EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2026
EMA/CHMP/78118/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Palbociclib Viatris

International non-proprietary name: palbociclib

Procedure No. EMEA/H/C/006624/0000

Note

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

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Administrative information

Name of the medicinal product:	Palbociclib Viatris
Applicant:	Viatris Limited Damastown Industrial Park Mulhuddart Dublin 15 Co. Dublin D15 XD71 IRELAND
Active substance:	palbociclib
International Non-proprietary Name:	palbociclib
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors (L01EF01).
Therapeutic indication(s):	Palbociclib Viatris is indicated 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.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	75 mg, 100 mg and 125 mg
Route(s) of administration:	Oral use
	blister (OPA/Alu/PVC/Alu), bottle (HDPE),

Packaging:	calendar (OPA/Alu/PVC/Alu) and calendar blister (OPA/Alu/PVC/Alu)
Package size(s):	21 tablets, 21 x 1 (unit dose) tablets, 63 tablets, 63 x 1 (unit dose) tablets and 100 tablets

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List of abbreviations

ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AP	Applicant's Part (or Open Part) of a ASMF
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the Curve
ANOVA	Analysis of variance
AST	Serum aspartate transaminase
AV	Atrioventricular
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BLQ	Below limit of quantitation
BMI	Body Mass Index
BP	Blood pressure
BCRP	Breast Cancer Resistance Protein
C_{max}	Maximum observed blood concentration
CI	Confidence Interval
CDK	Cyclin-dependent kinases
CRF	Case report form
CV	Coefficient of Variation
CYP	Cytochrome P450
CoA	Certificate of Analysis
CV	coefficient of variation
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EC	European Commission
ECG	Electrocardiogram
EDTA	Ethylene Diamine Tetra Acetic Acid
EMA	European medicines agency
ERA	Environmental risk assessment
ESR ANC	Absolute neutrophil count Erythrocyte Sedimentation Rate
ER	Estrogen receptor

K_2EDTA	Dipotassium Ethylene Diamine Tetra
Fpen	Fraction of market penetration
GC	Gas Chromatography
GLP	Good Laboratory Practice
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IP	Investigational Product
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
ISR	Incurred Sample Reanalysis
KF	Karl Fischer titration
LC/MS/MS	Liquid chromatography coupled to tandem mass spectrometry detection
LDPE	Low density polyethylene
Log Kow	Logarithm of octanol/water partition coefficient
LSM	Least-squares means
NMT	Not more than
NDEA	N-Nitrosodiethylamine
NDIPA	N-Nitrosodiisopropylamine
NDMA	N-Nitrosodimethylamine
NEIPA	N-Nitrosoethylisopropylamine
NF	National Formulary
NMT	Not more than
NOAEL	No-observed-adverse-effect level
OPA	Oriented Polyamide
PBT	Persistent, Bioaccumulative and Toxic
PDE	Permitted daily exposure
PECsw	Predicted environmental concentration in surface water
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic

PSBG	Product specific bioequivalence guidance
PTs	Preferred terms
PPI	Proton pump inhibitor
PVC	Polyvinyl chloride
QC	Quality Control
(Q)SAR	(Quantitative) Structure-Activity Relationship
RH	Relative Humidity
RP	Restricted Part (or Closed Part) of an ASMF
RSD	Relative Standard Deviation
SAE/s	Serious Adverse Event/s
SCARs	Severe cutaneous adverse reactions
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
TAMC	Total Aerobic Microbial Count
T_{max}	Time of maximum observed blood
TYMC	Total Combined Yeasts/Moulds Count
ULN	Upper limit of normal
UV	Ultraviolet
vPvB	very Persistent and very Bioaccumulative
WBC	White blood cells
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 5 May 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Palbociclib Viatris, 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 25 July 2024.

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 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:

Palbociclib Viatris is indicated 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.

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 IBRANCE 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: IBRANCE 75 mg, 100 mg & 125 mg film-coated tablets
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 09-11-2016
- Marketing authorisation granted by: Union
- Union Marketing authorisation numbers: EU/1/16/1147/010-018

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

- Product name, strength, pharmaceutical form: IBRANCE 75 mg, 100 mg & 125 mg film-coated tablets
- Marketing authorisation holder: Pfizer Europe MA EEIG

- Date of authorisation: 09-11-2016
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/16/1147/010-018

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: IBRANCE 125 mg film-coated tablets
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 09-11-2016
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/16/1147/014, EU/1/16/1147/015 & EU/1/16/1147/018
- Bioavailability study number(s): PALB-TFZ-1007 & PALB-TFZ-1008

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 did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

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 were:

Rapporteur: Jana Klimasová Co-Rapporteur: N/A

The application was received by the EMA on	5 May 2025
The procedure started on	22 May 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 August 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 August 2025

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	18 September 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2025
The following GCP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 2 CRO sites in India between 18 and 25 November 2025. The outcome of the inspection carried out was issued on	13 January 2026
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 February 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 February 2026
The CHMP Rapporteur circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	19 February 2026
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 February 2026
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	24 March 2026
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	9 April 2026
The CHMP Rapporteur circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 April 2026
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 Palbociclib Viatris on	23 April 2026

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation submitted via centralised procedure concerns a generic application according to article 10(1) of Directive 2001/83/EC for Palbociclib Viatris (palbociclib) from Viatris Limited.

The reference medicinal product is IBRANCE 75 mg, 100 mg & 125 mg film-coated tablets (MAA No: EU/1/16/1147/010-018, MAH: Pfizer Europe MA EEIG) for which a marketing authorisation was

granted in the European Union on 9 November 2016 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

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.

The applicant submitted 2 bioequivalence studies using the 125 mg strength to support this generic application in line with the recommendations from the product specific bioequivalence guidance for palbociclib (EMA/CHMP/802679/2018 Rev.1* Corr. 1**). In addition, the applicant submitted a biowaiver request for the lower strengths of palbociclib 75 mg and 100 mg film-coated tablets not tested in the bioequivalence studies based on conditions in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

The safety and efficacy profile of palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer has been demonstrated in several clinical trials for the reference medicinal product IBRANCE. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

The reference product IBRANCE is available as 75 mg, 100 mg and 125 mg film-coated tablets in pack sizes of 21 tablets in blister (PVC/OPA/Alu/PVC/Alu), blister (PVC/OPA/Alu/PVC/Alu) in wallet carton and 63 tablets in blister (PVC/OPA/Alu/PVC/Alu). Palbociclib Viatris is intended to be marketed as 75 mg, 100 mg and 125 mg film-coated tablets in pack sizes of 21, 63, 21 x 1 (unit dose), 63 x 1 (unit dose) tablets in blister (OPA/Alu/PVC/Alu), 21 tablets in calendar blister (OPA/Alu/PVC/Alu) and 100 tablets in bottle (HDPE).

This generic has applied for all the approved indications of the reference product IBRANCE:

Palbociclib Viatris is indicated 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.

The recommended dose is 125 mg of palbociclib once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. The treatment with Palbociclib Viatris should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

When co-administered with palbociclib, the aromatase inhibitor should be administered according to the dose schedule reported in the Summary of Product Characteristics. Treatment of pre/perimenopausal women with the combination of palbociclib plus an aromatase inhibitor should always be combined with an LHRH agonist (see section 4.4).

When co-administered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15, 29, and once monthly thereafter. Please refer to the Summary of Product Characteristics of fulvestrant. Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 75 mg, 100 mg and 125 mg of palbociclib as active substance.

Other ingredients are:

Core tablet: microcrystalline cellulose, lactose monohydrate, crospovidone, ascorbic acid, colloidal silica anhydrous, magnesium stearate

Film coating: hypromellose (E464), titanium dioxide (E171), triacetin (E 1518). In addition,

- for the 75 mg and 125 mg strengths: iron oxide red (E172) and iron oxide black (E172);

- for the 100 mg strength: indigo carmine aluminium lake (E132) and iron oxide yellow (E172).

The product is available in OPA/Alu/PVC/Alu blisters and HDPE bottle with white opaque polypropylene child-resistant screw cap, aluminium induction sealing with desiccant.

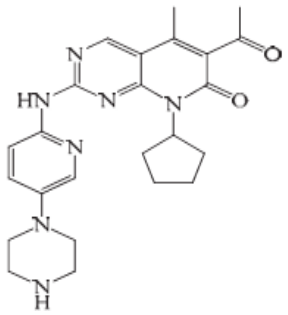
2.2.2. Active substance

An EU ASMF procedure has been used for the active substance palbociclib:

2.2.2.1. General Information

The chemical name of palbociclib is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one corresponding to the molecular formula $C_{24}H_{29}N_7O_2$. It has a molecular mass of 447.54 g/mol and the following structure:

Figure 1 Active substance structure



The chemical structure of palbociclib was elucidated by a combination of 1H and 13C NMR, MS, UV, IR and elemental analysis. The solid state properties of the active substance were measured by DSC and PXRD.

The active substance is a non-hygroscopic yellow to orange powder. Palbociclib is insoluble in water. It is a BCS class II (low soluble and high permeable) compound.

Palbociclib does not have any chiral centre and therefore does not exhibit stereoisomerism.

Polymorphism has been observed for palbociclib; two polymorphic forms are reported in literature (A and B). It has been demonstrated that the manufacturing process constantly produces single crystalline form; the consistency of this polymorphic form has been confirmed by XRPD spectra.

The crystalline form remains stable during stress conditions (pressure, thermal, UV light and hygroscopicity analysis). The polymorphic form is routinely controlled in the active substance specification.

2.2.2.2. Manufacture, characterisation and process controls

Palbociclib is synthesised in five main steps using well defined starting materials with acceptable specification.

The commercial manufacturing process for the synthesis of the active substance palbociclib utilizes three acceptable starting materials and is executed in four chemical reactions with isolation of four crystalline intermediates. Reprocessing, recovery of materials, reworking, micronisation of the active substance and blending of batches are not applied in the current manufacturing process.

Sufficient information on the synthesis route of the active substance is provided in the applicant's part of the ASMF. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

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 nine solvents used in the synthesis of palbociclib, are routinely tested in the final active substance; the limits are those stated in ICH Q3C guideline. No class 1 solvent is employed in the synthesis. Since absence of benzene, as a potential contaminant in simple alcohols and acetone, was demonstrated in palbociclib active substance, test for benzene is not included in the final active substance specification.

Palbociclib is used in the treatment of advanced cancer as defined in the scope of ICH S9. Therefore, ICH M7 guideline does not apply. Based on ICH S9 guideline potential genotoxic impurities can be controlled as per ICHQ3A(R2) Guidance.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. No significant changes were made during scale-up.

The active substance is packaged in a low density polyethylene (LDPE) bag, which complies with EC 10/2011 as amended. The LDPE bag is packed in black colour LDPE bag, kept in triple laminated bag and stored in high-density polyethylene (HDPE) container.

2.2.2.3. Specification(s)

The active substance specification includes tests for description (in-house), solubility (Ph. Eur.), identification (IR – Ph. Eur., HPLC – in-house), water content (KF - Ph. Eur.), sulfated ash (Ph. Eur.), related substances (HPLC – in-house), assay (HPLC – in-house), residual solvents (GC – in-house), palladium (ICP-MS – in-house), identification of polymorph (PXRD – in-house) and particle size distribution (Malvern – in-house).

The information related to the specification of the active substance provided by the applicant in section 3.2.S.4 is aligned with the information provided by the ASMF (applicant's part). The finished product manufacturer specification tests and analytical methods are the same as those of the active substance manufacturer specification with the additional control of particle size. The proposed specification of palbociclib meets the requirements of ICH Q3A and ICH Q6A. The limit of total impurities has been tightened based on batch analysis data and stability results, as requested during the assessment. Omission of the microbiological quality testing is supported by acceptable batch analyses data of sixteen commercial scale batches.

The description of all analytical methods has been provided. Validation of the method for particle size determination by the finished product manufacturer has been presented. For validation reports of the other methods used for quality control of active substance, reference to ASMF section is made. The analytical method transfer reports have been provided by the finished product manufacturer, and it can be concluded that the methods were successfully transferred. Overall, 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.

The batch analysis data for eleven commercial scale active substance batches are presented. 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 the intended commercial package for up to 60 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 following parameters were tested*:* description, identification, water content, related substances, assay and polymorphic identification. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under all conditions tested. No clear trends were observed. No restrictions concerning temperature storage conditions are needed since data from accelerated studies met the specification. Therefore, the ASMF holder was requested to remove any statements to temperature storage conditions originally proposed, in line with the EMA Guideline on Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances.

Photostability testing following the ICH guideline Q1B was performed on one batch which demonstrated that palbociclib is not sensitive to light.

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 60 months in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is presented as immediate release film-coated tablets for oral administration.

The product is available in three strengths, which can be distinguished from one another by differences in size, shape (round vs oval), colour (purple vs green) and debossed markings (PL1 vs PL2 vs PL3):

- Palbociclib 75 mg film-coated tablets are presented as a purple, film-coated, round, biconvex, bevelled edge tablets debossed with V on one side of the tablet and PL1 on the other side. Diameter: 9.60 ± 0.5 mm.
- Palbociclib 100 mg film-coated tablets are presented as green, film-coated, oval, biconvex, bevelled edge tablet debossed with V on one side of the tablet and PL2 on the other side. Dimensions: 14.40 ± 0.5 mm x 7.40 ± 0.5 mm.
- Palbociclib 125 mg film-coated tablets are presented as purple, film-coated, oval, biconvex, bevelled edge tablet debossed with V on one side of the tablet and PL3 on the other side. Dimensions: 15.50 ± 0.5 mm x 8.40 ± 0.5 mm.

The finished product has been developed to be a generic equivalent to the reference medicinal product Ibrance 75 mg, 100 mg and 125 mg film-coated tablets. The pharmaceutical development of Palbociclib 75 mg, 100 mg and 125 mg film-coated tablets was based on active substance characteristics and analysis of the reference product.

Palbociclib active substance used in the manufacturing process of the finished product is the crystalline form. The intactness of this polymorphic form during the manufacturing process and storage of the finished product was confirmed in a stability study storing samples of active substance, placebo tablets and palbociclib tablets packed in HDPE bottle, blisters, and simulated bulk packaging at 25°C/60 % RH and 40°C/75 % RH for 6 months and evaluating their XRD patterns.

Based on the physicochemical properties of the active substance, an initial risk assessment of active substance attributes impacting the finished product CQAs was performed.

The excipients used in the generic product were selected based on excipient compatibility studies and functionality. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, except of film-coating premixes which are proprietary materials purchased from an established commercial supplier. The individual compendial components used in the manufacturing of film-coating premix comply with the Ph. Eur. / NF monograph. The colourants used in film-coating premixes comply with Commission Regulation (EU) No 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients of the tablets is included in section 6.1 of the SmPC

The functionality-related characteristics of the excipients have been discussed and included in the excipients' specification as appropriate.

An active substance-excipient compatibility study has been performed, demonstrating that the selected excipients are compatible with the active substance.

Since palbociclib has poor to very poor flow characteristics, as indicated under API characterisation study, the direct compression process was not considered for manufacturing of tablets. Wet granulation process was not considered as it requires solvent and multiple processing steps. The prototype formulation development was initiated using the dry granulation process and optimisation studies focused on the influence of the concentration of several excipients were carried out. Additionally, the influence of several process parameters on tableting characteristics and dissolution was investigated. The formulation used during clinical studies is the same as that intended for marketing.

A dissolution method was developed for palbociclib tablets. The effect of different paddle speed was evaluated. Based on these observations, the agitation speed was selected. The selected dissolution

method for QC purposes has been sufficiently justified. The dissolution method was found to be discriminatory with respect to the influence of tablet composition and processing parameters To support the results obtained in the BE studies, a comparative dissolution study between the test bio-batch of the proposed 125 mg product and the reference product Ibrance 125 mg across the physiological pH range (0.1 N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8) was conducted. As more than 85 % of the labelled amount of the active was released within 15 minutes from both formulations in 0.1N HCl (release medium) and pH 4.5 acetate buffer, and the similarity factor (f2 value) between the reference and test products was found to be higher than 50 in pH 6.8 phosphate buffer, the dissolution profiles were considered similar. *In-vivo* bioequivalence has been evaluated and demonstrated between the test formulation and the reference product (see clinical section). Since the *in-vivo* results prevail, higher rotation speed used for comparative dissolution profile is accepted.

A biowaiver for the 75 mg and 100 mg strengths has been applied. The product meets the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01): all strengths are manufactured by the same manufacturing process; the qualitative composition is the same and quantitatively proportional. Comparative dissolution profiles were provided for the 75 mg strength and 100 mg strength versus the 125 mg bio-batch Batches were tested across the physiological pH range (0.1 N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8) at two agitation speeds. The dissolution profiles in 0.1N HCl (release media) and pH 4.5 acetate buffer at the lower agitation speed were considered similar, as more than 85 % of the labelled amount of the active was released within 15 minutes from the formulations. For pH 6.8 phosphate buffer, the similarity factors (f2 values) between the test product strength used in the bioequivalence studies (125 mg) and other strengths (75 mg and 100 mg) of the test product were calculated and found to be greater than 50. Since the observed % RSD value for 75 mg strength at the lower agitation speed in first time point was higher than the guideline requirement (RSD = 25.5 %), the biowaiver for the 75 mg strength could not be accepted at day 120. On the basis of a multidisciplinary major objection, the bootstrapping methodology was applied to compare the dissolution profile of the 75 mg with the 125 mg strength (bio-batch) in pH = 6.8. The results of the Bootstrap analysis performed using a validated SAS program showed that the two strengths were found to be similar, as f2 values at 5^{th} percentile, median and 95^{th} percentile are greater than 50. In line with Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98- Rev 01), the similarity between the bio-batch of 125 mg strength and bio-waiver lower strength of 75 mg has therefore been demonstrated.

The primary packaging is OPA/Alu/PVC/Alu blisters and HDPE bottle with white opaque polypropylene child-resistant screw cap, aluminium induction sealing with desiccant. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process consists of ten main steps: dispensing, sifting, pre-compaction blending, compaction, milling & sifting, mixing of granules, final blending with extra-granular material, compression, film coating, and packaging. The process is considered to be a standard manufacturing process.

In-process controls (IPCs) and acceptance criteria applied during the manufacturing process have been presented and IPCs applied during manufacturing process are sufficient.

The proposed batch size range has been defined Major steps of the manufacturing process have been validated by a number of studies. Process validation protocols for the higher batch size have been provided. Based on the submitted process validation data, the proposed batch sizes are considered acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specification(s)

The finished product specification include appropriate tests for this kind of dosage form: description (in-house), identification (UPLC – in-house), dissolution (UPLC – in-house), uniformity of dosage units by content uniformity (in-house), assay (UPLC – in-house) water (KF – Ph. Eur.), related substances (HPLC – in-house), microbial test (TAMC, TYMC, E. coli) (Ph. Eur.), colour identification (titanium dioxide, iron oxide, indigo carmine aluminum lake) (in-house), dimensions (in-house).

The release and shelf-life specification of the proposed finished product include universal and specific tests following the requirements of the guideline ICH Q6A and Ph. Eur. monograph for tablets 01/2018:0478. Parameters tested during stability studies are defined. The proposed skip testing for microbiological quality and colour identification is acceptable.

Limits for individual specification parameters are clearly defined. Limit for assay is in line with Directive 2001/83/EC. Dissolution of the active substance is tested and limit is set in accordance with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action and biobatch dissolution data.

Two impurities have been identified in the finished product. They are classified as degradation impurities and metabolites of the active substance. Although the originally proposed release limit for one of them was supported by toxicological risk assessment, the applicant was requested to tighten it in line with batch analyses data. The release specification limits for both specified impurities are now in compliance with the ICH Q3B guideline (identification and qualification threshold is 0.2 % for maximum daily dose 125 mg). Considering that one of these impurities is a metabolite of palbociclib, the observed levels during the stability study of the finished product and the toxicological risk assessment (see non-clinical section), the applicant proposed to revise its shelf-life limit %. The shelf-life limits for both specified impurities have been justified by the nature of the impurity and the toxicological risk assessment and is considered acceptable. The proposed release and shelf-life limit for any unknown impurity is NMT 0.2 % which corresponds with the identification and qualification thresholds defined by the ICH Q3B guideline. The limit for total impurities is the same for both specifications and it is acceptable.

Release limit for water content determined by KF has been tightened during the review to correlate with results from batch analyses. Shelf-life limit for water contentis in accordance with stability data.

Comparison of the impurity profiles of the proposed finished product and the reference product has been presented under the development section. The impurity profiles of the reference product and the proposed drug product are comparable

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The following sources of elemental impurities have been considered: the active substance, excipients, solvent (water), manufacturing equipment and primary packaging material. Since palladium is used in the manufacture of palbociclib active substance, palladium is controlled in the final active substance specification. Batch analysis data on three finished product batches per strength using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity (Class 1 and 2A) was not detected

above 30 % of the respective PDE. Based on the risk assessment and the presented batch data 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 potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the chemical structure of the active substance, there is a possibility to form three nitrosamines, N-nitroso palbociclib-1, N-nitroso palbociclib-2 and N-nitroso palbociclib-3. Based on experimental observations, it was concluded that there is no risk of formation of two of these, whereas formation of one of them is considered possible. This was detected by the active substance manufacturer in the active substance batches. Due to the presence of nitrosating agents in the finished product formulation, the finished product manufacturer conducted testing of the newly produced finished product batches and, as requested by CHMP during the review, also of batches closer to their expiry datefor the presence of that impurity,NDMA, NDEA, NEIPA and NDIPA. The impurities NDMA, NDEA, NEIPA and NDIPA were below the detection limit in all finished product batches.The third nitrosamine impurity referred above was detected in all tested batches (three batches per strength) below the reporting threshold of 0.2 % in line with ICH Q3B guideline. Based on the information provided, including the confirmatory testing results, 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 from each product 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 each finished product strength stored for up to 12 months under long term (25ºC / 60% RH) and intermediate (30 ± 2°C / 75 ± 5 % RH) conditions and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of Palbociclib Viatris are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing (proposed OPA/Alu/PVC/Alu blister and HDPE bottle).

Samples were tested for appearance, assay, dissolution, water content, related substances and microbial test. The analytical procedures used are stability indicating.

All parameters were within the specification limits, except for related substances, which were out of specification under accelerated storage conditions. While the results were generally comparable across both packaging types, the batches packaged in HDPE bottles exhibited slightly lower levels of impurities.

In the initial submission the applicant proposed a shelf-life of 24 months and the storage conditions "Do not store above 30°C". This extrapolation was not accepted given the limited data presented at the time (6 months under long and intermediate conditions) and the out of specification results observed under accelerated conditions. In his responses the applicant provided data from up to 12

months of storage under long and intermediate conditions and proposed extending shelf-life specification limit for one of the impurities %. This was accepted and as a result there are no more out of specification results under accelerated conditions. Based on the data provided, the shelf-life of the proposed finished product was revised to 18 months, in line with ICH Q1E, and the storage conditions were corrected to "The medicinal product does not require any special storage conditions", in line with the *Guideline on declaration of storage conditions* (CPMP/QWP/609/96/Rev 2).

In addition, during the review the CHMP requested the applicant to present in-use stability data for Palbociclib 75 mg, 100 mg, and 125 mg film-coated tablets in the multi-dose container 100's HDPE bottle pack on two batches of each strength in line with *CPMP Note for Guidance on In-use Stability Testing of Human Medicinal Products* (CPMP/QWP/2934/99) and Quality of medicines questions and answers, part 2., or a justification for non-establishing in-use shelf-life supported by experimental results. The applicant presented in-use stability data up to 180 days which were compliant with the product specification. An in-use stability protocol in line with the above-mentioned guidance was also provided and the applicant committed to continue the in-use stability study. No relevant changes were observed after 6 months, so in accordance with EMA's Quality of Medicines – Questions and Answers (Part 2), no in-use shelf life is set.

The forced degradation study of Palbociclib tablets determined the stability-indication nature of the employed methods (assay and related substances). Samples of finished product were exposed to acid and heat, oxidation, water and heat, humidity, heat, UV light and white light. The highest degradation was observed under oxidation.

A bulk stability study up on three bulk batches per strength stored for 6 months under accelerated (40 ± 2°C / 75 ± 5 % RH), up to 12 months under intermediate (30 ± 2°C / 75 ± 5 % RH), and up to 12 months under long-term (25 ± 2°C / 60 ± 5 % RH) conditions in a simulated bulk pack (polyethylene bag) has been provided. The samples were tested for description, dissolution, assay, water content, related substances and microbiological contamination. All data remained within the specification limits. Based on the available hold time stability data, the holding period of 12 months with storage conditions of "Do not store above 25°C and store in original container" is acceptable.

Based on available stability data, the proposed shelf-life of 18 months and with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

It is confirmed that the start of shelf life of the finished product shall be calculated on the basis of the recommendation outlined in the *CPMP Note for Guidance on start of shelf-life of the Finished Dosage Form* CPMP/QWP/072/96.

2.2.3.5. Post approval change management protocol(s)

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.

A confirmation of the vegetable origin of magnesium stearate has also been submitted, along with the corresponding TSE/BSE declaration.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product has been developed as an essentially similar generic version of the reference product Ibrance 75 mg, 100 mg and 125 mg film-coated tablets. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. Recommendation(s) 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.

Toxicological qualification was provided for the two drug product related impurities.

2.3.2. Pharmacology

Not applicable.

2.3.3. Pharmacokinetics

Not applicable.

2.3.4. Toxicology

2.3.4.1. Other toxicity studies

Studies on impurities

The related substance impurities are mentioned in the drug product specification with a limit of not more than (NMT) 0.5%, which exceeds the ICH Q3B(R2) qualification threshold based upon a maximum palbociclib daily dose of 125 mg and NMT 0.2%. A summary of the qualification strategy for

this impurity is described below. The metabolism of palbociclib involves glucuronidation, sulfonation, acetylation, formylation, oxidation and reduction. In humans, the glucuronide conjugate of palbociclib was the most abundant metabolite, at 14.8% of circulating radioactivity. The specific impurity, metabolite of palbociclib was present in plasma at low level (1.5%). As specifically stated in the ICH Q3B(R2), "*impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified*". Considering that this specific impurity is a metabolite of palbociclib, this impurity could be considered qualified at NMT 0.5%. Per the ICH Q3B(R2) and M7 Guidelines, a hazard assessment including database and literature searches was conducted. As no such data was identified in the public domain, an ICH M7-compliant computational toxicology assessment was performed for this impurity to predict the outcome of a bacterial mutagenicity assay. Two separate quantitative structure activity relationship (QSAR) programs were used for this analysis, including Derek Nexus (expert rule-based) and the Leadscope Model Applier (statistical-based and expert rule-based). Based upon the absence of structural alerts for bacterial mutagenicity via both analyses for this specific impurity it is considered to be a Class 5 impurity per ICH M7 and thus treated as non-mutagenic. Additionally, the All-Endpoints Derek Nexus analysis was conducted for both the impurity and the parent molecule using all available species *(in vitro* and *in vivo*) and endpoints. A minimum reasoning level of equivocal was used. Both the impurity and palbociclib did not fire any alerts at the selected reasoning level.

In addition, a repeat dose (28 days) oral toxicity study for the same impurity as conducted in Wistar rats. The details of the study are summarized below.

The study was conducted at three dose levels of test item (approximately 1-, 3- and 10-fold the maximum potential daily exposure in humans on a body surface area basis). Concurrent vehicle control group animals were treated with vehicle alone.

The assessment of toxicity was based on mortality, clinical signs, body weights, feed consumption, clinical and anatomic pathology. All animals survived up to the scheduled termination. All the animals were normal and free from all visible clinical signs throughout the study period. No abnormalities were detected in the ophthalmoscopic examination of animals before treatment in all animals and during the last week of exposure period in animals from the vehicle control and high dose groups. Body weight and food consumption of all the dose groups were comparable to the respective vehicle control groups throughout the experimental period in both sexes. No test item related changes were observed in any of the haematology, clinical chemistry, coagulation and urinalysis parameters in test item treated groups as compared with vehicle control group. No test item related organ weight changes were observed in any of the organ in test item treated groups as compared with vehicle control group. Gross pathological examination did not reveal any abnormalities attributable to the test item in any of the treated animals. On histopathological examination, no test item related findings were observed in high dose animals in both sex when compared with vehicle control animals.

Based on the above findings, it was concluded that the NOAEL of this specific impurity following 28-days repeated dose oral administration in Wistar rats was 0.65 mg/kg b.w./day.

Table 1 Repeat-dose toxicity study

Study details	**No:Sex/ Group**	**Dose** (mg/kg/ day)	**Major findings & NOAEL**
RAT (Wistar) 4 w PO GLP	6M/6F	[****]	No relevant salient findings at any of the tested doses. **NOAEL 0.65 mg/kg**
		[****]	
		[****]	
		[****]	

During the evaluation, a heightened specification limit of NMT 0.5 % (625 µg/day) was proposed by the Applicant for another impurity (acetic acid adduct, potential process and degradation impurity). As stated in the ICH Q3B(R2), impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified. As stated above, human metabolism of palbociclib also involves acetylation. This one is a minor metabolite which was present in human plasma at a level of 1.0 % (described as M12 in the Ibrance EPAR, 2016). Furthermore, this acetylation metabolite was also produced *in vivo* when palbociclib was orally administered to Sprague–Dawley rats followed by analysis of urine, faeces and plasma samples (described as M13 in Chavan et al. 2018).

Additionally, since there were no pharmacological and toxicological data in the public domain for this impurity, a computational approach was used to evaluate the mutagenic potential of this impurity. Results from the computational analysis using two complementary QSAR methodologies per the ICH M7 guideline indicate that the impurity is not considered mutagenic impurity.

2.3.5. Ecotoxicity/environmental risk assessment

Phase I of the Environmental Risk Assessment (ERA) was submitted.

As for hazard assessment, the applicant provided PBT/vPvB screening. The octanol-water distribution coefficient of palbociclib was determined at three environmentally relevant pH values via the shake flask method following the methodology of OECD test guideline 107. The resulting logD values were -0.92, 1.01 and 2.72 at pH values of 5, 7 and 9, respectively. These logD values across the environmentally relevant pH range are all below the action limit value of 4.5, indicating that no further PBT screening is required.

For Phase I of the risk assessment, the predicted environmental concentration in surface water (PECsw) was refined on treatment regime. The maximum daily dose of 93.75 mg was calculated as the maximum daily dose of 125 mg which is given on the first 21 days of a 28-day cycle (125 mg x 21/28). Using the default Fpen, the resulting PECsw was 0.47 µg/L, which exceeds the threshold of 0.01 µg/L. Therefore, a Phase II assessment should be conducted. However, according to the applicant, the introduction of Palbociclib Viatris is considered unlikely to result in any significant increase in the exposure of the environment to the active substance. The generic medicinal product does not add a new indication, patient population, route of administration or pharmaceutical form. It does not increase the maximum daily dose, nor is it applied for in a member state with a higher prevalence of the disease.

Table 2 Summary of main study results

Substance (INN/Invented Name): palbociclib			
CAS-number (if available): 571190-30-2			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD 107	-0.92 *at pH* 5.0 1.01 *at pH* 7.0 2.72 *at pH* 9.0	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B

Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (treatment regimen)	0.47	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =	List all values
Ready Biodegradability Test	OECD 301		
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =	Not required if readily biodegradable

2.3.6. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of palbociclib are well known. As palbociclib is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. Excipients contained in this medicinal product are standard excipients used in pharmaceutical preparations. New data was provided for the qualification of the drug product impurities.

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

Qualification of one palbociclib impurity

Among the related substance impurities, one impurity is specified at NMT 0.2 % (release) and NMT 0.5 % (shelf-life) in the drug product specification, which exceeds the ICH Q3B qualification threshold (NMT 0.2 %). According to ICH S9, exceeding the established limits for impurities identified in ICH Q3B could be appropriate for anticancer pharmaceuticals if a justification is provided.

As mentioned in section 3.2.P.5.6 of the dossier and the EPAR of the reference medicinal product Ibrance, this impurity is a human metabolite of palbociclib present in plasma at a level of 1.5 %. Although the degradation products that are also significant metabolites are generally considered qualified according to ICH Q3B, this impurity is a minor metabolite and no further discussion or justification was provided by the applicant which is considered acceptable.

No relevant toxicological effects of this impurity were observed in the GLP-compliant 28-day repeat dose oral toxicity study in Wistar rats conducted according to OECD No. 407. Mortality, clinical signs, body and organ weights, feed consumption, urinalysis, clinical and gross pathology were all assessed, and no toxicity was observed. The tested doses were selected as approximately 1-, 3- and 10-fold rat equivalent doses for the maximum potential human exposure to the impurity based on body surface area with the heightened qualification limit of NMT 0.5 % (625 µg/day). The safety margin with NOAEL

= 0.65 mg/kg bw/day is therefore sufficient to show that this impurity does not pose a substantial additional safety risk at the proposed specification limit.

It must however be mentioned that if the NOAEL is used in the permitted daily exposure (PDE) formula derived in ICH Q3C, the resulting PDE would be 65 µg/day for a 50 kg human. Thus, the expected human exposure would be almost 10-fold of the PDE value. Nevertheless, it is noted that no other NOAEL values are available and NOAEL from the conducted study was the highest tested dose with no salient findings in any of the tested animals throughout the whole testing period.

However, in future applications, in line with the 3Rs principle (EMA/CHMP/CVMP/3Rs/742466/2015), conduct of an animal study to toxicologically qualify an impurity is discouraged and should be considered only in rare cases where a remaining concern cannot be resolved otherwise. Instead, a discussion employing animal-free alternatives (e.g. read-cross approaches, SARs, literature-based assessments) should be provided, especially when the concerned impurity is a known human metabolite structurally similar to the active substance.

Moreover, two QSAR analyses using complementary programs (Derek Nexus, Leadscope Model Applier) were performed to predict bacterial mutagenicity of this impurity. No structural alerts were fired and there were no unclassified features or additional toxicophores in relation to the active substance. In addition, a Derek Nexus analysis of palbociclib and this impurity using all available endpoints and species also fired no alerts at the chosen reasoning level. The applicant also submitted validation of the QSAR analyses according to the OECD Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Model, 2007. Of note, the impurity would be of no mutagenic concern according to ICH M7 based on the negative QSAR results, although this guideline does not apply here.

Nevertheless, the ICH S9 Q&A document (Question 4.12) states that if the active substance is genotoxic and an impurity exceeds the 3QB threshold, genotoxicity assessment of impurities is not required. From the approved SmPC of the reference medicinal product Ibrance: "*Palbociclib was not mutagenic in a bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the in vitro human lymphocyte chromosome aberration assay. Palbociclib induced micronuclei via an aneugenic mechanism in Chinese Hamster Ovary cells in vitro and in the bone marrow of male rats at doses ≥ 100 mg/kg/day*." In the submitted dossier, a summarised study by Okada and colleagues (2024) provides compelling evidence to conclude that the positive outcome of the *in vivo* bone marrow micronucleus test resulting from treatment with palbociclib might not be attributed to its genotoxicity but rather that the observed micronucleus generation mechanism is indicative of cell cycle arrest. Considering the negative QSAR results, the uncertain genotoxicity conclusions for palbociclib and the target oncological indication, no further genotoxicity data for this impurity is considered required.

Additionally, there are other general aspects which further lower the level of safety concern apart from those already mentioned. The daily dose of the impurity is less than 1 mg; the route of administration is oral; this is a medicinal product used for a life-threatening disease indicated for the adult population so falling under ICH S9.

Overall, this palbociclib impurity is considered qualified up to the limit of NMT 0.5 %.

Qualification of the other impurity

During the evaluation, the applicant proposed another impurity to be specified at NMT 0.5 % (shelf-life) in the drug product specification, which exceeds the ICH Q3B qualification threshold (NMT 0.2 %). As mentioned in section 3.2.P.5.6 of the dossier and the EPAR of the reference medicinal product Ibrance, this impurity is a human metabolite of palbociclib present in the plasma at a level of 1.0 %. This impurity has also been identified as a rat acetylation metabolite by Chavan et al. (2018).

Furthermore, two QSAR analyses using complementary programs (Derek Nexus, Leadscope Model Applier) were performed to predict bacterial mutagenicity of this impurity. No structural alerts were fired and there were no unclassified features or additional toxicophores in relation to the active substance. In addition, a Derek Nexus analysis of palbociclib and this impurity using all available endpoints and species also fired no alerts at the chosen reasoning level. The applicant also submitted validation of the QSAR analyses according to the OECD Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Model, 2007. Of note, the impurity would be of no mutagenic concern according to ICH M7 based on the negative QSAR results, although this guideline does not apply here.

No further data for this impurity is required.

This impurity is considered qualified up to the limit of NMT 0.5 %.

Environmental risk assessment

Log Kow of palbociclib was determined experimentally according to the OECD 107 method at pH 5, 7 and 9. A bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required.

The ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.) states that in the specific instance of generics where data sharing is not agreed, if a relevant ERA was considered satisfactory by an EU National Competent Authority, repetition of ERA studies will generally not be required. The applicant provided sufficient justification that the scientific conclusions reached for Ibrance remain applicable to its generic product. Furthermore, no additional assessment triggered by the updated guideline is necessary in terms of groundwater risk, terrestrial risk, or secondary poisoning. Palbociclib is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The application is approvable from the non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing palbocicib. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies: one was with cross-over design under fasting conditions and the other was also with cross-over design under fasting conditions but with pre-treatment with a proton pump inhibitor.

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.

A routine GCP inspection was conducted to verify the compliance with ICH GCP and applicable regulations for bioequivalence studies PALB-TFZ-1007 and PALB-TFZ-1008. Both trials are concluded to have been generally conducted in acceptable compliance with GCP and internationally accepted ethical standards.

Exemption

The applicant provided *in vitro* tests complementary to the bioequivalence studies, which confirmed similarity of dissolution profiles between bio-batches of the reference product IBRANCE 125 mg film coated tablet and the tested product palbociclib 125 mg film coated tablet.

In addition to the two bioequivalence studies, the applicant submitted a biowaiver request for the lower strengths of palbociclib 75 mg and 100 mg film-coated tablets not tested in the bioequivalence studies based on conditions in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **): same qualitative composition of all the strengths (75 mg, 100 mg and 125 mg), the quantitatively proportional composition of all the strengths, linear pharmacokinetic of palbociclib, the same manufacturer at the same site using the same manufacturing process and comparative *in vitro* dissolution data.

Biowaiver request for Palbociclib 75 mg and 100 mg film-coated tablets - Comparative dissolution profiles at a lower rpm:

The applicant has generated the multimedia release profile data at a lower rpm on test product batches for Palbociclib 75 mg, 100 mg and 125 mg film-coated tablets to support the biowaiver for Palbociclib 75 mg and 100 mg film-coated tablets. More than 85% of the labelled amount of the drug is released within 15 minutes from both the formulations in 0.1N HCl and pH 4.5, thus the dissolution profiles for the 125 mg strength vs the 75 mg and 100 mg strengths can be considered as similar without further mathematical calculations in these media.

In the pH 6.8 phosphate buffer medium, the f2 value between formulations has been found greater than 50, however, the % Relative Standard Deviation (RSD) for palbociclib 75 mg has been observed above 20% in the first time point. Therefore, the similarity factor (f2) for the dissolution profiles between the bio-batch 125 mg and the proposed lower strength 75 mg in phosphate buffer pH 8.6 has been calculated using a bootstrapping method with percentiles (5^{th}, 50^{th} (median), and 95^{th}). For the bootstrapping method, 10,000 replicate samples of each lot consisting of 12 tablets dissolution profiles and all time points were considered. The results indicate that the 90% confidence interval (CI) for the similarity factor at pH 6.8 exceeds the threshold of 50 in the tested medium. The dissolution profiles can be considered similar.

Tabular overview of clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies.

Table 3 Overview of clinical studies

Type of Study	Study Identifier	Location of Study report	Objectives of the study	No of Subjects	Study Design & type of control	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	PALB-TFZ-1007	m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\palb-tfz-1007--fasted-study\Study Report	The objective of this study was to investigate the bioequivalence of Palbociclib Film Coated Tablet 125 mg with IBRANCE® (Palbociclib) 125 mg film-coated tablets, in healthy adult human subjects under fasting condition and to monitor the safety of the subjects.	**Enrolled:** 28+02* Subjects **Dosed: 28** Subjects **Completed:** 27 Subjects completed both periods of the study. *02 additional subject (EID: E01 & E02) were enrolled in the study and were checked out after dosing of all 28 subjects in period 1.	A single dose, open labelled, randomized, balanced, two treatment, two-period, two sequence, crossover, truncated, oral bioequivalence study	**Test Product (T):** Palbociclib Tablets 125 mg (Oral) **Reference Product (R):** IBRANCE® 125 mg Filmtabletten Palbociclib (Ch.-B.-HN5082) (Oral)	Normal Healthy Human Adult Subjects	Single Dose	Completed; Abbreviated New Drug Application

Type of Study	Study Identifier	Location of Study report	Objectives of the study	No of Subjects	Study Design & type of control	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	PALB-TFZ-1008	m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\palb-tfz-1008--fasted-study\Study Report	The objective of this study was to investigate the bioequivalence of Palbociclib Film Coated Tablet 125 mg with IBRANCE® (Palbociclib) 125 mg film-coated tablets, in healthy adult human subjects under fasting conditions of multiple day pre-treatment with a proton pump	**Enrolled:** 28+02* Subjects **Dosed: 27** Subjects **Completed:** 26 Subjects completed both periods of the study.	A single dose, open labelled, randomized, balanced, two treatment, two-period, two sequence, crossover, truncated, oral bioequivalence study	**Test Product (T):** Palbociclib Tablets 125 mg (Oral) **Reference Product (R):** IBRANCE® 125 mg Filmtabletten Palbociclib (Ch.-B.-HN5082) (Oral) **Proton Pump Inhibitor (PPI):** Pantazol® 40 mg Enteric coated tablet (Ch.-B: 542244) (Oral)	Normal Healthy Human Adult Subjects	Single Dose	Completed; Abbreviated New Drug Application

			inhibitor (PPI), and also to monitor the safety of the subjects.						

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

***Study PALB-TFZ-1007*:** A single dose, open labelled, randomized, balanced, two treatment, two period, two sequence, cross-over, truncated, oral bioequivalence study of Palbociclib Film Coated Tablet 125 mg with IBRANCE (Palbociclib) 125 mg film-coated tablets Manufactured by: Pfizer Manufacturing Deutschland GmbH, Betriebsstätte Freiburg Mooswaldallee 1 79090, Freiburg Germany in healthy adult human subjects under fasting condition.

Methods

- **Study design**

The objective of this study was to investigate the bioequivalence of Palbociclib Film Coated Tablet 125 mg with IBRANCE (palbociclib) 125 mg film-coated tablets, in healthy adult human subjects under fasting condition and to monitor the safety of the subjects. The study was initiated with 28+02 healthy subjects. Each subject received a single, oral dose of 125mg (1 x 125mg) Mylan's Palbociclib tablets 125 mg (Batch No.# 2028092) or 125mg (1 x 125mg) dose of Pfizer's IBRANCE 125 mg film coated tablets palbociclib (Ch.-B # HN5082) with 150 mL of water as per randomisation schedule. Following a 14-day washout period, all subjects were dosed with the alternative treatment as per the randomization. In each study period, blood samples were collected within 02.00 hours prior to dose administration (0 hour) and post-dose at study hours: 01.00, 02.00, 03.00, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 08.00, 09.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours. During each study period, 20 blood samples were collected (1 X 5.0 mL) from each subject in prespecified precooled K_2EDTA vacutainers. At the end of the study, all samples were shipped for analysis to a bioanalytical facility. The analytical team performing the bioanalysis was blinded to the treatment which the subjects were receiving. The method developed for the analysis of Palbociclib in 0.200mL human plasma containing K_2EDTA involved liquid-liquid extraction followed by LC-MS/MS analysis, which had a limit of quantification of 0.500 ng/mL for palbociclib.

- **Test and reference products**

Test Product (Treatment T):

Drug Product Information: Palbociclib Tablets 125 mg
Dosage Form: tablet
Dose Administered: 125 mg

Reference Product (Treatment R):

Drug Product Information: IBRANCE® 125 mg Filmtabletten Palbociclib
Ch.-B: HN5082

Expiration Date: March 2026
Marketing authorisation holder: Pfizer Europe MA EEIG, Boulevard de la Plaine 171050 Brussel Belgein
Country of origin: Germany
Manufactured by: Pfizer Manufacturing Deutschland GmbH, Betriebsstätte Freiburg Mooswaldallee 1, 79090, Freiburg Germany
Assay: 100.5%
Dosage Form: film coated Tablet
Dose Administered: 125 mg

Population studied

A total of 28 + 2 (additional subjects) subjects were enrolled in the study. Of the 28 subjects enrolled in the study 27 subjects completed both two-treatment periods of the study and they were included in the pharmacokinetic and statistical analysis as per protocol. One subject did not report to the study facility on the day of period-2 check in and therefore was considered as a dropout from the study. The main inclusion criteria were normal healthy adult human subjects of age 18-45 years, with BMI of 18-30 kg/m2, body weight more than 50 kg, non-smokers, with no evidence of underlying disease during the screening and in medical history, negative test for alcohol and negative urine drugs of abuse test, with 12 lead ECG recording either normal or within acceptable limits and with normal WBC counts [WBC count ≥3.5× 109 /L (3500/mm^3) and absolute neutrophil count ≥2.0× 109 /L (2000/mm^3)].

- **Analytical methods**

Bioanalytical Method Validation

A high-performance liquid chromatographic method with mass spectrometric detection for the determination of palbociclib in human K_2EDTA plasma was validated by the Bioanalytical Laboratory over the concentration range of 0.500 to 250.00 ng/mL. Validation was performed according to SOP, Bioanalytical method validation plan, principles of Good Laboratory Practice and applicable regulatory requirements.

Study samples analysis

The samples were received at Bioanalytical Laboratory and logged into deep freezer and stored at -70±10°C. Out of 1080 samples, 1 sample was repeated for individual sample internal standard response variation, and the percentage of repeats was 0.09. Out of 1080 samples, 108 samples were selected for incurred sample reanalysis (ISR), in which 96.30% (104) of incurred sample reanalysis concentrations were found to be within ± 20% of the mean of initial and incurred concentrations.

Sixteen acceptable calibration curves were generated for study sample analysis. The calibration curves were found to be linear over the concentration range of 0.504 to 247.000ng/mL.

- **Pharmacokinetic variables**

The primary pharmacokinetic parameters (C_{max} and AUC_{0-72}) and secondary pharmacokinetic parameters (T_{max}) of palbociclib from Test Product (T) and that from the Reference Product (R) have been evaluated.

Single-dose pharmacokinetic parameters for palbociclib were calculated using non-compartmental techniques. The maximum concentration (C_{max}) and the time at which it occurred relative to the administered dose (T_{max}) were determined from the observed plasma concentration-time profile over

the sampling time interval. The area under the concentration-time curve from time zero to 72 hours (with quantifiable concentration) was calculated using the linear trapezoidal method (AUC_{0-72}).

- **Statistical methods**

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of the SAS Software (SAS Institute, Version 9.4). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters T_{max} was analysed statistically using the non-transformed data. The natural log transformed parameters $lnAUC_{0-72}$ and lnC_{max} were also analysed. The tests were performed to analyse statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure. The acceptance range for bioequivalence is 80.00 -125.00% for the 90% CI for difference of means of ln-transformed C_{max} and AUC_{0-72} with respect to palbociclib.

Results

Figure 2 Mean palbociclib plasma concentration

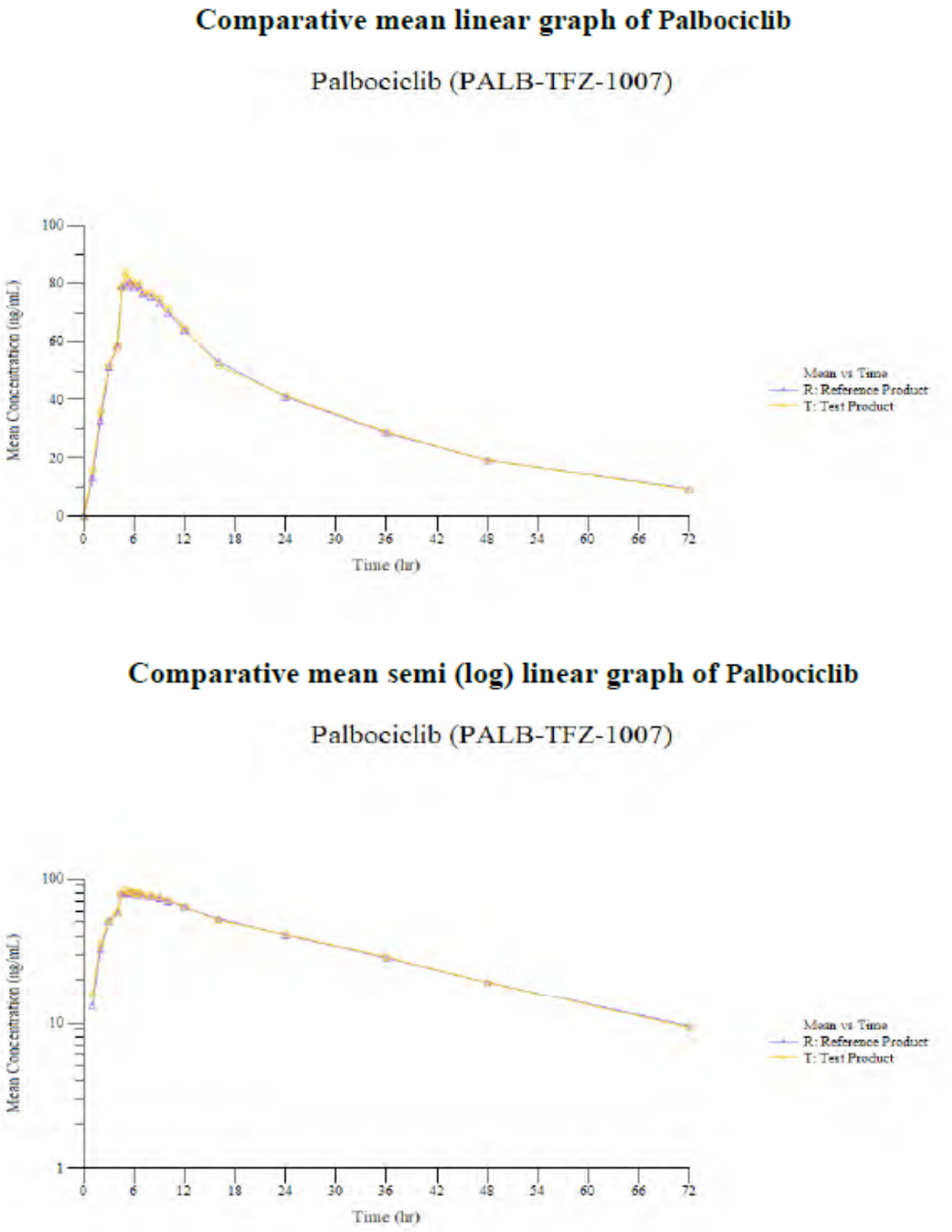


Table 4 Palbociclib Geometric Least Square Mean Values of Test(T) and Reference (R)

Parameter	Geometric Least Square Mean of Test (T)	Geometric Least Square Mean of Reference (R)
AUC_{0-72} (hr*ng/mL)	2342.410	2323.015
C_{max} (ng/mL)	90.030	85.791

Table 5 Mean Palbociclib Pharmacokinetic Parameters

Mean (%CV) Palbociclib Pharmacokinetic Parameters in 27 Healthy Adult Male Subjects Following a Single 125mg Oral Dose of Palbociclib Under Fasting Conditions				
Parameter	**Arithmetic Mean (%CV) Test Product (T)**	**Arithmetic Mean (%CV) Reference Product (R)**	**Geometric LSMEANS Ratio (T/R)***	**90% Confidence Interval****
AUC_{0-72} (hr*ng/mL)	2387.5015 (21.17%)	2375.1599 (21.51%)	100.83	(96.78,105.06)
C_{max} (ng/mL)	92.5838 (23.99%)	88.4735 (24.94%)	104.94	(97.45,113.01)
T_{max} (hours)$	5.030 (4.500-7.000)	5.500 (4.500-8.000)		

* Ratio (T/R) = $e^{[LSMEAN\ of\ (LNT - LNR)]}$; ** Used Natural Log Transformed Parameter; $- median (range)

Source: Appendix 16.2.6

- **Safety data**

Seven subjects experienced a total of 10 treatment emergent adverse events (AEs) over the course of the study. All 10 reported AEs were mild in severity. No AEs resulted in treatment discontinuation. No Serious Adverse Events (SAEs) were reported. The reported AE following administration of treatment T was rash which was reported by 01 out of 28 subjects (3.57%).

Conclusion

For study **PALB-TFZ-1007**, the 90% confidence intervals for the AUC_{0-72} and C_{max} ratios for the test and reference product comparison were 96.78-105.06 and 97.45 – 113.01 respectively and are within the acceptance range of 80.00 – 125.00 %. One subject has been found to be statistical outlier; however, investigation of this case did not reveal any statistical correlation.

Palbociclib Viatris 125 mg film coated tablets exhibited equivalent rate and extent of absorption compared to the reference product IBRANCE 125 mg film coated tablets after single oral dose under fasting condition.

Study PALB-TFZ-1008: A single dose, open labelled, randomized, balanced, two treatment, two-period, two sequence, cross-over, truncated, oral bioequivalence study of Palbociclib Film Coated Tablet 125 mg with IBRANCE (palbociclib) 125 mg film-coated tablets Manufactured by: Pfizer Manufacturing Deutschland GmbH, Betriebsstätte Freiburg Mooswaldallee 1 79090, Freiburg Germany in healthy adult human subjects under fasting conditions of multiple day pretreatment with a proton pump inhibitor (PPI).

Methods

- **Study design**

The objective of this study was to investigate the bioequivalence of Palbociclib Film Coated Tablet 125 mg with IBRANCE (palbociclib) 125 mg film-coated tablets, in healthy adult human subjects under fasting conditions and of multiple day pre-treatment **with a proton pump inhibitor (PPI)**, and to monitor the safety of the subjects. The study was initiated with 28+02 healthy subjects. After subject's enrolment into the study (Day 00), they were asked to report to the facility the next day (Day 01).

Subjects were pretreated with Pantazol 40 mg Enteric coated tablet manufactured by Takeda GmBH as PPI for 4 days before investigational product (IP) administration as per predefined schedule (morning and night dose). On the day 5, the subjects were dosed with pantazol 40 mg enteric coated tablet 02:00 hour before IP administration and then by treatment as per the randomisation scheme. In each study period, blood samples were collected within 02.00 hours prior to dose administration (0 hour) and post-dose at study hours: 01.00, 02.00, 03.00, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 08.00, 09.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours. The actual time at which each blood sample was collected was recorded by clinical staff. The analytical team performing the bio analysis was blinded to the treatment which the subjects were receiving. A sample of 10.0 mL was collected from each subject in pre-specified vacuum tubes containing K_2EDTA with the pre-dose sample in each study period. Samples were assayed for palbociclib by liquid-liquid extraction followed by LC-MS/MS analysis with limit of quantification of 0.500 ng/mL for palbociclib.

- **Test and reference products**

Test Product (Treatment T):

Drug Product Information:	Palbociclib Tablets 125 mg Dosage Form: tablet Dose Administered: 125 mg

Reference Product (Treatment R):

Drug Product Information:	IBRANCE® 125 mg Filmtabletten Palbociclib Ch.-B: HN5082 Expiration Date: March 2026 Marketing authorisation holder: Pfizer Europe MA EEIG, Boulevard de la Plaine 171050 Brussel Belgein Country of origin: Germany Assay: 100.5% Dosage Form: film coated tablet Dose Administered: 125 mg

Proton Pump Inhibitor (PPI):

Drug Product Information:	Pantazol 40 mg Enteric coated tablet Ch.-B: 542244 Expiration Date: November 2025 Manufactured by: Takeda GmBH, Byk-Gulden-Straße 278467 Konstanz, Germany Assay: 103.0% Country of origin: Netherlands Dosage Form: enteric-coated tablet Dose Administered: 40 mg

- **Population studied**

A total of 28+02 (additional subjects) subjects were enrolled in the study. Two additional subject were enrolled in the study and one subject was replaced by E02 [subject experienced an adverse event prior to dosing in period 1 and was not administered with any treatment and checked out from study] and one subject was replaced by E01 due to not complying with the protocol requirement- the subject did not report to the facility for pretreatment with PPI dose 1 (day 01 morning) and was not administered with any treatment and checked out from study].

The main inclusion criteria were normal healthy adult human subjects of age 18-45 years, with a BMI of 18-30 kg/m2, a body weight more than 50 kg, non-smokers, with no evidence of underlying disease

during the screening and in medical history, negative test for alcohol and negative urine drugs of abuse test, with 12 lead ECG recording either normal or within acceptable limits and with normal WBC counts [WBC count ≥3.5× 109 /L (3500/mm^3) and absolute neutrophil count ≥2.0× 109 /L (2000/mm^3)].

- **Analytical methods**

Bioanalytical Method Validation

A high-performance liquid chromatographic method with mass spectrometric detection for the determination of palbociclib in human K_2EDTA plasma was validated by the Bioanalytical Laboratory over the concentration range of 0.500 to 250.00 ng/mL. Validation was performed according to SOP, bioanalytical method validation plan, principles of Good Laboratory Practice and applicable regulatory requirements.

Study samples analysis

The samples were received at Bioanalytical Laboratory and logged into deep freezer and stored at -70±10°C. None of the samples were repeated during the study. Out of 1040 samples, 104 samples were selected for ISR, in which 96.15 % of incurred sample reanalysis concentrations were found to be within ± 20% of the mean of initial and incurred concentrations.

Fourteen acceptable calibration curves were generated for study sample analysis. The calibration curves were found to be linear over the concentration range of 0.508 to 249.125 ng/mL.

- **Pharmacokinetic variables**

The primary pharmacokinetic variables for assessment of bioequivalence are C_{max} and AUC_{0-72} for Palbociclib.

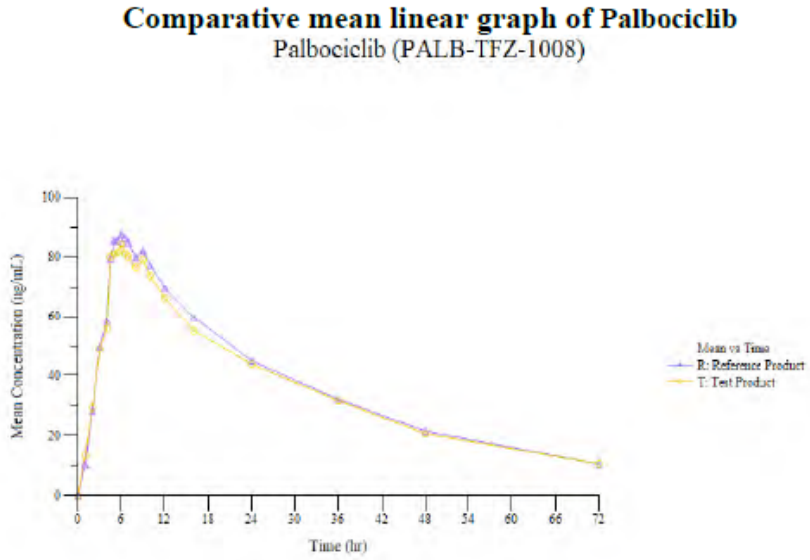
Single-dose pharmacokinetic parameters for palbociclib were calculated using non-compartmental techniques. The maximum concentration (C_{max}) and the time at which it occurred relative to the administered dose (T_{max}) were determined from the observed plasma concentration-time profile over the sampling time interval. Area under the concentration-time curve from time zero to the 72 hours (with quantifiable concentration) calculated using the linear trapezoidal method (AUC_{0-72}). The acceptance range for bioequivalence is 80.00-125.00% for the 90% confidence intervals for the difference of means of In-transformed C_{max} and AUC_{0-72} with respect to palbociclib.

- **Statistical methods**

Statistical analyses were done on concentration values and pharmacokinetic parameters of palbociclib using SAS package (SAS® Institute Inc., USA, and Version 9.4). Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Version 9.4). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: T_{max} was analysed statistically using the non-transformed data. The natural log transformed parameters: $lnAUC_{0-72}$ and lnC_{max} were also analysed. The tests were performed to analyse statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

Results

Figure 3 Mean palbociclib plasma concentration



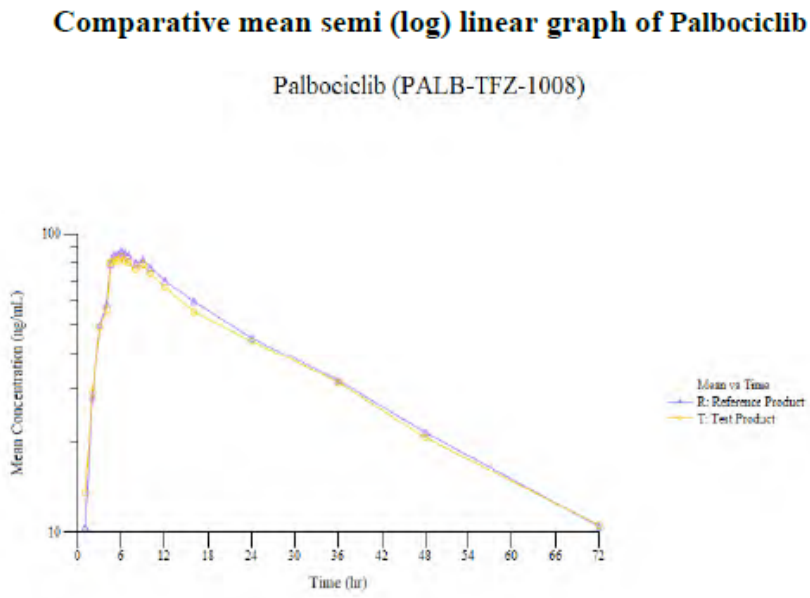


Table 6 Palbociclib geometric least square mean values of Test (T) and Reference (R)

Parameter	Geometric Least Square Mean of Test (T)	Geometric Least Square Mean of Reference (R)
AUC_{0-72} (hr*ng/mL)	2557.510	2557.720
C_{max} (ng/mL)	94.635	95.461

Table 7 Mean palbociclib pharmacokinetic parameters

Mean (%CV) Palbociclib Pharmacokinetic Parameters in 26 Healthy Adult Male Subjects Following a Single 125mg Oral Dose of Palbociclib Under Fasting Conditions of multiple day pre-treatment with a proton pump inhibitor (PPI).				
Parameter	**Arithmetic Mean (%CV) Test Product (T)**	**Arithmetic Mean (%CV) Reference Product (R)**	**Geometric LSMEANS Ratio (T/R)***	**90% Confidence Interval****
AUC_{0-72} (hr*ng/mL)	2509.8093(29.11%)	2598.9660 (21.19%)	99.99	(96.35,103.77)
C_{max} (ng/mL)	94.2125 (34.39%)	99.1045 (27.67%)	99.14	(92.77,105.94)
T_{max} (hours)$	5.750 (0.000-10.000)	5.750 (4.500-16.000)		

* Ratio (T/R) = $e^{[LSMEAN\ of\ (LNT - LNR)]}$; ** Used Natural Log Transformed Parameter; $- median (range)

- **Safety data**

Seven subjects experienced a total of 11 treatment emergent adverse events over the course of study. Among 11 AEs reported, 10 AEs were mild in severity, and one was severe in severity. The reported AE following administration of treatment R was Pyrexia which was reported by 02 out of 26 subjects (7.69%). One serious adverse event was reported in the study. This serious adverse event was reported in the post study safety assessment in a subject with a history of a fall from a running train and a sustained injury to his right leg. Of 11 AE reported, 8 were resolved and 3 were ongoing (for the subject with a history of a fall).

Conclusion

For study **PALB-TFZ-1008,** the 90% confidence intervals for the AUC_{0-72} and C_{max} ratios for the test and reference product comparison were 96.35-103.77 and 92.77-105.94 respectively, (geometric LSmeans ratio for AUC_{0-72} 99.99 and C_{max} 99.14) and are within the acceptance range of 80.00 – 125.00 %.

One subject did not have measurable concentrations in the plasma in the period for tested product. Clinical investigation and bioanalytical investigations did not reveal any root cause for this phenomenon. This subject was excluded from the statistical analysis in line with ICH M13A guideline (EMA/CHMP/ICH/953493/2022).

Palbociclib Viatris 125mg film coated tablets exhibited equivalent rate and extent of absorption compared to the reference product IBRANCE 125 mg film coated tablets after single oral dose under fasting condition and multiple pre-treatments with a proton pump inhibitor.

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

To support this application for marketing authorisation, the applicant submitted two bioequivalence studies and a biowaiver request. The essential similarity is claimed to the reference product IBRANCE 125 mg film coated tablets (Pfizer Europe MA EEIG (Belgium)) approved via the centralised procedure.

To support the bioequivalence of the proposed medicinal product Palbociclib Viatris 125 mg film coated tablets vs the reference product IBRANCE 125 mg film coated tablets, the applicant submitted two bioequivalence studies, one under fasting conditions with the 125 mg palbociclib (study PALB-TFZ-1007), and one under fasting conditions with multiple day pre-treatment with a proton pump inhibitor (study PALB-TFZ-1008). Palbociclib is low soluble in pH 6.8 phosphate buffer, and higher solubility in 0.1N HCl and pH 4.5 has been demonstrated. Since the solubility of palbociclib is pH dependent, also a bioequivalence study under fasting conditions with a PPI is required in addition to the standard bioequivalence study under fasting condition. This approach is in accordance with the product specific bioequivalence guidance for palbociclib (EMA/CHMP/802679/2018 Rev.1* Corr. 1**).

The study **PALB-TFZ-1007** was an open label, single dose, randomized, two-treatment, two period, two sequence, cross-over, study to investigate the bioequivalence of palbociclib 125 mg film coated tablet with IBRANCE 125 mg film-coated tablets in healthy adult human under fasting conditions. Overall, the design is appropriate. The chosen sampling periods covers sufficiently the period around the predicted T_{max}. To minimize the possibility of a carry-over effect, a washout period of at least 14 days was selected for the study considering the elimination half-life of 28.8 hours in patient with advanced breast cancer. The chosen population is acceptable and in line with the inclusion criteria set in the protocol. The validation and partial validations were conducted according to the requirements of the ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019) and are considered acceptable. Total sample storage duration from the first sample collection to the end of sample analysis was 25 days at -70±10°C. Thus, the period of maximal storage is covered by the established long-term stability of 740 days at -70 ± 10 °C. The number of assayed samples (108 out of 1080) as ISR is sufficient and in line with the requirements of the ICH M10 guideline on bioanalytical method validation (EMA/CHMP/ICH/172948/2019) and 96.30% of the repeated results are within the acceptance criteria of the 20%. The method is considered reliable and reproducible.

The chosen primary and secondary pharmacokinetic variables are adequate and in line with the product specific bioequivalence guidance for palbociclib (EMA/CHMP/802679/2018 Rev.1* Corr. 1**). Proposed bioequivalence acceptance criteria are standard and acceptable. No subjects had measurable pre-dose plasma levels, and no subjects reached C_{max} at the first sampling time point. One subject has been found to be a statistical outlier; however, investigation of this case did not reveal any statistical correlation.

Statistical analysis confirmed that he 90% confidence intervals for the AUC_{0-72} and C_{max} ratios for the test and reference product comparison were 96.78-105.06 and 97.45 – 113.01 respectively and are within the acceptance range of 80.00 – 125.00 %. It can be concluded that Palbociclib Viatris 125mg film coated tablets exhibited equivalent rate and extent of absorption compared to the reference product IBRANCE 125 mg film coated tablets after single oral dose under fasting condition. The bioequivalence has been shown appropriately.

In addition, the study **PALB-TFZ-1008** under fasting condition and with pre-treatment with PPI has been conducted considering the pH dependent solubility of palbociclib. This study was a single dose, open label, randomized, two-treatment, two period, two sequence, cross-over design to investigate the bioequivalence of palbociclib 125 mg film coated tablets with IBRANCE 125 mg film-coated tablets in healthy adult human under fasting conditions with multiple day pre-treatment with proton pump

inhibitor. The design of this study is acceptable and follows all requirements of the relevant guidelines. The chosen sampling periods covers sufficiently the period around the predicted T_{max}. To minimize the possibility of a carry-over effect, a washout period of at least 14 days was selected for the study, this is acceptable. The chosen population is acceptable and in line with the inclusion criteria set in the protocol. The validation and partial validations were conducted according to the requirements of the ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019). The validated calibration range from ng/mL covers C_{max} and LLOQ is <5% of C_{max}. Total sample storage duration from the first sample collection to end of the sample analysis was 26 days at -70±10°C. Thus, the period of maximal storage is covered by the established long-term stability of 740 days at -70 ± 10 °C.

The number of assayed samples (104 out of 1040) as ISR is sufficient and in line with the requirements of the ICH M10 guideline on bioanalytical method validation (EMA/CHMP/ICH/172948/2019). 96.15 % of the repeated results are within the acceptance criteria of 20%. The method is considered reliable and reproducible. The chosen primary and secondary pharmacokinetic variables are adequate and in line with the product specific bioequivalence guideline for palbociclib (EMA/CHMP/802679/2018 Rev.1* Corr. 1**).

Statistical analysis confirmed that he 90% confidence intervals for the AUC_{0-72} and C_{max} ratios for the test and reference product comparison were 96.35-103.77 and 92.77-105.94 respectively and are within the acceptance range of 80.00 – 125.00 %. It can be concluded that Palbociclib Viatris 125mg film coated tablets exhibited equivalent rate and extent of absorption compared to the reference product IBRANCE 125 mg film coated tablets after single oral dose under fasting condition and multiple pre-treatments with a proton pump inhibitor. The bioequivalence has been shown appropriately.

To support the biowaiver for the lower strengths, the applicant submitted dissolution profiles comparison between palbociclib 125 mg, 100 mg and 75 mg based on the condition of manufacturing of all strengths by the same manufacturer at the same manufacturing site and using the same process, based on the same qualitative composition of all strengths, quantitatively proportional composition of all strengths and based on similar *in vitro* dissolution data. From the data provided it can be concluded that that dissolution profiles of the 100 mg strength of palbociclib in all media (0.1N HCl, pH4.5 and pH 6.8) are similar to the compared 125 mg strength (bio-batch). Thus, it can be concluded that the request for biowaiver for palbociclib 100 mg is acceptable.

For the formulation palbociclib film coated tablet 75 mg, the dissolution profiles are similar to the compared strength in 0.1N HCl and pH 4.5. However, in the medium with pH 6.8, a high %RSD has been observed (25.5%), therefore the standard calculation of similarity factor is not appropriate. To obtain the biowaiver for Palbociclib Viatris 75 mg, the applicant provided calculation of similarity factor (f2) by bootstrapping method with percentiles (5^{th}, 50^{th} (median), and 95^{th}), considering all the tested sampling times. The analysis results indicate that the 90% confidence interval (CI) for the similarity factor at pH 6.8 exceeds the threshold of 50 in the tested medium. Based on these findings, the biowaiver for the additional palbociclib 75 mg strength is considered acceptable.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence studies, Palbociclib Viatris 125 mg film-coated tablets is considered bioequivalent with IBRANCE 125 mg film-coated tablets.

Palbociclib Viatris 125mg film coated tablets exhibited equivalent rate and extent of absorption compared to the reference product IBRANCE 125 mg film coated tablets after single oral dose under fasting condition and multiple pre-treatments with a proton pump inhibitor.

The results of bioequivalence studies PALB-TFZ-1007 and PALB-TFZ-1008 with palbociclib 125 mg formulation can be extrapolated to the other 75 mg and 100 mg strengths, according to the conditions in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), section 4.1.6, since the dissolution profiles in all media tested are considered similar. Thus, the marketing authorisation for formulations of palbociclib 75 mg, 100 mg and 125 mg can be granted.

2.5. Risk Management Plan

2.5.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 0.2, signed 11-12-2025:

Table 8 Summary of safety concerns

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

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 0.2 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Duloxetine Mylan 30 mg hard gastro-resistant capsules, EMEA/H/C/003981 and IBRANCE 75 mg, 100 mg, 125 mg film-coated tablets, EMEA/H/C/003853. The bridging report submitted by the applicant has been found.

3. Benefit-risk balance

This application concerns a generic version of Palbociclib 75 mg, 100 mg, 125 mg film-coated tablets. The reference product IBRANCE is indicated 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.

No pivotal 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. Palbociclib is not expected to pose a risk to the environment and is not considered a PBT/vPvB substance.

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 is considered sufficient.

To support the bioequivalence of the proposed medicinal product Palbociclib Viatris 125 mg film-coated tablets vs the reference product IBRANCE 125 mg film-coated tablets, the applicant submitted two bioequivalence studies: one single dose, open labelled, randomised, two period, two sequence crossover under fasting conditions with the 125 mg palbociclib (study PALB-TFZ-1007), and one single dose, open labelled, randomised, two period, two sequence, crossover study with the 125 mg palbociclib under fasting conditions with multiple day pre-treatment with a proton pump inhibitor (study PALB-TFZ-1008).

The design of both studies is considered adequate to evaluate the bioequivalence of this formulation. 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 are adequate.

The test formulation of Palbociclib Viatris 125 mg film-coated tablet met the protocol-defined criteria for bioequivalence when compared with the IBRANCE 125 mg film-coated tablet. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72}, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

The results of studies PALB-TFZ-1007 and PALB-TFZ-1008 with palbociclib 125 mg formulation can be extrapolated to the other 75 mg and 100 mg strengths, according to the conditions in the Guideline on

the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) considering similar dissolution profiles in all media tested. Thus, the marketing authorisation for formulations of palbociclib 75 mg, 100 mg and 125 mg and can be granted.

4. Recommendations

Outcome

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

Palbociclib Viatris is indicated 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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.