EU RISK MANAGEMENT PLAN

PEMETREXED

RMP version to be assessed as part of this application	
RMP version number	5.0
Data lock point for this RMP	30 November 2024
Date of final sign off	16 January 2025
Rationale for submitting an updated RMP	RMP document prepared to: • Remove the Important potential risk of "Medication errors" in line with PSUSA recommendation (EMEA/H/C/PSUSA/00002330/202402) • Consolidation of Teva Pemetrexed RMPs into one joint RMP document

QPPV Details	
QPPV name:	Iva Novak
QPPV oversight signature:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV/deputy. The signature is available on file.

Table 1: Summary of Significant Changes in This RMP Version

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part I Product(s) overview	4.0 (approved 25 June 2020) 4.2 (approved 20 November 2019)	Update of administrative data.
Part II - Module SI Epidemiology of the indication(s) and target population(s)	4.0 (approved 25 June 2020)	Not applicable.
Part II - Module SII Non-clinical part of the safety specification	4.0 (approved 25 June 2020)	Not applicable.
Part II - Module SIII Clinical trial exposure	4.0 (approved 25 June 2020)	Not applicable.
Part II - Module SIV Populations not studied in clinical trials	4.0 (approved 25 June 2020)	Not applicable.
Part II - Module SV Post-authorisation experience	4.0 (approved 25 June 2020)	Not applicable.
Part II - Module SVI Additional EU requirements for the safety specification	4.0 (approved 25 June 2020)	Not applicable.
Part II - Module SVII Identified and potential risks	4.0 (approved 25 June 2020) 4.2 (approved 20 November 2019)	Important potential risk of 'Medication errors' was removed from the list of safety concerns in line with the PSUSA recommendation (EMEA/H/C/PSUSA/00002330/202402).
Part II - Module SVIII Summary of the safety concerns	4.0 (approved 25 June 2020) 4.2 (approved 20 November 2019)	Safety concerns aligned with recommendation from PSUSA (EMEA/H/C/PSUSA/00002330/202402).
Part III Pharmacovigilance plan (including post-authorisation safety studies)	4.0 (approved 25 June 2020)	Not applicable.
Part IV	4.0 (approved 25 June 2020)	Not applicable.

Plans for post-authorisation efficacy studies		
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	4.0 (approved 25 June 2020)	Not applicable.
Part VI Summary of the risk management plan	4.0 (approved 25 June 2020) 4.2 (approved 20 November 2019)	Safety concerns aligned with PSUSA recommendation (EMEA/H/C/PSUSA/00002330/202402). Update of administrative data.
Part VII Annexes	4.0 (approved 25 June 2020) 4.2 (approved 20 November 2019)	Annex 8 revised.

Details of the currently approved RMP		
Version number	4.0	4.2
Approved with procedure	EMEA/H/C/004109	SE/H/1490/001-003/DC; DE/H/5019/001-003/DC DE/H/4360/001/DC, DE/H/4509/001-003/DC
Date of approval (opinion date)	25 June 2020	20 November 2019

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CP	Centralized procedure
CTD	Common Technical Document
DCP	Decentralized procedure
e.g.	example given
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary Of Product Characteristics

Part I: Product(s) Overview

Table 2: Product(s) Overview

Active substance(s) (INN or common name)	**Pemetrexed**
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, antimetabolites, folic acid analogues (L01BA04)
Marketing Authorisation Holder/Applicant	[EMEA/H/C/004109] Actavis Group PTC ehf. Dalshraun 1, Hafnarfjoerdur 220 Iceland [DE/H/5019/001-003/DC;DE/H/4360/001/DC] TEVA B.V. Swensweg 5 2031GA Haarlem The Netherlands
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	[EMEA/H/C/004109] Armisarte 25 mg/ml concentrate for solution for infusion [DE/H/5019/001-003/DC] [pemetrexed] 100 mg, 500 mg, 1000 mg powder for concentrate for solution for infusion [DE/H/4360/001/DC] [pemetrexed] 25 mg/ml concentrate for solution for infusion
Marketing authorisation procedure	Centralised Decentralised
Brief description of the product	**Chemical class**: Folic acid analogue
	Summary of mode of action: Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.
	Important information about its composition:

	Not applicable.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indication(s) in the EEA	**Current**: Malignant pleural mesothelioma: Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma. Non-small cell lung cancer: Pemetrexed in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. Pemetrexed is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	**Current**: The recommended dose of pemetrexed when in combination with cisplatin and as a monotherapy is 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current**: 25 mg/ml concentrate for solution for infusion 100 mg, 500 mg, 1000 mg powder for concentrate for solution for infusion
	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)

Not applicable.

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

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The safety concerns in the initial Pemetrexed EU RMPs (approved via CP and DCP procedures: v1.2 approved on 05 February 2016, and v3.1 approved on 15 March 2016), prepared in line with GVP Module V Rev. 1 requirements, were defined as follows:

Table 3: Safety Concerns in Pemetrexed EU RMP v4.0

List of important risks and missing information	
Important identified risks	• Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities • Bone marrow suppression • Renal disorders • Gastrointestinal disorders • Interstitial pneumonitis • Radiation pneumonitis • Radiation recall • Sepsis • Bullous skin reaction including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)
Important potential risks	• None
Missing information	• None

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Reasons for the removal of the Important Potential Risk in the List of Safety Concerns in RMP v5.0

Important potential risk of 'Medication errors' was included in previously approved Pemetrexed EU RMPs (v4.0 (EMEA/H/C/004109) and v4.2 (SE/H/1490/001-003/DC; DE/H/5019/001-003/DC DE/H/4360/001/DC, DE/H/4509/001-003/DC)) following recommendation from PSUSA procedure for pemetrexed (EMEA/H/C/PSUSA/00002330/201802).

Following recommendation from latest PSUSA procedure for pemetrexed (EMEA/H/C/PSUSA/00002330/202402), important potential risk of 'Medication errors' is removed from the summary of safety concerns in RMP v5.0.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 4: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Specific adverse reaction follow-up questionnaires:

Not applicable.

Other forms of routine pharmacovigilance activities:

Not applicable.

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

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

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

V.1 Routine Risk Minimisation Measures

Not applicable.

V.2 Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of Risk Minimisation Measures

Not applicable.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Armisarte 25 mg/ml concentrate for solution for infusion

This is a summary of the risk management plan (RMP) for Armisarte 25 mg/ml concentrate for solution for infusion (hereinafter referred to as Pemetrexed). The RMP details important risks of Pemetrexed, how these risks can be minimised, and how more information will be obtained about Pemetrexed's risks and uncertainties (missing information).

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

This summary of the RMP for Pemetrexed 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 Pemetrexed's RMP.

I. The Medicine and What It is used for

Pemetrexed is authorised for the treatment of malignant pleural mesothelioma in combination with cisplatin and in the treatment of non-small cell lung cancer in combination with cisplatin and as monotherapy in the maintenance treatment and second line treatment in patients with non-small cell lung cancer (see SmPC for the full indication). It contains pemetrexed as the active substance and it is given intravenously.

Further information about the evaluation of Pemetrexed’s benefits can be found in Pemetrexed’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/armisarte-previously-pemetrexed-actavis.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Pemetrexed, together with measures to minimise such risks and the proposed studies for learning more about Pemetrexed'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 Pemetrexed are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Pemetrexed. 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).

Table 5: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

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 Pemetrexed.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Pemetrexed.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for PEMETREXED 25 mg/ml concentrate for solution for infusion and PEMETREXED 100 mg, 500 mg, and 1000 mg powder for concentrate for solution for infusion

This is a summary of the risk management plan (RMP) for PEMETREXED 25 mg/ml concentrate for solution for infusion and PEMETREXED 100 mg, 500 mg, and 1000 mg powder for concentrate for solution for infusion (hereinafter referred to as Pemetrexed). The RMP details important risks of Pemetrexed, how these risks can be minimised, and how more information will be obtained about Pemetrexed's risks and uncertainties (missing information).

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

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

I. The Medicine and What It is used for

Pemetrexed is authorised for the treatment of malignant pleural mesothelioma in combination with cisplatin and in the treatment of non-small cell lung cancer in combination with cisplatin and as monotherapy in the maintenance treatment and second line treatment in patients with non-small cell lung cancer (see SmPC for the full indication). It contains pemetrexed as the active substance and it is given intravenously.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Pemetrexed, together with measures to minimise such risks and the proposed studies for learning more about Pemetrexed'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 Pemetrexed are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Pemetrexed. 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).

Table 6: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

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 Pemetrexed.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Pemetrexed.

Part VII: ANNEXES

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Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.