HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

# Public Assessment Report

# Scientific discussion

## Nilotinib Zentiva
## 50 mg, 150 mg, 200 mg hard capsule

## (nilotinib hydrochloride dihydrate)

## HU/H/0885/001/DC

## Date: 17.02.2026

**This module reflects the scientific discussion for the approval of Nilotinib Zentiva 50 mg, 150 mg, 200 mg hard capsules. The procedure was finalised at** Day 210, 28.05.2024**. For information on changes after this date please refer to the module 'Update'.**

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for **Nilotinib Zentiva 50 mg, 150 mg, 200 mg hard capsules** from **PharOS Pharmaceutical Oriented Services Limited.**

The product 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

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

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.

# II. QUALITY ASPECTS

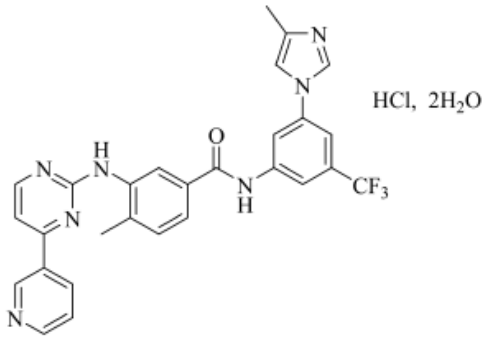
## II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Nilotinib 50 mg, 150 mg and 200 mg hard capsules via a decentralised procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application). The products have been developed by PharOS Ltd., Greece. Reference products are Tasigna hard capsules containing nilotinib as active ingredient, which are the original products of Novartis Europharm Limited.

## II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

International non-proprietary name (INN): nilotinib
Chemical name: (4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide, monohydrochloride, dihydrate
Structure:




The active substance is an off-white or yellowish solid, soluble in methanol, sparingly soluble in ethanol, and practically insoluble in toluene. It shows polymorphism, the manufacturers consistently produce the correct isomer and the same polymorphic form.

The ASMF holders presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by Infra-Red Spectrum (IR), Ultraviolet-Visible Spectrum (UV-Vis), Nuclear Magnetic Resonance Spectroscopy (NMR) (1H-NMR, 13C-NMR, 19F-NMR, COSY, HSQC and HMBC), High-resolution Mass Spectroscopy (HRMS), X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Nilotinib hydrochloride dihydrate is not described in the Ph. Eur., although a monograph for the monohydrate form exists. Therefore, an in-house specification has been set for the active substance by the drug product manufacturer, according to the following requirements of the active substance manufacturer: description, identification, sulphated ash, water content, related substances, genotoxic impurities, assay, residual solvents, HCl content. The specification of the drug product manufacturer is supplemented by additional specifications for particle size distribution, and microbiological purity.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A, ICH Q3A and ICH Q3C guidelines. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturers and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable in the prescribed packaging material.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

## II.3 Medicinal Product

The aim was to develop immediate release hard capsules for oral administration, containing 50 mg, 150 mg and 200 mg of the active substance Nilotinib in the form of hydrochloride dihydrate, bioequivalent and pharmaceutically equivalent to the European brand Tasigna from Novartis.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

50 mg: White to yellowish powder in hard HPMC capsule with red opaque cap and light yellow opaque body, size 4 (approximate length 14.4 mm), with black horizontal imprint “50 mg” on body
150 mg: White to yellowish powder in red opaque hard HPMC capsules, size 1 (approximate length 19.3 mm), with black horizontal imprint “150 mg” on body
200 mg: White to yellowish powder in light yellow opaque hard HPMC capsules, size 0 (approximate length 21.4 mm), with black horizontal imprint “200 mg” on body

The excipients used are lactose monohydrate, crospovidone, colloidal anhydrous silica and magnesium stearate. Components of the capsule shell are hypromellose, carrageenan, potassium chloride, titanium dioxide, yellow iron oxide, and in case of the 50 mg and 150 mg strengths, erythrosine and red iron oxide. All excipients used comply with their respective European Pharmacopoeia monograph or the relevant EU guidelines. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure systems of the product are Aluminium- PVC/PE/PVdC blisters or Aluminium-OPA/Alu/PVC blisters. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of "no special storage conditions" for the strengths 50, 150 and 200 mg stored in Aluminium-OPA/Alu/PVC blisters , "no special storage conditions" for 150 and 200 mg stored in Aluminium-PVC/PE/PVdC blisters and "Do not store above 30ºC" for 50 mg stored in Aluminium-PVC/PE/PVdC blisters are approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

*Conclusion*: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

## III. NON-CLINICAL ASPECTS

### III.1 Introduction

As the pharmacology, pharmacokinetics and toxicology of nilotinib are well known, no further non-clinical studies are required in support of this marketing authorisation.
The Applicant submitted a nonclinical overview based on a literature review of the pre clinical pharmacology, pharmacokinetic and toxicology characteristics of nilotinib which is considered adequate. No further studies are required.

### III.2 Pharmacology

No new non-clinical pharmacological studies were conducted by the Applicants.

### III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicants.

### III.4 Toxicology

Published information on toxicological studies with nilotinib was the basis for the evaluation.
No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

### III.5 Ecotoxicity/environmental risk assessment (ERA)

Since **Nilotinib Zentiva 50 mg, 150 mg, 200 mg hard capsules** are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.6 Discussion on the non-clinical aspects

The dossier concerned an abridged application that avoids the need for repetitive tests on animals and humans.
This product is a generic formulation of **Tasigna 50 mg, 150 mg, 200 mg hard capsules by Novartis Europharm Limited, Ireland.**

Tasigna® 200 mg has been centrally authorized in the European community since 19/11/2007 (EMEA/H/C/000798). Tasigna® 150 mg hard capsule was approved in the EU on 20/12/2010 (EMEA/H/C/000798/X/0028) as a line extension to the 200 mg strength. More recently, on 15/11/2017 (Procedure EMEA/H/C/000798/X/0088/G), an extension of the marketing authorization to add a new strength of 50 mg hard capsules has been approved.

Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Nilotinib is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required. For this generic application, the MAH has submitted a bioequivalence study, and the biowaiver has requested for the lower strengths (50mg, 150mg) which are discussed below.

## IV.2 Pharmacokinetics

Absorption
Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%. The absolute bioavailability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. In healthy volunteers, Cmax and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively, compared to fasting conditions when nilotinib is given with food. Administration of nilotinib 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively (see sections 4.2, 4.4 and 4.5).

Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution
The blood-to-plasma ratio of nilotinib is 0.71. Plasma protein binding is approximately 98% on the basis of in vitro experiments.

Biotransformation
Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib. Nilotinib is primarily metabolised by CYP3A4, with possible minor contribution from CYP2C8.

Elimination
After a single dose of radio labelled nilotinib in healthy subjects, more than 90% of the dose was eliminated within 7 days, mainly in faeces (94% of the dose). Unchanged nilotinib accounted for 69% of the dose.

The apparent elimination half-life estimated from the multiple-dose pharmacokinetics with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib pharmacokinetics was moderate to high.

Linearity/non-linearity
Steady-state nilotinib exposure was dose-dependent, with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once-daily dosing. Daily systemic exposure to nilotinib with 400 mg twice-daily dosing at steady state was 35% higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13.4% higher than at a dose level of 300 mg twice daily. The average nilotinib trough and peak concentrations over 12 months were approximately 15.7% and 14.8% higher following 400 mg twice-daily dosing compared to 300 mg twice daily. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice daily to 600 mg twice daily.

Steady-state conditions were essentially achieved by day 8. An increase in serum exposure to nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice-daily dosing.

**Bioequivalence study**

One pivotal bioequivalence study was performed in order to show bioequivalence between the Pharos Ltd. developed Nilotinib 200 mg hard capsules and the originator product, Tasigna® 200 mg hard capsules, under fasting conditions.

The study was conducted on 132 subjects under fasting conditions. After an overnight fasting of at least 10 hours, a single 200 mg oral dose of investigational product was administered to the subjects as per the randomization schedule in a sitting posture with about 240 mL of water at ambient temperature in each period under the supervision of trained study personnel. Investigational products (Test or Reference) were swallowed whole and were not chewed, crushed or divided.

In each period, total 24 venous blood samples (02 mL each) were collected in vacutainers containing $K_2$EDTA at pre-dose (0.0 hour) and at 0.5, 1.0, 1.5, 2.0, 2.333, 2.667, 3.0, 3.333, 3.667, 4.0, 4.333, 4.667, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours post dose. LC/MS/MS method to quantify Nilotinib in human plasma has been validated and found to be specific and sensitive.

Criteria for conclusion of bioequivalence:

The 90% confidence interval of the test/reference ratio (difference in least squares means) from the ANOVA of the Ln-transformed data for the PK parameter Cmax and AUC0-t should fall within 80.00% to 125.00% (both inclusive).

**Bioequivalence evaluation of Nilotinib**

| Pharmacokinetic parameter | Geometric Mean Ratio Test/Ref | Confidence Intervals | CV% |
|---|---|---|---|
| AUCt (ng*hr/mL) | 101.98 | 95.23% - 109.20% | 34.100 |
| Cmax (ng/mL) | 104.58 | 97.32% - 112.39% | 35.970 |

Safety

A total of ten (10) adverse events were reported by seven (07) subjects during the entire study. All AEs were mild in severity.

**Biowaiver**

Based on the presented data, the biowaiver requested for the lower strengths (50mg, 150mg) is acceptable.

## IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

## IV.4 Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy profile of nilotinib.

## IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

No new clinical safety studies were presented and no such studies are required for this application. The applicant has provided an adequate review of clinical trials published in the literature, describing the safety profile of nilotinib.

## IV.6 Discussion on the clinical aspects

The dossier concerned an abridged applications avoid the need for repetitive tests on animals and humans.

For this authorisation, reference is made to the clinical studies and experience with the innovator product **Tasigna 50 mg, 150 mg, 200 mg hard capsules by Novartis Europharm Limited, Ireland.**

Tasigna® 200 mg hard capsule has been centrally authorized in the European community since 19/11/2007 (EMEA/H/C/000798). The strength of 150 mg since 20/12/2010 (EMEA/H/C/000798/X/0028) and the strength of 50 mg since 15/11/2017 (EMEA/H/C/000798/X/0088/G) have been approved as a line extension to the 200 mg strength

No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## IV.7 Pharmacovigilance

**Product's name:** Nilotinib Zentiva 50 mg, 150 mg, 200 mg hard capsules
**Active substance:** nilotinib hydrochloride dihydrate
**MAH:** Zentiva, k.s.
**Reference number:** HU/H/0885/001-003/DC

### 1. Summary of Pharmacovigilance System

The Applicant (PharOS Ltd.) has submitted a signed Summary of the proposed MAHs' Pharmacovigilance System:

- dated on 27/04/2023 for Zentiva Group a.s. in the HU/H/0885/001-003/DC procedure

Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

## 2. Risk Management Plan

The following Risk Management Plans were acceptable.

- RMP, version 1.0, date of sign off: 27/03/2024 for the procedure HU/H/0885/001-003/DC where the MAH is Zentiva k.s.

### 2.1 Summary of safety concerns

| Summary of safety concerns | |
|---|---|
| Important identified risks | • Significant bleeding<br>• Severe infections<br>• Growth retardation |
| Important potential risks | • Reproductive toxicity/pregnancy<br>• Skin malignancy |
| Missing information | • Peadiatric patients below 2 years of age |

The summary list of safety concerns is acceptable, as it complies with the reference product's updated RMP (Tasigna hard capsules Version number: 25.0, dated on 18-May 2021).

### 2.2 Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which was endorsed.
However, follow-up questionnaires are in place in the originator's RMP as routine pharmacovigilance activities beyond ADRs reporting and signal detections for the following risks:

- Significant bleeding
- Severe infections
- Reproductive toxicity/pregnancy

Applicant has mentioned these questionnaires in Part III.1 and introduced them into Annex 4.

### 2.3 Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to products containing nilotinib. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

## 3. PSUR

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.

# V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

**Nilotinib Zentiva 50 mg, 150 mg, 200 mg hard capsules** have a proven chemical pharmaceutical quality and are a generic form of **Tasigna 50 mg, 150 mg, 200 mg hard capsules**. Tasigna is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.
**Nilotinib Zentiva 50 mg, 150 mg, 200 mg hard capsules** were registered in Hungary on 24. September 2024. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.
With reference to Article 8 of Regulation (EC) No 141/2000, (as defined in Article 3 of Commission Regulation (EC) No. 847/2000), there is no authorised orphan product in the treatment of CML so it does not prevent the granting of the marketing authorisation of Nilotinib.
The concerned member states, on the basis of the data submitted, have therefore granted a marketing authorisation.
The decentralised procedure was finalised with a positive outcome on Day 210, 28.05.2024.

**HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY**

# Modul 6
# Steps taken after the initial procedure with an influence on the Public Assessment Report

| Procedure number | Type of modification [1] | Date of start of the procedure | Date of end of procedure | Approval/non approval |
|---|---|---|---|---|
| HU/H/0885/IB/001/G | B.II.b).2.a). . Replacement or addition of a site where batch control/testing takes place B.II.d).1.g). Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue | 2024.08.06 | 2024.10.03 | Approved |
| HU/H/0885/2-3/IA/003 | B.II.e).5.a).1. Change within the range of the currently approved pack sizes | 2024.09.05 | 2024.10.05 | Positive |
| HU/H/0885/1/IB/002 | B.II.f).1.d). . Change in storage conditions of the finished product or the diluted/reconstituted product | 2024.09.05 | 2024.10.05 | Approved |

| | | | | |
|---|---|---|---|---|
| HU/H/0885/1-3/IB/004 | B.I.a).1.z). Other variation | 2024.09.25 | 2024.12.04 | Approved |
| HU/H/0885/1-3/IA/007 | B.I.a).3.a). Up to 10-fold increase compared to the originally approved batch size | 2025.10.22 | 2025.12.19 | Positive |