



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2024
EMA/283170/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Apexelsin

International non-proprietary name: paclitaxel

Procedure No. EMEA/H/C/005997/0000

Note

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



Table of contents

1. Background information on the procedure	6
1.1. Submission of the dossier.....	6
1.2. Legal basis, dossier content.....	6
1.3. Information on paediatric requirements.....	7
1.4. Information relating to orphan market exclusivity.....	7
1.4.1. Similarity.....	7
1.5. Scientific advice	7
1.6. Steps taken for the assessment of the product.....	7
2. Scientific discussion	8
2.1. Introduction.....	8
2.2. Quality aspects	9
2.2.1. Introduction.....	9
2.2.2. Active substance	10
2.2.3. Finished medicinal product.....	11
2.2.4. Discussion on chemical, and pharmaceutical aspects.....	15
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects	15
2.2.6. Recommendation(s) for future quality development	15
2.3. Non-clinical aspects	15
2.3.1. Introduction.....	15
2.3.2. Pharmacology	15
2.3.3. Pharmacokinetics.....	16
2.3.4. Ecotoxicity/environmental risk assessment	18
2.3.5. Discussion on non-clinical aspects.....	18
2.3.6. Conclusion on the non-clinical aspects.....	19
2.4. Clinical aspects	19
2.4.1. Introduction.....	19
2.4.2. Clinical pharmacology	21
2.4.3. Clinical efficacy	21
2.4.4. Clinical safety.....	21
2.4.5. Discussion on clinical aspects	21
2.4.6. Conclusions on clinical aspects	22
2.5. Risk Management Plan	22
2.5.1. Safety concerns.....	22
2.5.2. Pharmacovigilance plan	23
2.5.3. Risk minimisation measures	23
2.5.4. Conclusion	23
2.6. Pharmacovigilance.....	23
2.6.1. Pharmacovigilance system	23
2.6.2. Periodic Safety Update Reports submission requirements	23
2.7. Product information	23
2.7.1. User consultation.....	23

3. Benefit-risk balance 23

4. Recommendations 24

5. Appendix 26

5.1. CHMP AR on similarity dated 30 May 2024..... 26

List of abbreviations

3Rs	Replacement, reduction, refinement
AUC	Area under the ROC Curve
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human Use
CI	Clearance
Cmax	Maximum concentration
CQA	Critical Quality Attribute
Cryo-TEM	Cryogenic Transmission Electron Microscopy
DLS	Dynamic light scattering
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EURD	European Union reference dates
FDA	Food and Drug Administration (US)
FT-IR	Fourier Transform-infrared
GC	Gas Chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPH	High-pressure homogenisation
HPLC	High performance liquid chromatography
HSA	Human Serum Albumin
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MO	Major objection
nab-P	nanoparticle albumin-bound paclitaxel
NMR	Nuclear Magnetic Resonance

PD	Pharmacodynamics
PDE	Permitted Daily Exposure
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PhV	Pharmacovigilance
q.s.	Sufficient quantity
QTPP	Quality target product profile
RMP	Reference Medicinal Product
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half-life
Tmax	Time to maximum concentration
UV	Ultraviolet
Vz	Volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Whiteoak Pharmaceutical B.V. submitted on 30 December 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Apexelsin, 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 16 September 2021.

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 indications:

Apexelsin monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated (see section 4.4).

Apexelsin in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

Apexelsin in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

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 non-clinical studies to demonstrate comparative pharmacokinetics and similar anti-tumour effects with the reference medicinal product Abraxane .

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: Abraxane 5 mg/ml powder for dispersion for infusion
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 11 January 2008
- Marketing authorisation granted by: Union
- Union Marketing authorisation number: EU/1/07/428/001; EU/1/07/428/002

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

- Product name, strength, pharmaceutical form: Abraxane, 5 mg/ml, powder for suspension for infusion
- Marketing authorisation holder: Bristol-Myers Squibb
- Date of authorisation: 11-01-2008
- Marketing authorisation granted by:
 - Union
- Marketing authorisation number: EU/1/07/428/001

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The Applicant received Scientific Advice on the development of albumin-bound paclitaxel on 27 January 2022. The Scientific Advice pertained to Quality, Non-clinical and Clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Eva Skovlund

The application was received by the EMA on	30 December 2021
The procedure started on	20 January 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 April 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	12 April 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 May 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	08 August 2022
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy	

assessment of the product:	
— A GMP inspection at one manufacturing site was performed on 22 - 26 January 2024. The outcome of the inspection carried out was issued on 30 April 2024.	22 January 2024 – 26 January 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	14 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	13 October 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	30 April 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Paclitaxel WhiteOak on	30 May 2024
The CHMP adopted a report on similarity of Apexelsin with Lutathera and Onivyde on (Appendix on similarity)	30 May 2024

2. Scientific discussion

2.1. Introduction

Paclitaxel is a naturally occurring complex product extracted from the bark of the western yew (*Taxus brevifolia*) while it was originally isolated in a precursor form from the needles of the European yew. Paclitaxel possesses scientifically proven anticancer activity against e.g., breast, lung, and advanced ovarian cancers. The mechanism of action of paclitaxel is to promote and stabilise microtubules and inhibit late G2 or M phases of cell cycle, thereby causing the cell death.

Paclitaxel is indicated for the treatment of metastatic breast cancer (second-line treatment) and for combination therapy with gemcitabine in metastatic adenocarcinoma of the pancreas and with carboplatin in non-small cell lung cancer.

The reference product Abraxane is a nanoparticle albumin-bound paclitaxel (also referred as nab-paclitaxel in this report). This formulation allows the administration of insoluble lipophilic agents, such as paclitaxel. Nab-paclitaxel is an amorphous form of paclitaxel bound to albumin (at a concentration of 3–4%). Nanoparticle albumin-bound paclitaxel (nab-paclitaxel; nab-P) is Cremophor EL(CrEL)-free, consisting only of unmodified paclitaxel and human albumin. By eliminating CrEL from its formulation, nab-paclitaxel has a reduced risk of hypersensitivity reactions, does not require premedication and can be administered over a shorter period (30 min) of time without special IV tubing.

The first commercial product based on protein nanoparticles was a 130-nanometer albumin-bound paclitaxel, approved by the US Food and Drug Administration (FDA) in 2005 and by the European Commission in 2008 for the treatment of metastatic breast carcinoma, and later on for the treatment of metastatic pancreatic cancer (2013) and advanced non-small cell lung carcinoma (2015).

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Apexelsin 5 mg/ml powder for dispersion for infusion. The applicant is Whiteoak Pharmaceutical B.V. Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles. After reconstitution, each ml of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) as well as the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011).

The applicant has sought CHMP Scientific Advice on the acceptability of the quality and pre-clinical data for the acceptance of a biowaiver, and the compliance with the respective guidance documents indicated above. The SA procedure was however not finalised before the MA application was submitted.

This marketing application (MAA) for Apexelsin is based upon "essential similarity" to the original product Abraxane in accordance with Article 10(1) of Directive 2001/83/EC (as amended by Directive 2004/27/EC). According to the dossier, Apexelsin has the same qualitative and quantitative composition and the same pharmaceutical form (powder for dispersion for infusion) as the reference product Abraxane. The reference product Abraxane is a nanoparticle albumin-bound paclitaxel (also referred as nab-paclitaxel in this report). The main function of the paclitaxel nanoparticles is to overcome the poor solubility of paclitaxel in the infusion solution. The albumin-bound nanoparticles rapidly dissociate into soluble individual albumin-paclitaxel complexes upon dilution/ intravenous administration.

No clinical data has been presented to characterise the pharmacodynamics and the pharmacokinetics of paclitaxel and the albumin-based formulation. Eligibility for biowaiver has been requested by the Applicant based on the known PD/PK profile of the reference product Abraxane.

2.2. Quality aspects

2.2.1. Introduction

Apexelsin is a powder for dispersion for infusion. Each vial contains 100 mg of paclitaxel, as active substance, formulated as albumin bound nanoparticles.

After reconstitution, each ml of dispersion contains 5 mg paclitaxel formulated as albumin bound nanoparticles.

Other ingredients are: human albumin solution (containing sodium caprylate and *N*-acetyl-L-tryptophan).

The product is available in a 50 ml vial (type 1 glass) with a 20 mm stopper (bromobutyl rubber) and 20 mm cap (aluminium) with flip off seal as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General information

The chemical name of paclitaxel is 4, 10 β -Bis (acetyloxy)-13 α -[[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl] oxy]-1,7 β -dihydroxy-9-oxo-5 β , 20-epoxytax-11-en-2 α -yl benzoate corresponding to the molecular formula C₄₇H₅₁NO₁₄. It has a relative molecular mass of 853.91 g/mol and the following structure:

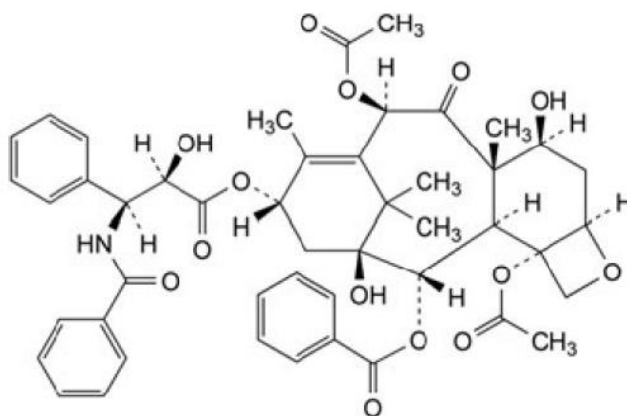


Figure 1: active substance structure

The active substance is a white or almost white, crystalline powder. It is slightly hygroscopic and practically insoluble in water.

Paclitaxel exhibits stereoisomerism due to the presence of 11 chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation.

As there is a monograph of paclitaxel in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for paclitaxel which has been provided within the current Marketing Authorisation Application. Paclitaxel is dissolved during the manufacture of the finished product, therefore the physical properties of the active substance (particle size, morphology) are not critical.

2.2.2.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

2.2.2.3. Specification(s)

The active substance specification includes tests for appearance (visual observation), identity (specific optical rotation, IR, both Ph. Eur.), specific optical rotation (Ph. Eur.), water content (Ph. Eur.), appearance of solution (Ph. Eur.), assay (Ph. Eur.), heavy metals (Ph. Eur.), related substances (Ph. Eur.), residual solvents (GC), bacterial endotoxins (Ph. Eur.) and microbial quality (Ph. Eur.).

The analytical methods and the reference standards used were assessed during evaluation of the CEP.

Batch analysis data from 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents.

2.2.2.4. Stability

Stability data was assessed during evaluation of the CEP. No additional data was provided with the present application.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is a powder for dispersion for infusion. It is a white to yellow lyophilised cake or powder. Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles. After reconstitution, each ml of dispersion contains 5 mg paclitaxel formulated as albumin bound nanoparticles.

The finished product has been developed to be a generic equivalent to the reference medicinal product Abraxane. Consequently, the objective was to prepare a powder for dispersion for infusion being essentially similar to the reference medicinal product.

All excipients and solvents and processing aids that are removed during manufacture are well known pharmaceutical ingredients. Confirmation that their quality is compliant with Ph. Eur. standards has been provided. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The applicant has compared relevant quality characteristics of the proposed generic product with the reference product sourced from the EU market.

The applied indications, route of administration, dosage form and strength (100 mg) for Apexelsin are the same as for Abraxane, except for the 250 mg strength, which is authorised for Abraxane, but which was not applied for in the current marketing authorisation procedure.

No clinical bioequivalence studies have been provided. The applicant applied for a waiver for bioequivalence studies/clinical studies on the basis of the qualitative and quantitative comparability with the reference product. Although the proposed finished product is not an aqueous intravenous solution but a "complex" formulation, the applicant has justified that generic albumin-bound paclitaxel is eligible to qualify for biowaiver as the following requirements are met:

- rapid disassembly of the micelle on dilution occurs and the finished product is not designed to control drug release or disposition
- the method and rate of administration is the same as the currently approved reference product
- the excipients do not affect the disposition of the active substance.

The main function of the paclitaxel nanoparticles is to overcome the poor solubility of paclitaxel in the infusion solution and not to control release or disposition in the blood stream. The albumin-bound nanoparticles rapidly dissociate into soluble individual albumin-paclitaxel complexes upon dilution/intravenous administration. Albumin in these soluble albumin-bound paclitaxel complexes is expected to be largely comprised of endogenous albumin (since the infused albumin is <5% of serum albumin in blood). Thus, the finished product formulation does not control the drug release or disposition of the active substance, and the only excipient, albumin, has been shown in *in vitro* characterisation studies

to be adequately characterised. There are no significant differences between the proposed generic product and the reference product when comparing in vitro dissociation kinetics. Three batches of the reference product were compared to the three process validation batches of the proposed generic product.

The physicochemical characterisation studies that support the comparison of the proposed finished product with the reference product comprise:

- qualitative and quantitative composition, including paclitaxel:albumin ratio
- particle size distribution
- crystallinity of paclitaxel (amorphous form)
- fraction of free vs. bound paclitaxel
- nature of paclitaxel/HSA bond
- morphology of particles
- in vitro release kinetics upon dilution
- oligomeric status of albumin in the reconstituted solution
- surface potential

The physico-chemical characterisation of the finished product and the reference product is the basis for biowaiver. During the procedure, the applicant provided further discussion, statistics and justification to support the comparison of reconstitution time and particle size distribution for the reference product and the proposed generic product.

The manufacturing process is based on the information in the Abraxane EPAR, and includes mixed solvent preparation, oil-water phase preparation, nano-emulsion preparation, high-pressure homogenisation (HPH), solvent evaporation, sterilising filtration, aseptic filling and lyophilisation. The manufacturing process development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified. During the procedure, the applicant provided additional justification for the shear rate and -speed of the primary emulsification process, and its impact on the particle size distribution of the product.

The primary packaging is a 50 ml vial (type 1 glass) with a 20 mm stopper (bromobutyl rubber) and 20 mm cap (aluminium) with flip off seal. The material complies 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

The manufacturing process consists of the following main steps: compounding, primary emulsification, microfluidic high-pressure homogenisation, thin-film evaporation, dilution, sterile filtration, filling and semi-stoppering, lyophilisation and full-stoppering, capping, visual inspection and packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. Process validation data was presented on three commercial scale batches. The holding times during filtration and filling were covered by the process validation, with additional sampling, on 3 production scale batches. Aseptic process validation, including media fills, has been performed. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

During the procedure, a major objection (MO) was raised to request confirmation of GMP compliance for the finished product manufacturing site. After inspection of the finished product manufacturing site, the applicant was able to provide the EU GMP certificate.

2.2.3.3. Product specification

The finished product release specifications includes appropriate tests for this kind of dosage form: appearance (visual inspection), identification of paclitaxel (HPLC, UV), identification of HSA (HPLC), water content (Ph.Eur.), reconstitution time (in-house method), particulate contamination – sub-visible particles (Ph.Eur.), particle size and distribution (Ph.Eur.), related substances (HPLC), HSA assay (HPLC), residual solvents (GC), uniformity of dosage units (Ph.Eur.), paclitaxel assay (HPLC), bacterial endotoxins (Ph.Eur.), sterility (Ph.Eur.), pH and osmolality of reconstituted solution (Ph.Eur.).

The specification tests and limits are acceptable and has been set in line with relevant Ph. Eur. Requirements, ICH guidelines, batch and stability data. During the procedure, several specification parameters were tightened or further justified, as requested.

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. Batch analysis data on three batches was provided, demonstrating that each relevant elemental impurity 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. 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 information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results are provided for three production scale batches 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 production scale batches of finished product packaged in the primary packaging proposed for marketing, stored for 24 months under long term conditions (25 °C / 60% RH) and for six months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided.

Samples were tested for appearance, water content, reconstitution time, particle size distribution, related substances, assay (paclitaxel and HSA), bacterial endotoxin and sterility. The reconstituted solution was tested for pH and osmolality. The analytical methods used were the same as for release and were stability indicating.

The observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, one batch of finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study demonstrated photosensitivity of the finished product, necessitating storage of the latter in the outer carton to protect from light.

An in-use stability study was conducted to evaluate the stability of the product reconstituted in the intended infusion fluid (0.9% NaCl) in the primary packaging and in the intended infusion bag. Product from one batch was reconstituted and tested following storage in the original vial inside the carton, or in the infusion bag, under refrigerated conditions, followed by 4 hours storage in the infusion bag under ambient conditions. Stability was demonstrated in both formats for up to 24 hours at refrigerated conditions followed by 4 hours at ambient conditions.

Based on chemical and physical in-use stability, the total combined storage time of reconstituted medicinal product in the vial and in the infusion bag when refrigerated and protected from light is 24 hours, which may be followed by storage in the infusion bag for 4 hours below 25 °C, as prescribed in the Product Information. However, from a microbiological point of view, unless the method of reconstituting and filling of the infusion bags precludes the risks of microbial contamination, the product should be used immediately after reconstitution and filling of the infusion bags.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Based on available stability data, and as stated in the SmPC (sections 6.3 and 6.4), the proposed shelf-life is 36 months without any special temperature storage conditions, this for the unopened vials, when kept in the outer carton in order to protect from light.

2.2.3.5. Adventitious agents

The HSA, which is human origin used in the finished product has been already marketed in the EU, and is linked to a certified plasma master file (PMF). Documentation in accordance with section 10 of the Guideline on Plasma-Derived Medicinal Products (CHMP/BWP/706271/2010) is included in section 3.2.A.2 of the dossier.

2.2.3.6. Post approval change management protocol

A post-approval change management protocol for introduction of a second finished product manufacturing site was included in the submission, and is considered approvable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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. A major objection (MO) was raised to request confirmation of GMP compliance for the finished product manufacturing site. After inspection of the finished product manufacturing site, the applicant was able to provide the EU GMP certificate.

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.

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 both new *in vivo* studies in mice and dogs, and scientific literature. The new studies included one pharmacodynamic (PD) study and two pharmacokinetic (PK) studies, in order to demonstrate comparative pharmacokinetics and similar anti-tumour effects between the proposed drug product and the reference drug product. Validation reports for the analytical methods have also been submitted. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic study

The applicant has performed the following primary pharmacodynamic study:

Study No. N19-153-PD: Pivotal Studies of Apexelsin 5 mg/ml Powder for Dispersion for Infusion in BALB/c Nude Mice Subcutaneously Transplanted with MCF-7 Human Breast Carcinoma Cells.

The purpose of this PD study was to establish the model of BALB/c nude mouse subcutaneous transplanted with MCF-7 human breast carcinoma cells, investigate the anti-tumour effect of the test product on subcutaneous transplantation, and provide a pharmacodynamic basis for clinical evaluation. Seventy tumour-bearing mice were screened and divided into 7 groups randomly: Group 1 (negative control group, sodium chloride injection), Group 2 to 4 (positive control- Paclitaxel for Injectable Suspension (Albumin-bound) by Celgene Corporation Fresenius Kabi, 7.5, 15, 30 mg/kg), Group 5 to 7 (test products, 7.5, 15, 30 mg/kg), each group of 10 animals, the dosing volume was 10 mL/kg, intravenous injection. The administration was performed once a week for 4 consecutive weeks and then the animals were euthanised on D29. During the study, the general clinical symptoms of the

animals were observed twice a day, and the body weight and tumour size were measured twice a week.

Table 1. Statistics of tumour weight and tumour weight inhibition rate (N19-153-PD)

Group	Test Product /Control	Dosage (mg/kg)	Animal No. (n)	Tumor Weight (g)	IR _{Tw} (%)
1	Sodium Chloride Injection	—	10	1.174±0.287	—
2	Positive Control	7.5	10	1.018±0.544	13.34
3	Positive Control	15	10	0.271±0.149 ^a	76.90 [▲]
4	Positive Control	30	10	0.001±0.002 ^a	99.92 [▲]
5	Test Product	7.5	10	1.023±0.272	12.86
6	Test Product	15	10	0.341±0.155 ^a	70.93 [▲]
7	Test Product	30	10	0.002±0.002 ^{aef}	99.86 [▲]

Note: 1. Compared with Group 1, a means $P \leq 0.05$; compared with Group 5, e means $P \leq 0.05$; compared with Group 6, f means $P \leq 0.05$;

2. $IR_{Tw} (\%) = (W_{\text{sodium chloride injection}} - W_{\text{treatment group}}) / W_{\text{sodium chloride injection}} \times 100 \%$;

3. [▲] means $IR_{Tw} \% \geq 60\%$.

2.3.3. Pharmacokinetics

The applicant has performed two pharmacokinetic studies:

Study No. N19-153-PK: Tissue distribution study of Apexelsin 5 mg/ml Powder for Dispersion for Infusion administered intravenously to tumour-bearing nude mice.

This study investigated the distribution characteristics of Apexelsin 5 mg/ml Powder for Dispersion for Infusion intravenously administered to tumour-bearing nude mice and compared it with the reference medicinal product to provide data support for subsequent studies. In this study, 48 female nude mice that were successfully inoculated with MCF-7 (human breast cancer cells) were divided into 8 groups with 6 animals in each group. The test product and the reference medicinal product were administered to tumour-bearing nude mice at a single dose of 30 mg/kg. Blood samples and major tissues (including heart, liver, spleen, lung, kidney, stomach, jejunum, gonad, brain, fat, skeletal muscle, tumour and bone marrow) were collected 0.5, 2, 8, and 48 hours after the start of administration for the test product group and the reference medicinal product group, 6 animals were tested at each time point. The validated LC-MS/MS analysis method was used to detect the content of total paclitaxel in plasma and various tissues. The lower limit of quantification of total paclitaxel in plasma is 1 ng/mL, and the lower limit of quantification of total paclitaxel in various tissues is 5 ng/g.

Table 2. Total paclitaxel metabolic kinetic parameters (AUC) (N19-153-PK study)

Tissues	AUC _(0-48h) h*ng/g		AUC _{INF} h*ng/g	
	Test Product	Reference Medicinal Product	Test Product	Reference Medicinal Product
	Mean	Mean	Mean	Mean
Heart	130761.17	116428.92	130853.34	116490.69
Lung	77233.23	62223.67	77822.91	63026.66
Liver	1078670.10	1002570.65	1079436.85	1003629.98
Spleen	86930.50	63600.51	87011.87	63688.59
Fat	93029.14	74909.00	93160.70	NA
Kidney	282201.23	218667.03	282359.77	218895.29
Stomach	296727.68	198808.57	298284.79	201230.23
Jejunum	350479.40	433851.13	351085.06	434499.51
Gonad	39379.72	67877.06	46449.18	69129.32
Skeletal	48426.79	37771.35	48465.14	37825.27
Brain	9970.91	10528.17	14902.18	19774.19
Bone	56190.73	69102.86	56235.57	69204.43
Plasma	34082.68	32460.39	34090.79	32470.99
Tumor	270407.55	288162.74	458415.59	559152.14

Note: NA means it cannot be calculated

Study No. D19-153-2PK: Pharmacokinetic study of Apexelsin 5 mg/ml Powder for Dispersion for Infusion administered intravenously to beagle dogs.

This study investigated the consistency of the *in vivo* pharmacokinetic characteristics of Apexelsin 5 mg/ml Powder for Dispersion for Infusion and the reference medicinal product (Abraxane) administered to beagle dogs by a single intravenous drip, to provide data support for subsequent studies. A total of 20 beagle dogs were used in the study, divided into 2 groups, 10 in each group, half male and half female. The animals in the first group were given the test products, and the animals in the second group were given the reference medicinal products. All animals were given a single intravenous infusion of the test product/reference medicinal product at a dose of 6.5 mg/kg, the administration volume per animal was 1.3 mL/kg, and the infusion rate was 0.15 mL/kg/min. Plasma samples were collected from all animals before administration, immediately after administration (approximately 8.7 minutes), and 30 minutes, 1, 2, 4, 6, 8, 24, and 48 hours after administration. The validated LC-MS/MS method was used to determine the content of total paclitaxel and free paclitaxel in beagle dog plasma.

Table 3. Main kinetic parameters of total paclitaxel (D19-153-2PK study)

Group		t _{1/2} (h)	T _{max} (h)	C _{max} (ng/mL)	AUC _(0-t) (h*ng/mL)	AUC _{INF} (h*ng/mL)	V _z (mL/kg)	Cl (mL/h/kg)	MRT (h)
Test Product	Mean	10.49	0.15	9598.21	4366.83	4414.24	22803.71	1500.60	2.92
	SD	0.77	0.00	1277.11	616.08	619.22	4436.97	227.57	0.33
	CV%	7.33	0.00	13.31	14.11	14.03	19.46	15.17	11.20
Reference medicinal product	Mean	9.88	0.15	10005.11	4513.00	4560.86	20950.29	1474.16	2.84
	SD	1.14	0.00	1721.91	837.49	861.81	4405.92	293.45	0.57
	CV%	11.57	0.00	17.21	18.56	18.90	21.03	19.91	20.05
P value		0.18	NA	0.56	0.66	0.67	0.36	0.82	0.69

Note: The p value represents the independent sample T test results of the test product group and the reference medicinal product group at the same dose, and p<0.05 indicates a statistical difference.

Table 4. Main kinetic parameters of free paclitaxel (D19-153-2PK study)

Group		t _{1/2} (h)	T _{max} (h)	C _{max} (ng/mL)	AUC _(0-t) (h*ng/mL)	AUC _{INF} (h*ng/mL)	V _z (mL/kg)	Cl (mL/h/kg)	MRT (h)
Test Product	Mean	8.26	0.15	265.80	104.52	107.08	738043.73	62251.57	1.74
	SD	1.58	0.00	52.25	17.21	17.49	166919.77	10690.84	0.57
	CV%	19.10	0.00	19.66	16.47	16.33	22.62	17.17	32.86
Reference medicinal product	Mean	7.72	0.15	278.89	107.72	110.32	662966.37	61588.10	1.62
	SD	1.88	0.00	67.62	23.85	23.89	142808.93	13995.08	0.63
	CV%	24.39	0.00	24.25	22.14	21.65	21.54	22.72	39.06
p value		0.50	NA	0.63	0.73	0.73	0.29	0.91	0.68

Note: The p value represents the independent sample T test results of the test product group and the reference medicinal product group at the same dose, and p<0.05 indicates a statistical difference.

2.3.4. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was considered acceptable as the introduction of Apexelsin manufactured by Whiteoak Pharmaceutical B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all paclitaxel containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.5. Discussion on non-clinical aspects

In order to demonstrate the comparability of the pharmacology between Apexelsin and the reference product (Abraxane), the applicant conducted one pharmacodynamic (PD) study and two pharmacokinetic (PK) studies. Since this is a marketing authorisation application for a generic medicinal product where the bioequivalence should primarily be based on *in vitro* comparative characterisation studies submitted in Module 3 of the dossier, the conduct of non-clinical *in vivo* studies is considered superfluous and not in line with the 3Rs.

Nonetheless, the results of these studies were evaluated by the CHMP:

Study No. N19-153-PD: Under the conditions of the pharmacology study in mice transplanted with MCF-7 human breast carcinoma cells, Apexelsin had a clear dose-dependent anti-tumour effect. At the same dose level, the effect of Apexelsin was similar to the reference medicinal product (Abraxane).

Study No. N19-153-PK: Tissue distribution was studied in mice. When comparing paclitaxel exposure (AUC_{0-48h}) in tissues between the groups administered Apexelsin and Abraxane, the results are considered comparable.

Study No. D19-153-2PK: Absorption was investigated in one study using beagle dogs. Statistical analysis of the measured PK parameters did not detect any significant difference between Apexelsin and Abraxane.

Additionally, the submitted overview reviews relevant published non-clinical data concerning paclitaxel and is considered adequate (data not shown).

The SmPC sections 4.6 and 5.3 of Apexelsin are identical to Abraxane and are therefore considered acceptable.

No Environmental Risk Assessment studies were submitted. This was considered acceptable as the introduction of Apexelsin manufactured by Whiteoak Pharmaceutical B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all paclitaxel containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.6. Conclusion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of Apexelsin has been provided by the applicant, which is based on both new *in vivo* studies in mice and dogs, and scientific literature. These data show that Apexelsin does not differ significantly in properties with regards to the safety and efficacy of the reference product and was accepted by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for powder for dispersion for infusion containing paclitaxel formulated as albumin-bound paclitaxel. The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of paclitaxel based on published literature. The SmPC is in line with the SmPC of the reference product.

Exemption

The applied indications, route of administration, dosage form and strength (100 mg) for Apexelsin are the same as for Abraxane, except for the following:

- The 250 mg strength, which is authorised for Abraxane, was not applied for in this MA procedure.

No clinical bioequivalence studies have been provided. The applicant applied for a waiver for bioequivalence studies/clinical studies on the basis of the qualitative and quantitative comparability with the reference product.

Although the proposed drug product is not an aqueous intravenous solution but a “complex” formulation, the applicant has justified that generic albumin-bound paclitaxel is eligible to qualify for biowaiver as the following requirements are met:

- rapid disassembly of the micelle on dilution occurs and the drug product is not designed to control drug release or disposition; paclitaxel nanoparticles is to overcome the poor solubility of paclitaxel in the infusion solution and not to control release or disposition in the blood stream. The albumin-bound nanoparticles rapidly dissociate into soluble individual albumin-paclitaxel complexes upon dilution/ intravenous administration.
- the method and rate of administration is the same as the currently approved reference product (Abraxane); Albumin in these soluble albumin-bound paclitaxel complexes is expected to be largely comprised of endogenous albumin (since the infused albumin is <5% of serum albumin in blood). Thus, the drug formulation does not control the drug release or disposition of the active substance.
- the excipients do not affect the disposition of the drug substance. The only excipient, albumin, has been shown in *in vitro* characterisation studies to be adequately characterised and that there are no significant differences between the Test and Reference product when comparing *in vitro* dissociation kinetics for a range of albumin contents.

The physicochemical characterisation studies that support the comparison of the proposed drug product with the reference product are presented in section 2.2 Quality

1. Particle size distribution

Particle size impacts the dissolution rate of particles, as it is known that the dissolution time depends on the initial particle size. Three batches of test product and three batches of RMP showed similar mean particle size and size distribution.

2. Crystallinity of paclitaxel

The crystallinity of paclitaxel in the finished product of Apexelsin and Abraxane was studied using pXRD. The detectability of crystalline paclitaxel is demonstrated by 2% spiked into the isolated particles.

3. Fraction of free vs. bound paclitaxel

Fraction of free and bound paclitaxel is critical for functional attributes and stability. As per the literature-based understanding of Abraxane, the paclitaxel present in nanoparticles is encapsulated by a surface layer of albumin which is denoted as ‘bound paclitaxel’ and the rest is denoted as ‘free paclitaxel’.

4. Nature of paclitaxel/HSA bond

To demonstrate the similarity in ‘nature of bond between paclitaxel and human serum albumin (HSA)’, Apexelsin and Abraxane products were characterised using Nuclear Magnetic Resonance (NMR), Fourier Transform-infrared (FT-IR) spectroscopy. The observed trends for both products were comparable (data not shown).

5. Morphology

Particle shape and surface area can affect particle solubility and dissolution rate. To evaluate sameness of particle morphology between Abraxane and Apexelsin, cryogenic transmission electron microscopy (Cryo-TEM) was used. Cryo-TEM images showed similar morphology (irregular shaped particles) and size distribution. Further, albumin coating around the particles was found similar in both products (data not shown).

6. In vitro release kinetics upon dilution

In vitro release kinetics of paclitaxel were calculated in 0.9% NaCl and in human plasma using the Dynamic light scattering (DLS) method (data not shown).

7. Oligomeric status of albumin

The oligomeric status of the albumin is important to understand the changes that occur to the albumin at molecular level during the manufacturing process. This demonstrates the composition of albumin with respect to monomer, dimer, oligomer and polymer. The results showed that the oligomeric status of Apexelsin and Abraxane are similar (data not shown).

8. Surface potential

The colloidal stability of the particles is a critical attribute of the functional performance of the product. The stability of suspension is due in part to the particle surface charge which stabilizes the particles from aggregation, thereby maintaining the desired size distribution. The zeta potential is the electrostatic property of the particles that plays a role in colloidal aggregation stability of the suspension.

The applicant has presented statistically based support that the reference product and the test product are 'similar'.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

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

2.4.2.2. Pharmacodynamics

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

2.4.3. Clinical efficacy

Not applicable.

2.4.4. Clinical safety

Not applicable.

2.4.4.1. Post marketing experience

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

2.4.5. Discussion on clinical aspects

The applicant has claimed a biowaiver on the basis that the relevant pharmaceutical properties of paclitaxel (Apexelsin) are essentially similar to the reference product Abraxane.

Article 10(1) of European Directive 2001/83/EC (as amended) states that the applicant shall not be required to provide the results of clinical testing if it can be demonstrated that the product is essentially similar to a product which has been authorised within the European Union for 6-10 years (depending on territory) provided that the product is intended for the same therapeutic use at the same dosage and route of administration as the existing authorised product.

Apexelsin has the same method and rate of administration, indications, dosage form and strength (100 mg) as Abraxane.

The applicant provided an adequate clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of paclitaxel-albumin based on published literature. The summary of literature refers to the proposed indications, which are the same as approved for the reference product.

Although the proposed drug product is not an aqueous intravenous solution but a “complex” formulation, the Applicant has presented rationale and analytical data to support a request for biowaiver: The drug product is not designed to control the drug release or disposition of paclitaxel following injection, but to improve the solubility of paclitaxel. The amorphous paclitaxel/albumin complex is rapidly disassembled upon dilution. Following injection, circulating paclitaxel is expected to be in an equilibrium state between free paclitaxel and bound to both, endogenous and infused human serum albumin.

The applicant performed physicochemical characterisation studies including: qualitative and quantitative composition, particle size distribution, crystallinity, fraction of free vs. bound paclitaxel, morphology, *in vitro* release kinetics upon dilution, oligomeric status of albumin and surface potential. These studies support the comparison of Apexelsin with the reference product (Abraxane), and are considered acceptable by the CHMP.

2.4.6. Conclusions on clinical aspects

The waiver for bioequivalence studies/clinical studies on the basis of the qualitative and quantitative comparability with the reference product is considered to be acceptable, and Apexelsin is considered bioequivalent to Abraxane.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 5. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

In line with the reference product, there are no important identified or potential risks or missing information in the RMP for Apexelsin. The summary of safety concerns is line with the reference product and therefore accepted.

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are no routine pharmacovigilance activities beyond legislative requirements.

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.5.3. Risk minimisation measures

The safety information in the proposed Product Information is aligned to the reference medicinal product.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.1 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

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

3. Benefit-risk balance

This application concerns a generic version of paclitaxel powder for dispersion for infusion. The reference product is Abraxane 5 mg/ml powder for suspension for infusion indicated:

- in monotherapy for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated,

- in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas,
- in combination with carboplatin for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

The non-clinical dossier consists of both new *in vivo* pharmacology and pharmacokinetic studies in mice and dogs as well as published data. However, since this is a marketing authorisation application for a generic medicinal product where the bioequivalence should primarily be based on *in vitro* comparative characterisation studies submitted in Module 3 of the dossier, the conduct of non-clinical *in vivo* studies is considered superfluous and not in line with the 3Rs. An adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the Applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

Although the proposed drug product is not an aqueous intravenous solution but a "complex" formulation, the Applicant has presented rationale and analytical data to support a request for biowaiver, which was considered adequate.

Exemption from the need to conduct a bioequivalence study was considered adequately substantiated.

Satisfactory comparisons, supported by statistics, of relevant physico-chemical characteristics between the reference product Abraxane and the proposed drug product have been presented.

Based on the quality, non-clinical and clinical data submitted, the benefit/risk balance of Apexelsin is considered positive, comparable to the reference medicinal product.

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

4. Recommendations

Similarity with authorised medicinal products

The CHMP by consensus is of the opinion that Apexelsin is not similar to Lutathera and Onivyde within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix.

Outcome

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

- in monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated (see section 4.4);
- in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas;
- in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

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.

5. Appendix

5.1. CHMP AR on similarity dated 30 May 2024