LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Palsiva
(palbociclib)

SE/H/2705/001-003/DC

This module reflects the scientific discussion for the approval of Palsiva. The procedure was finalised at 2026-02-11. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Palsiva, 75 mg, 100 mg, 125 mg, Film-coated tablet.

The active substance is palbociclib. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EF01

Mechanism of action
Palbociclib is a highly selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation

Claimed indication
For the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:
- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1).
In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

II.2 General comments on the submitted dossier

The applications for Palsiva, 75 mg, 100 mg, 125 mg, film-coated tablet, are Generic Art. 10(1) applications submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and MT as CMS.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ibrance, 125 mg, capsule, hard, authorised in the Union since 2016, with Pfizer Europe MA EEIG as marketing authorisation holder.

The reference product used in the bioequivalence study is Ibrance, 125 mg, film-coated tablet, from Germany with Pfizer Europe MA EEIG as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP

Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturers responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted studies has been provided. The clinical and the bioanalytical facilities were inspected by the UK authority (MHRA) in 2021, without any critical findings. No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of palbociclib are well known. As palbociclib is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

The nonclinical overview is written by Bala Krishna Rao Dabbir and contains 28 references spanning up to 2024.

Briefly, palbociclib is intended for treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination 1) with an aromatase inhibitor, 2) with fulvestrant in women who have received prior endocrine therapy.

Environmental Risk Assessment (ERA)
The applicant has provided an updated ERA document estimating the environmental exposure of Palbociclib and reached the conclusion that no increase in the environmental exposure is expected. Herein the applicant has calculated an PECsw and Italy was selected when refining Fpen yielding a PEC_{SW} of 0.0093 $\mu g/L$, which is below the threshold value of 0.01 µg/L. For the preliminary PBT/vPvB screening an experimental octanol/water partition coefficient Kow of 0.86 was provided and the Applicant concluded that no further PBT/vPvB assessment is needed for Palbociclib, since the Kow is < 4.5.

Phase I Risk Assessment

An initial calculation of PECsw was performed by the Applicant, using a default Fpen, estimating a maximum daily dose of 125 mg/patient/day. The resulting PECsw was estimated to 0.62 $\mu g/L$ which is above the threshold value of 0.01 µg/L. The Applicant proceeded with calculating a refined PEC_{SW} using a refined Fpen based on Italy as the country with highest disease prevalence. The refined PECsw was calculated to 0.0093 $\mu g/L$ concluding that Phase II of the ERA is not required for Palbociclib.

Preliminary PBT/vPvB screening
The Applicant provided experimental data determining a LogKow for Palbociclib of 0.86, which is below the trigger value of of Kow < 4.5, concluding that no further PBT/vPvB assessment is needed

Based on the data provided by the Applicant, Palsiva is not expected to pose a risk to the environment.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies (one under fasting conditions and one under fasting conditions and with pre-treatment with a proton pump inhibitor (PPI)) comparing Palsiva with the reference product Ibrance.

Pharmacokinetic properties of the active substance
Absorption: Palbociclib has an oral bioavailability of 46 %. Following an oral dose of palbociclib maximal plasma concentrations occur at approximately 4 to 12 hours. Food effect: The AUC_{inf} and C_{max} of palbociclib increased by 22% and 26%, respectively, when palbociclib tablets were given with a high-fat, high-calorie meal, and by 9% and 10%, respectively, when palbociclib tablets were given with a moderate fat, standard-calorie meal, compared to palbociclib tablets given under overnight fasted conditions. Based on these results, palbociclib tablets may be taken with or without food.

Linearity: The pharmacokinetics of palbociclib is linear within the dose range 25-225 mg.

Elimination: The terminal half-life is 29 hours.

Study NCS-935-23-CS (fasting condition)

Methods

This was a single-dose, two-way crossover study conducted in 30 (29 included in the statistical analysis) healthy volunteers, comparing palbociclib, 125 mg, film-coated tablets with Ibrance, 125 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of palbociclib were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 29 Aug and 22 Oct 2024.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for palbociclib n=29. (Study NCS-935-23-CS, single dose fasting).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2236.618 ±452.580**	**90.360±27.961**	**5.26 (4.50-10.00)**
Reference	**2238.860 ±458.732**	**88.362±25.849**	**6.50 (4.50-11.00)**
***Ratio (90% CI)**	**100.10 (97.61-102.66)**	**102.76 (98.95-106.72)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study NCS-934-23-CS (fasting condtion with multiple day pre-treatment with PPI)

Methods

This was a single-dose, two-way crossover study conducted in 30 (29 included in the statistical analysis) healthy volunteers, comparing palbociclib, 125 mg, film-coated tablets with Ibrance, 125 mg, film-coated tablets under fasting conditions and with multiple day pre-treatment with a PPI, i.e. pantoprazole (40 mg b.i.d. for 4 days). On day 5, pantoprazol was administered 4 hours prior to the investigational drug. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of palbociclib were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 27 Aug and 21 Oct 2024.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for palbociclib n=29. (Study NCS-934-23-CS, single dose, fasting conditions and pre-dosed with PPI (pantoprazole))

Treatment	AUC_{0-t} xg*h/ml	C_{max} xg/ml	t_{max} h
Test	**2679.287 ±684.011**	**101.673 ± 28.598**	**6.26 (4.50-8.52)**
Reference	**2509.749 ±578.985**	**97.692 ± 24.526**	**6.00 (3.50-10.03)**
***Ratio (90% CI)**	**106.41 (103.13-109.79)**	**103.85 (98.83-109.12)**	
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

A biowaiver was sought for the additional strengths of 75 mg and 100 mg.

Discussion and overall conclusion
The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022) as well as in EMA's product specific bioequivalence guidance for palbociclib. The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 75 mg and 100 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of palbociclib is linear between 25 mg and 225 mg.

Based on the submitted bioequivalence studies, Palsiva is considered bioequivalent with Ibrance.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: Adalvo Limited

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. 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.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Palsiva.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 11-11-2024 and proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Reproductive and Developmental Toxicity
Missing information	• None

The summary of safety concern is in line with the summary of safety concerns for the originator IBRANCE and is thus considered acceptable.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 11-11-2024 is considered acceptable.

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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Palsiva is found adequate. There are no objections to approval of Palsiva, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to IBRANCE, EMEA/H/C/003853

regarding content and Ticagrelor 60/90 mg film-coated tablets, EE/H/0338/001-002/DC regarding layout.
The bridging report submitted by the applicant has been found acceptable and applies to Palsiva.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-