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EU Risk Management Plan for Apexelsin

RMP version to be assessed as part of this application:

RMP Version number: 0.2

Data lock point for this RMP: 24.07.2024

Date of final sign-off: 01.08.2024

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Paclitaxel
Pharmacotherapeutic group(s) (ATC Code)	L01CD01
Marketing Authorisation Applicant	Applicant: WhiteOak Pharmaceutical B.V. Address: Teleportboulevard 130, 1043EJ, Amsterdam, Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Apexelsin 5 mg/ml Powder for Dispersion for Infusion
Marketing authorisation procedure	centralised
Brief description of the product	antineoplastic agents (taxanes)
	The active substance in the proposed drug product, paclitaxel, belongs to the group of cancer medicines known as the 'taxanes'. Paclitaxel blocks a stage of cell division in which the cell's internal 'skeleton' is dismantled to allow the cell to divide. By keeping this structure intact the cells cannot divide and they eventually die. Apexelsin 5 mg/ml Powder for Dispersion for Infusion (herein after referred to as Apexelsin) also affects non-cancer cells such as blood and nerve cells, which can cause side effects. Paclitaxel has been available as a cancer medicine since 1993. In Apexelsin 5 mg/ml Powder for Dispersion for Infusion, unlike conventional paclitaxel-containing medicines, the paclitaxel is attached to a human protein called albumin in tiny particles known as 'nanoparticles'. This makes it easy to prepare a suspension of paclitaxel, which can be infused into a vein.
	Apexelsin is a powder that is made up into a suspension for infusion (drip) into a vein. It contains the active substance paclitaxel attached to a human protein called albumin. Apexelsin 5 mg/ml Powder for Dispersion for Infusion. It is supplied as a white to yellow, sterile and lyophilized powder and contains 800 mg albumin per 100mg paclitaxel prior to reconstitution with 0.9% saline. After reconstitution, each ml of suspension contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.
Hyperlink to the Product Information	eCTD Module 2.3 Instruction
Indication(s) in the EEA	Current: Metastatic breast cancer, Non-small cell lung cancer and Metastatic adenocarcinoma of the pancreas
	Proposed (if applicable): Not applicable

Dosage in the EEA	Current: Breast cancer: The recommended dose of Apexelsin is 260 mg/m2 administered intravenously over 30 minutes every 3 weeks. Pancreatic adenocarcinoma: The recommended dose of Apexelsin in combination with gemcitabine is 125 mg/m2 administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m2 administered intravenously over 30 minutes immediately after the completion of Apexelsin administration on Days 1, 8 and 15 of each 28-day cycle. Non-small cell lung cancer: The recommended dose of Apexelsin is 100 mg/m2 administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the end of Apexelsin administration.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Apexelsin 5 mg/ml powder for dispersion for infusion. 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.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication breast cancer

Incidence and prevalence

Breast cancer is the most frequent malignancy in women worldwide and is curable in ~70-80% of patients with early-stage, non-metastatic disease (Harbeck, 2019). In 2018, according to the prediction of the European Cancer Information System (ECIS), breast cancer continues to be the most common female cancer, with the incidence in the European Union (EU-28) accounting for 29.2% of all cancers in women (Dafni, 2019).

Demographics of the population in the proposed indication and risk factors for the disease

Some of the important risk factors include aging, family history, lifestyle including an unhealthy diet, obesity, and consumption of alcohol, exposure to exogenous hormones including long-term hormone replacement therapy and reproductive factors such as early menarche, late menopause, late age at first pregnancy and low parity (Sun, 2017).

The main existing treatment options

Treatment strategies differ according to molecular subtype. Management of breast cancer is multidisciplinary; it includes locoregional (surgery and radiation therapy) and systemic therapy approaches (Harbeck, 2019).

Systemic therapy of metastatic breast cancer may include chemotherapy, endocrine therapy, and targeted therapies (e.g., antibody-based approaches). These agents may be employed alone or in combination based on the patient's breast cancer subtype. Novel therapeutic approaches include immunologic therapies, poly-(ADP-ribose) polymerase inhibitors, phosphatidylinositol-3-kinase inhibitors, and cyclin-dependent kinases (CDK)4/6 inhibitors (Liedtke, 2016).

In cases with an indication for chemotherapy, monochemotherapy is usually applied. For monotherapy, a large number of agents may be considered which includes, taxanes like paclitaxel, anthracyclines, platinum compounds, vinorelbine, capecitabine, eribulin, and gemcitabine (Liedtke, 2016).

Natural history of the indicated condition in the population, including mortality and morbidity

Advanced breast cancer with distant organ metastases is considered incurable with currently available therapies. On the molecular level, breast cancer is a heterogeneous disease; molecular features include activation of human epidermal growth factor receptor 2 (HER2, encoded by ERBB2), activation of hormone receptors (oestrogen receptor and progesterone receptor) and/or BRCA mutations (Harbeck, 2019).

Breast cancer represents a major public health concern due to its high morbidity and mortality rates, with EUROSTAT reporting that it accounted for 1.8% of all deaths in the EU-28 in 2015 and 3.6% (i.e., double) of deaths in women (Dafni, 2019).

Indication pancreatic adenocarcinoma

Incidence and prevalence

Pancreatic ductal adenocarcinoma is an aggressive form of cancer with a dismal prognosis (De Dosso, 2021). The highest incidence rates are found in Northern America (7.4 per 100,000) and Europe (6.8 per 100,000). Incidence is higher in men than in women, with global incidence rates per 100,000 of 4.9 for men and 3.6 for women, consistent across all regions.

Demographics of the population in the proposed indication and risk factors for the disease

Multiple environmental and genetic risk factors have been implicated in the development of pancreatic ductal adenocarcinoma. The most important risk factors include cigarette smoking, high body weight and diabetes (Simoes, 2017).

The main existing treatment options

Gemcitabine monotherapy has been the standard of care for patients with metastatic pancreatic cancer for several decades (Thota, 2014). The current front-line treatment landscape in local stages comprises surgical resection, adjuvant chemotherapy (De Dosso, 2021) and targeted agents (Anti-epidermal growth factor receptor (EGFR) agents (Teague, 2015). New combination chemotherapies of gemcitabine with nanoparticle albumin bound technology (nab)-paclitaxel or combination chemotherapy with leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) have emerged as the main front-line treatment options for patients with good performance status in the treatment of metastatic pancreatic adenocarcinoma (Thota, 2014; Teague, 2015).

Indication non-small cell lung cancer

Incidence and prevalence

[redacted]

Lung cancer has a poor prognosis; over half of people diagnosed with lung cancer die within one year of diagnosis and the 5-year survival is less than 18% (Zappa, 2016). It is the most common form of cancer globally, claiming an estimated 1,796,144 deaths in 2020 (World Health Organization, 2020). Lung cancer is also a second leading cause of cancer-related deaths in Europe, responsible for approximately 384,176 deaths in 2020, or about 19.6% of all cancer deaths (World Health Organization, 2020).

Demographics of the population in the proposed indication and risk factors for the disease

Non-small cell lung cancer (NSCLC) one of the subtypes of lung cancer accounts for the majority of all lung cancer cases (Zappa, 2016). Risk factors for developing NSCLC have been identified, with cigarette smoking being a major factor along with other environmental and genetic risk factors (Zappa, 2016).

The main existing treatment options

Depending on the staging of lung cancer, patients are eligible for certain treatments ranging from surgery to radiation to chemotherapy as well as targeted therapy. Approximately 40% of newly diagnosed lung cancer patients are stage IV. The goal for treating these patients is to improve survival and reduce disease-related adverse events. For stage IV NSCLC, cytotoxic combination chemotherapy is the first-line therapy, which might be influenced by histology, age vs. comorbidity, and performance status (Zappa, 2016). Administration of a platinum compound in combination with a taxane (paclitaxel or docetaxel), gemcitabine, vinorelbine, or irinotecan is considered optimal first-line therapy for patients with advanced-stage NSCLC who have a good performance status (Ramalingam, 2005).

Part II: Module SII - Non-clinical part of the safety specification

Not applicable

Part II: Module SIII - Clinical trial exposure

Not applicable

Part II: Module SIV - Populations not studied in clinical trials

Not applicable

Part II: Module SV - Post-authorisation experience

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable

Part II: Module SVII - Identified and potential risks

There are no important identified or potential risks or missing information.

Part II: Module SVIII - Summary of the safety concerns

There are no important identified or potential risks or missing information.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are no routine pharmacovigilance activities beyond legislative requirements

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

There are no studies required for Apexelsin.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

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

Part VI: Summary of the risk management plan

Summary of risk management plan for Apexelsin 5mg/ml powder for dispersion for infusion

This is a summary of the risk management plan (RMP) for Apexelsin (herein after referred to as Apexelsin). The RMP details important risks of Apexelsin, how these risks can be minimised, and how more information will be obtained about Apexelsin's risks and uncertainties (missing information).

Apexelsin's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Apexelsin should be used.

This summary of the RMP for Apexelsin should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Apexelsin's RMP.

I. The medicine and what it is used for

Apexelsin is authorised 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;

- and 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 (see SmPC for the full indication).

It contains paclitaxel (albumin bound) as the active substance and it is given by intravenous route of administration.

Further information about the evaluation of Apexelsin's benefits can be found in Apexelsin's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage Apexelsin | European Medicines Agency (EMA) (europa.eu).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Apexelsin 5 mg/ml Powder for Dispersion for Infusion, together with measures to minimise such risks and the proposed studies for learning more about Apexelsin 5 mg/ml Powder for Dispersion for Infusion 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Apexelsin 5 mg/ml Powder for Dispersion for Infusion are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered/taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Apexelsin 5 mg/ml Powder for Dispersion for Infusion. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

There are no important identified or potential risks or missing information.

II.B Summary of important risks

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

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Apexelsin 5 mg/ml Powder for Dispersion for Infusion.

[redacted]

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Apexelsin 5 mg/ml Powder for Dispersion for Infusion.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

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Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

None

Table 2 Annex II: Completed studies

None

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

None

Annex 4 - Specific adverse drug reaction follow-up forms

None

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

None

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

None

[redacted]

Annex 7 - Other supporting data (including referenced material)

1. Harbeck, N., Penault-Llorca, F., Cortes, J. et al. Breast cancer. Nat Rev Dis Primers 5, 66 (2019).
2. Dafni U, Tsourti Z, Alatsathianos I. Breast Cancer Statistics in the European Union: incidence and survival across European countries. Breast Care. 2019;14(6):344-53.
3. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, Shi W, Jiang J, Yao PP, Zhu HP. Risk factors and preventions of breast cancer. International journal of biological sciences. 2017;13(11):1387.
4. De Dosso S, Siebenhüner AR, Winder T, Meisel A, Fritsch R, Astaras C, Szturz P, Borner M. Treatment landscape of metastatic pancreatic cancer. Cancer Treatment Reviews. 2021 May 1;96.
5. Simoes PK, Olson SH, Saldia A, Kurtz RC. Epidemiology of pancreatic adenocarcinoma. Chinese clinical oncology. 2017 Jun 1;6(3):24-.
6. Thota R, Pauff JM, Berlin JD. Treatment of metastatic pancreatic adenocarcinoma: a review. Oncology (Williston Park). 2014 Jan 15;28(1):70-4.
7. Teague A, Lim KH, Wang-Gillam A. Advanced pancreatic adenocarcinoma: a review of current treatment strategies and developing therapies. Therapeutic advances in medical oncology. 2015 Mar;7(2):68-84.
8. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Translational lung cancer research. 2016 Jun;5(3):288.
9. World Health Organization- International Agency for Research on Cancer. World Fact Sheet. Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf. Accessed May 2020.

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
1	At the time of authorisation	First version