissolution limits as revised following a MO from CHMP are acceptable.

Comparative dissolution studies have been performed comparing the lower strengths (50 mg and 150 mg) with the applied biobatch (200 mg). The studies were performed at 3 different pHs (1.2, 4.5 and 6.8) and similarity factor calculated. A biowaiver of strengths 50 mg and 150 mg has been applied. The product meets the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01). Based on the information provided the biowaiver can be accepted.

The manufacturing process development has been explained. Dry granulation by roll compaction was selected as the manufacturing process for this nilotinib product due to the poor flow properties and poor compressibility (Hausner ratio, bulk and tapped density). There are no critical steps or process parameters identified.

The primary packaging is PVC/PVdC-aluminium blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and appears adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of dispensing, sifting, blending, compaction encapsulating and packaging. The process is considered to be a standard manufacturing process.

Each strength is manufactured from a common blend. This can be distributed in numerous variations for the three strengths i.e.50 mg, 150 mg, 200mg, depending on the desired strength. There are no critical steps declared. The manufacturing process is controlled by several in-process controls that are performed at various stages of the process. Based on the data provided, the proposed hold time is accepted.

The manufacturing process has been validated at commercial scale for the common blend, divided into three batches for each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process for hard capsules filled with powder blend.

2.2.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, UV), water content (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution (HPLC), release (HPLC), related substances (HPLC), microbial limits (Ph. Eur.).

During the review the CHMP raised MO 4 on the originally proposed specification limit for dissolution since it was not fully in line with the results from the biobatch and the EMA reflection paper on the dissolution

specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017). This was satisfactorily addressed by the applicant.

The relevant limits for the impurities in the specification are acceptable, based on qualification and the batch analysis results.

The control of potential genotoxic impurities complies with ICH M7 and Ph. Eur. monograph from nilotinib.

The dissolution acceptance criteria and measurement time point were justified from various points of view, mainly that the pharmaceutical form of capsules gives certain variability the selected time point the most suitable, the variability escalates slightly during stability due to gelatine cross-linking.

Finally, the proposed limit for water content is accepted, limits at release and shelf life were tightened.

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*. Based on the risk assessment 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 assessment concerning the presence of nitrosamine impurities in the finished product was performed and a corresponding risk evaluation was submitted. However, the applicant did not consider the carry-over of dimethylacetamide to the finished product (with potential source of dimethylamine)., leading to a potential risk of formation of NDMA (96 ng/day). In addition, the active substance itself and degradation impurities do contain an amine, i.e. a diarylamine that, if nitrosated, would be considered as CPCA category 5, with an AI of 1500 ng/day. Therefore a MO 5 was raised asking the applicant to revise his risk assessment and evaluation. The applicant presented batch analysis data demonstrating the NDMA, DNDEA and NPYR were not detected and NMPA were below the qualification limit. The applicant also evaluated the active substance and finished product for the presence of N-nitroso nilotinib. The impurity was not detected. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific 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.

Batch analysis results are provided for three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of finished product from each strength stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive stability data from product in HDPE bottles (not proposed for registration) were also provided.

Samples were tested for description, identification (HPLC), water content, dissolution, assay, related substances and microbial quality. The analytical procedures used are the same as for release and were stability indicating.

No impurity was found above the reporting threshold, assay and genotoxic impurities were stable, and an increase in water content within the proposed limits was observer for all strengths under both storage

conditions. Variability was observed in dissolution results, these more pronounced under accelerated conditions. The CHMP asked the applicant to address this variability (MO 6). The applicant explained this as related to capsule/gelatin cross linking and improved results were seen when pepsin (tier 2) dissolution media was used. Consequently, the dissolution method was revised to include two methods:

Tier 1 dissolution method: For routine analysis of the dissolution samples.

Tier 2 dissolution method: When crosslinking is observed in the samples under analysis., in in line with Ph. Eur. 2.9.3.

This was shown to reduce the variability and is considered acceptable.

Bulk stability data was provided for all three strengths stored both at long term and accelerated conditions. At long term conditions a slight drop in dissolution was observed. At accelerated conditions the variability and sometime drop in dissolution was also seen, but all results were within the proposed specification.

Forced degradation studies were performed demonstrating the stability indicating nature of the related substances and assay methods. Conditions tested were acidic and basic hydrolytic conditions, oxidative conditions, solution containing iron, treatment with high heat and humidity and finally, photolytic degradation. For the finished product some or minor degradation was observed at acidic and oxidative conditions. No degradation was observed at basic, neutral, thermal, photolytic and high humidity.

In addition, one batch of each strength stored in the proposed blisters was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. There was no significant change in description, assay and related substances, concluding that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable

2.2.3.5. Post approval change management protocol.

Not applicable.

2.2.3.6. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is stated to be used in the product but some information is missing that is stated to be there, clarification is requested on this.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product has been developed as a generic of Tasigna. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Several quality major objections were raised during the procedure, i.e. MO1 on the selection of some of the starting materials and the control of nitrosamines in the active substance synthesis, MO2 on the discussion of

genotoxic impurities, MO3 on the control in the active substance specification of a genotoxic impurity not mentioned in Ph. Eur. monograph , MO4 on the dissolution specification limits, MO5 on the risk assessment on nitrosamines impurities, MO6 on the proposed shelf-life and storage conditions given the variability observed in the dissolution results, and a multidisciplinary major objection seeking clarity on the administration of the product to (paediatric) patients who might have difficulty with swallowing intact capsules. All these were satisfactorily addressed by the applicant.

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 when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

It is justified that the different form of nilotinib within the proposed generic product does not differ significantly in properties with regards to safety and efficacy of the reference product.

The impurity profile has been discussed and was considered acceptable.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Nilotinib 50 mg, 150 and 200 mg hard capsules by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the use of nilotinib-containing products and the exposure of the environment to the active substance. Additionally, no specific requirements are included in the SmPC and PIL in line with the reference product SmPC. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The applicant has not performed non-clinical studies. Non-clinical data are submitted from published

literature data. This is reasonable and acceptable since nilotinib is a well-known active substance. Grounds for not providing new non-clinical data are adequately justified. Therefore, the CHMP agreed that no further non-clinical studies are required.

The justification that the different form of nilotinib (nilotinib base) does not differ significantly in properties with regards to safety and efficacy of the reference product is acceptable.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

The impurity profile has been discussed and was considered acceptable.

Omission of Environmental Risk Assessment is justified and agreed.

2.3.4. Conclusion on the non-clinical aspects

Data presented are acceptable from the non-clinical point of view. There are no objections to the approval of Nilotinib Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

To support this marketing authorisation application the applicant submitted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for this 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 aspect

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.

Exemption

The bioequivalence study submitted in support of this application was performed using the highest strength (200mg hard capsule). An exemption for the lower strengths (50 mg and 150 mg) was included in the application.

The literature data presented by the applicant demonstrate the pharmacokinetics of nilotinib is dose-proportional within the submitted strengths (50-200mg) so the choice of the highest strength for the bioequivalence study is acceptable.

The dissolution comparison for the conclusion of similar dissolution profiles in support of a biowaiver for other strengths is acceptable since more than 85% is dissolved for the bio-batch strength and the additional strengths at pH 1.2, the only pH where any release of nilotinib occurs. The volume of 1000 mL is not considered to affect the comparative *in-vitro* dissolution results (refer to Quality assessment).

The biowaiver for the additional strengths is therefore accepted in line with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 09170/22-23: An open-label, balanced, randomized, single oral dose, two-treatment, two-sequence, four period, fully replicate crossover bioequivalence study of Nilotinib Capsules 200 mg of Shilpa Medicare Limited (India) with Tasigna (nilotinib) 200mg capsules of Novartis Europharm Limited in healthy, adult, human study participants under fasting conditions.

Methods

- **Study design**

The study was an open label, randomised, single dose, 4-period, 2-sequence, crossover bioequivalence study comparing two 200 mg nilotinib capsule formulations in healthy adult subjects under fasting conditions.

The primary objective was to assess the single oral dose bioequivalence of the sponsor's test product relative to that of reference product after single oral dose administration in normal, healthy, adult, human subjects under fasting condition.

Secondary objective was to monitor the safety of the subjects and tolerability and tolerability of nilotinib formulations under fasting conditions.

All subjects either received test product or reference product in each period according to the randomization schedule after ensuring maintenance of pre-dose restrictions (fasting for 10 hours prior to drug administration).

- **Test and reference products**

Test product: Nilotinib Accord capsules, 200mg manufactured by Shilpa Medicare Limited (India).

Reference product: Tasigna 200mg capsules marketed by Novartis Europharm Limited (Ireland).

- **Population(s) studied**

Eighty-one (81) study participants were enrolled, of which 62 study participants were found eligible for the study and found fit during screening tests performed.

Fifty-four (54) healthy adult subjects (all male; 22-45 years, BMI 18.6-29.9 kg/m^2) were dosed in Period I of the study.

Fifty-two (52) subjects, who completed at least two periods (one test and one reference treatment), were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

The study samples were analysed by a liquid chromatography (LC) method with tandem mass spectrometry (MS/MS) detection after liquid-liquid extraction using nilotinib-D6 as internal standard for the detection of nilotinib.

The method was validated over the calibration curve range from 4.005 to 4017.616 ng/ml.

A total of 4664 samples were analysed (520 missing samples). A total of 9 samples (0.19%) were re-analysed due to internal standard variation.

For incurred sample reanalysis 390 samples were run. All samples (100%) were found to be within a variation of 20% from the mean value.

The maximum sample storage period from the first blood draw to last analysis was 77 days at -70±15ºC for nilotinib. The sample storage period is supported by long term stability data of the analyte in the matrix (338 days at -70±15ºC) at LQC and HQC concentrations.

- **Pharmacokinetic variables**

Primary pharmacokinetic parameters: Cmax, AUC_{0-t}.

Secondary pharmacokinetic parameters: $AUC_{0-\infty}$, T_{max}, K_{el}, $t_{1/2}$ and extrapolated AUC.

- **Statistical methods**

The Ln-transformed pharmacokinetic parameters (Cmax and AUC0-t) were statistically analyzed using PROC GLM ANOVA model with the main effect of treatment, period, sequence and subject nested with in the sequence as fixed effects. A separate ANOVA model was used to analyze each of the pharmacokinetic parameters. The sequence effect was tested at the 0.10 level of significance using subject nested within the sequence mean square from the ANOVA as the error term. All the other main effects were tested at 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

Results

Table 3. Pharmacokinetic parameters for nilotinib in Study 09170/22-23 (non-transformed values)

Pharmacokinetic parameter	**Treatment T_1 (N=50)**	**Treatment T_2 (N=47)**	**Treatment R_1 (N=52)**	**Treatment R_2 (N=45)**
	arithmetic mean ± SD	**arithmetic mean ± SD**	**arithmetic mean ± SD**	**arithmetic mean ± SD**
$AUC_{(0-t)}$ (h*ng/mL)	11288.78 ± 4446.349	11113.88 ± 4194.945	11407.86 ± 3551.627	12642.90 ± 4144.313
$AUC_{(0-\infty)}$ (h*ng/mL)	12075.13 ± 4877.077	11755.72 ± 4581.956	12253.04 ± 3963.033	13445.88 ± 4765.978
C_{max} (ng/mL)	614.39 ± 185.731	587.34 ± 186.654	571.21 ± 164.775	615.56 ± 188.956
T_{max}*	2.33 (0.75 – 4.50)	2.67 (0.75 – 4.50)	3.67 (1.50 – 5.00)	3.67 (1.00 – 6.00)

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table 4. Statistical analysis for nilotinib (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Within-subject variability for reference product (%)	Within-subject CV%* (Test vs. Reference)
$AUC_{(0-t)}$ (h*ng/mL)	91.58	84.00 – 99.83%	20.26	37.23
C_{max} (ng/mL)	100.15	91.81 – 109.24%	20.59	37.51
* estimated from the Residual Mean Squares				

- **Safety data**

A total of 33 post-dose adverse events (AEs) were reported by 15 of the 54 subjects included in the study. Fifteen (15) AEs were reported after the single dose administration of the test product, nine (9) AEs were reported after the single dose administration of the reference product and nine (9) AEs were reported during post clinical assessment.

Of these 33 AEs, 25 AEs were considered mild in severity, 4 AEs were considered moderate in severity and 4 AEs were considered severe in severity.

Two (2) serious adverse events (swelling and pain of forearm) were reported in 2 subjects. The subjects were hospitalized for further management and treated accordingly, including required medications. For both subjects the SAEs were considered severe in severity and judged to be unlikely related to the study drug. Both SAEs were followed up until resolved.

2.4.2.2. Pharmacodynamics

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

2.4.2.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

This application concerns a generic version of nilotinib hard capsules. The reference product is Tasigna (50, 150 and 200mg hard capsules).

To support this application, the applicant submitted one bioequivalence study (study number 09170/22-23). The study was a single-dose, randomization, four-period, two-treatment, two sequence, cross-over bioequivalence study of two products of nilotinib capsules 200mg in healthy, adult, human subjects under fasting conditions. A total of 54 subjects were enrolled and dosed in Period 1, in line with the protocol. Fifty-two (52) subjects were included in the PK and statistical analysis.

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the design of the study is acceptable. The pivotal bioequivalence study was conducted in line with the general bioequivalence guidance in terms of design, analyte and parameters for bioequivalence assessment.

The results of study 09170/22-23 indicate that the test product was bioequivalent with the EU reference product under fasting conditions as the 90% CI of the ratio for geometric least square means of log-transformed data of AUC_{0-t} and C_{max} for nilotinib of the test product and reference product fell within the conventional acceptance criterion of 80.00-125.00%.

The within-subject reference product variability did not demonstrate nilotinib to be a highly variable drug product. The widening of the acceptance range for C_{max} was thus not possible and not needed since the 90% CI of the ratio for geometric least square means of ln-transformed data of C_{max} fell within 80.00-125.00%

The results of the bioequivalence study performed with the 200mg strength can be extrapolated to the additional strengths (50 and 150mg) according to conditions in Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr*, section 4.1.6).

The clinical-, bioanalytical- and statistical sites have limited experience with inspections by EU authorities according to the list of inspections provided. However, the latest inspections of the clinical-, and bioanalytical sites in 2023 assure acceptable GCP standards of the sites.

A summary of the literature with regard to clinical data of nilotinib and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

The SmPC of the originator product mention that the product should not be taken with food. However, in the same SmPC it is indicated that, for patients unable to swallow intact capsules, the content of the capsules may be dispersed in one teaspoon of apple sauce and taken immediately. The applicant of this generic product did not mention the use of the generic product dispersed in apple sauce due to a patent that the innovator holds for the oral administration of nilotinib dispersed in apple sauce.

The SmPC of the generic product indicates that patients with swallowing difficulties (including paediatric patients) who are unable to swallow the hard capsules, should be treated with other suitable product containing nilotinib.

In order to mitigate the risks for the patients who are used to dispersing the innovator product in apple sauce, and who might therefore do the same with the generic product, and be reassured of the efficacy of the generic product if by any chance dispersed in apple sauce, the CHMP requested the applicant to present *in-vitro* studies which demonstrate the compatibility of the test product with apple sauce and thus comparable pharmaceutical performance between the products. These studies were performed and submitted and they demonstrate the compatibility of the test product with apple sauce.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study (09170/22-23) Nilotinib Accord is considered bioequivalent with Tasigna.

The results of the bioequivalence study performed with the 200mg formulation can be extrapolated to other strengths (150mg and 50mg) according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 5: Summary of safety concerns

Important identified risks	• Significant bleeding • Severe infections • Growth retardation
Important potential risks	• Reproductive toxicity/pregnancy • Skin malignancy
Missing information	• Pediatric patients below 2 years of age

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of nilotinib hard capsules. The reference product Tasigna is indicated for the treatment of:

- adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase,
- adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available,
- paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical 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 09170/22-23 forms the pivotal basis with a cross-over design under fasting conditions. 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 Nilotinib Accord 200mg hard capsules met the protocol-defined criteria for bioequivalence when compared with the Tasigna 200mg hard capsules. 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.

Extrapolation of the in vivo data of the 200mg strength to the additional strengths (150mg and 50mg) is accepted.

This application contains a different salt of the active substance. A summary of the literature with regard to non-clinical and clinical data of Tasigna and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and accepted by the CHMP. This is in accordance with the relevant guideline and additional (non-) clinical studies were not considered necessary.

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. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Nilotinib Accord is not similar to Scemblix within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

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

Nilotinib Accord is indicated for the treatment of:

- adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase,
- adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available,
- paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

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 marketing authorisation holder (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.