EU Risk Management Plan
for
Paclitaxel 6 mg/ml Concentrate for Solution for Infusion
Naveruclif 5 mg/ml powder for dispersion for infusion

(Paclitaxel)

RMP version to be assessed as part of this application:

RMP Version number	2.2
Data lock point for this RMP	25-Aug-2023
Date of final sign off	15-Sept-2023

Rationale for submitting an updated RMP: The Risk Management Plan (RMP) has been updated in line with the Rapporteurs day 150 joint CHMP and PRAC response assessment report, dated 21-Aug-2023.

Summary of significant changes in this RMP:

Significant changes have been made in following sections of the RMP: Part I, Part II (Module SVII), Part III, Part VI and Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version	Date of approval (opinion date)	Submitted within Procedure
1.1	02-Aug-2018	NL/H/1444/001/II/027

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QPPV signature: [redacted]

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Paclitaxel
Pharmacotherapeutic group(s)(ATC Code)	**Pharmacotherapeutic group**: Antineoplastic agents, plant alkaloids and other natural products, taxanes **ATC Code**: L01C D01
Marketing Authorisation Holder	Accord Healthcare B.V., Netherlands Accord Healthcare S.L.U, Spain
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)	**Centralised procedure (EMEA/H/C/0006173)** Naveruclif 5 mg/ml powder for dispersion for infusion **Decentralised procedure (NL/H/1444/001)** Paclitaxel 6 mg/ml Concentrate for Solution for Infusion
Marketing authorisation procedure	Centralised procedure (EMEA/H/C/0006173) Decentralised (NL/H/1444/001)
Brief description of the product	*Chemical class:* Antineoplastic agents (taxanes)
	Summary of mode of action: Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of

	microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.
	Important information about its composition: **Paclitaxel 6 mg/ml Concentrate for Solution for Infusion** Each ml of concentrate for solution for infusion contains 6 mg of paclitaxel. A vial of 5 ml contains 30 mg of paclitaxel. A vial of 16.7 ml contains 100 mg of paclitaxel. A vial of 25 ml contains 150 mg of paclitaxel. A vial of 50 ml contains 300 mg of paclitaxel. A vial of 100 ml contains 600 mg of paclitaxel. Excipient(s) with known effect: Polyoxyl 35 castor oil (Macrogolglycerolricinoleate 35) 527.0 mg/ml and anhydrous ethanol 391 mg/ml **Naveruclif 5 mg/ml powder for dispersion for infusion** Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles.
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC
Indication(s) in the EEA	*Current:* **Paclitaxel 6 mg/ml Concentrate for Solution for Infusion** **Ovarian carcinoma**: in the first-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of patients with advanced carcinoma of the ovary or with residual disease (> 1 cm) after initial laparotomy, in combination with cisplatin.

	In the second-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy. **Breast carcinoma**: in the adjuvant setting, Paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy. Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express HER-2 (human epidermal growth factor receptor 2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable. As a single agent, Paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy. **Advanced non-small cell lung carcinoma**: Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy. **AIDS-related Kaposi's sarcoma:** Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy.
	Proposed: **Naveruclif 5 mg/ml powder for dispersion for infusion** Naveruclif 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.

<table>
<tr><td></td><td>Naveruclif in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

Naveruclif 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.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

<u>Posology</u>

Paclitaxel 6 mg/ml Concentrate for Solution for Infusion

Paclitaxel should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents. All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to Paclitaxel 6 mg/ml, concentrate for solution for infusion, e.g.

<table>
<tr><th>Medicinal product</th><th>Dose</th><th>Administration prior to Paclitaxel</th></tr>
<tr><td>dexamethasone</td><td>20 mg oral* or IV</td><td>For oral administration: approximately 12 and 6 hours or for IV administration: 30 to 60 min</td></tr>
<tr><td>diphenhydramine**</td><td>50 mg IV</td><td>30 to 60 min</td></tr>
<tr><td>cimetidine or ranitidine</td><td>300 mg IV

50 mg IV</td><td>30 to 60 min</td></tr>
</table>
*8–20 mg for KS patients

** or an equivalent antihistamine e.g. chlorpheniramine.</td></tr>
</table>

	First-line chemotherapy of ovarian carcinoma: although other dosage regimens are under investigation, a combination regimen of paclitaxel and cisplatin is recommended. According to duration of infusion, two doses of paclitaxel are recommended: paclitaxel 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 every three weeks or paclitaxel 135 mg/m², in a 24-hour infusion, followed by cisplatin 75 mg/m², with a 3 week interval between courses. **Second-line chemotherapy of ovarian carcinoma:** the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3 week interval between courses. **Adjuvant chemotherapy in breast carcinoma:** the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours every 3 weeks for four courses, following AC therapy. **First-line chemotherapy of breast carcinoma:** when used in combination with doxorubicin (50 mg/m²), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses. When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses. Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated. **Second-line chemotherapy of breast carcinoma:** the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3-week interval between courses. **The treatment of advanced non-small-cell lung carcinoma (NSCLC)**: the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, followed by cisplatin 80 mg/m², with a 3-week interval between courses.

	The treatment of AIDS-related KS: the recommended dose of paclitaxel is 100 mg/m^2 administered as 3-hour intravenous infusion every two weeks. Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be re-administered until the neutrophil count is ≥ 1,500/mm³ (≥ 1,000/mm³ for KS patients) and the platelet count is ≥ 100,000/mm³ (≥ 75,000/mm³ for KS patients). Patients who experience severe neutropenia (neutrophil count < 500/mm³ for a week or longer) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients). **Method of administration** Precautions to be taken before handling or administering the medicinal product. The concentrate for solution for infusion must be diluted before use and should only be administered intravenously. Paclitaxel should be administered intravenously through an in-line filter with a microporous membrane 0.22 µm.
	Proposed: **Naveruclif 5 mg/ml powder for dispersion for infusion** **Breast cancer:** The recommended dose of Naveruclif is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks. **Pancreatic adenocarcinoma:** The recommended dose of Naveruclif in combination with gemcitabine is 125 mg/m^2 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/m^2 administered intravenously over 30 minutes immediately after the completion of Naveruclif administration on Days 1, 8 and 15 of each 28-day cycle.**Non-small cell lung cancer:** The recommended dose of Naveruclif is 100

	mg/m^2 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 Naveruclif administration **Method of administration** Administer reconstituted Naveruclif dispersion intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose.
Pharmaceutical form(s) and strengths	*Current:* **Decentralised procedure (NL/H/1444/001)** Concentrate for solution for infusion. 6 mg/ml *Proposed:* **Centralised procedure (EMEA/H/C/0006173)** Powder for dispersion for infusion. 5 mg/ml
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

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

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

The reference product of Paclitaxel 6 mg/ml Concentrate for Solution for Infusion (Taxol) has no RMP in place. In the current SmPC the risks are sufficiently addressed. Hence there are no safety concerns for paclitaxel.

Naveruclif 5 mg/ml powder for dispersion for infusion: There is a valid RMP in place for the reference medicinal product Abraxane® 5 mg/mL powder for dispersion for infusion, with no safety concerns. There is no change proposed by MAH in these safety concerns mentioned in Module SVIII.

Hence this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risk (s)	• None
Important potential risk (s)	• None
Missing information	• None

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for Paclitaxel 6 mg/ml Concentrate for Solution for Infusion and Naveruclif 5 mg/ml powder for dispersion for infusion.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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 products.

Hence this section remains "Not applicable".

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

None proposed.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for Naveruclif 5 mg/ml powder for dispersion for infusion (paclitaxel)

This is a summary of the risk management plan (RMP) for Naveruclif 5 mg/ml powder for dispersion for infusion. The RMP details important risks of Naveruclif 5 mg/ml powder for dispersion for infusion, how these risks can be minimised, and how more information will be obtained about Naveruclif 5 mg/ml powder for dispersion for infusion's risks and uncertainties (missing information).

Naveruclif 5 mg/ml powder for dispersion for infusion's summary of product characteristics (SmPC) give essential information to healthcare professionals and patients on how Naveruclif 5 mg/ml powder for dispersion for infusion should be used.

This summary of the RMP for Naveruclif 5 mg/ml powder for dispersion for infusion 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 Naveruclif 5 mg/ml powder for dispersion for infusion's RMP.

I. The medicine and what it is used for

Naveruclif 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.

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

Naveruclif 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.

It contains paclitaxel as the active substance, and it is given by intravenous route.

Further information about the evaluation of Naveruclif 5 mg/ml powder for dispersion for infusion's benefits can be found in Naveruclif 5 mg/ml powder for dispersion for infusion's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page >.

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

Important risks of Naveruclif 5 mg/ml powder for dispersion for infusion together with measures to minimise such risks and the proposed studies for learning more about Naveruclif 5 mg/ml powder for dispersion for infusion 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 Naveruclif 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 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 Naveruclif 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);

Important identified risk (s)	• None
Important potential risk (s)	• None
Missing information	• None

II.B Summary of important risks

The safety information in the proposed product information are aligned to the reference medicinal products.

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 Naveruclif 5 mg/ml powder for dispersion for infusion.

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

There are no studies required for Naveruclif 5 mg/ml powder for dispersion for infusion

Summary of risk management plan for Paclitaxel 6 mg/ml Concentrate for Solution for Infusion (paclitaxel)

This is a summary of the risk management plan (RMP) for Paclitaxel 6 mg/ml Concentrate for Solution for Infusion. The RMP details important risks of Paclitaxel 6 mg/ml Concentrate for Solution for Infusion, how these risks can be minimised, and how more information will be obtained about Paclitaxel 6 mg/ml Concentrate for Solution for Infusion's risks and uncertainties (missing information).

Paclitaxel 6 mg/ml Concentrate for Solution for Infusion's summary of product characteristics (SmPC) and their package leaflets give essential information to healthcare professionals and patients on how Paclitaxel 6 mg/ml Concentrate for Solution for Infusion should be used.

Important new concerns or changes to the current ones will be included in updates of Paclitaxel 6 mg/ml Concentrate for Solution for Infusion's RMP.

I. The medicine and what it is used for

Ovarian carcinoma: in the first-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of patients with advanced carcinoma of the ovary or with residual disease (> 1 cm) after initial laparotomy, in combination with cisplatin.

In the second-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy.

Breast carcinoma: in the adjuvant setting, Paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with Paclitaxel should be regarded as an alternative to extended AC therapy.

Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express HER-2 (human epidermal growth factor receptor 2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.

As a single agent, Paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy.

Advanced non-small cell lung carcinoma: Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

AIDS-related Kaposi's sarcoma: Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy.

It contains paclitaxel as the active substance, and it is given by intravenous route.

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

Important risks of Paclitaxel 6 mg/ml Concentrate for Solution for Infusion together with measures to minimise such risks and the proposed studies for learning more about Paclitaxel 6 mg/ml Concentrate for Solution for Infusion 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 Paclitaxel 6 mg/ml Concentrate for Solution 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 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 Paclitaxel 6 mg/ml Concentrate for Solution 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);

Important identified risk (s)	• None
Important potential risk (s)	• None
Missing information	• None

II.B Summary of important risks

The safety information in the proposed product information are aligned to the reference medicinal products.

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 Paclitaxel 6 mg/ml Concentrate for Solution for Infusion

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

There are no studies required for Paclitaxel 6 mg/ml Concentrate for Solution for Infusion

Part VII: Annexes

Table of Contents

Annex 1 – EudraVigilance Interface

Not applicable.

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

Not applicable.

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

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

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

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.