[redacted]

1.8.2 Risk Management Plan

[redacted]

(lorazepam)

0.5 mg, tablets

1.0 mg, tablets

2.5 mg, tablets

[redacted]

March 2022

EU Risk Management Plan for [redacted] 0.5 mg, 1.0 mg, 2.5 mg, tablets

RMP version to be assessed as part of this application:	
RMP Version number:	0.2
Data lock point for this RMP:	25.02.2022
Date of final sign off:	03.03.2022
QPPV name:	[redacted]
QPPV signature:	

Table of content

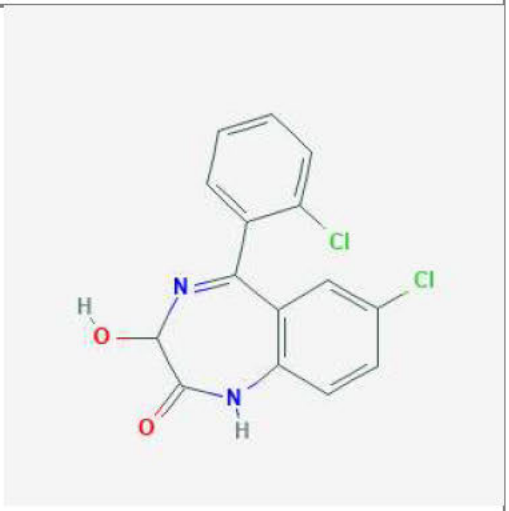
Abbrevation

API	Active Pharmaceutical Ingredient
CHMP	The Committee for Medicinal Products for Human Use
CMDh	The Coordination Group for Mutual Recognition and Decentralised Procedures - Human
EEA	European Economic Area
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
GVP	Guideline on good pharmacovigilance practices
MAH	Marketing Authorisation Holder
NCA	National Competent Authorities
PASS	Post-marketing Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
RMP	Risk Management Plan
QPPV	Qualified Person for Pharmacovigilance
SmPC	Summary of Product Characteristics

[redacted] 0.5 mg, 1 mg, 2.5 mg tablets

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	*Lorazepam*
Pharmacotherapeutic group(s) (ATC Code)	anxiolytic, benzodiazepine (tranquilliser) (ATC Code: N05BA06)
Marketing Authorisation Holder	Tarchomińskie Zakłady Farmaceutyczne "Polfa" Spółka Akcyjna ul. A. Fleminga 2 03-176 Warszawa
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	[redacted]
Marketing authorisation procedure	Decentralised
Brief description of the product	Chemical class *Chemical name:* 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-1,4-benzodiazepin-2-one *Molecular formula:* $C_{15}H_{10}Cl_2N_2O_2$ *Structural formula:* *Molecular weight:* 321.2 g/mol *CAS:* 846-49-1 [PubChem Substance: Lorazepam 2021] 
	Summary of mode of action Lorazepam is a psychotropic substance in the class of the 1,4-benzodiazepines with tension, agitation and anxiety-depressant properties, as well as sedative and hypnotic effects. Furthermore, lorazepam acts to reduce muscle tone and is an anticonvulsant. Lorazepam exhibits a very high receptor affinity to specific binding sites in the central nervous system. These benzodiazepine receptors are in close functional association with the receptors of the inhibitory

[redacted] 0.5 mg, 1 mg, 2.5 mg tablets

	neurotransmitter, gamma-aminobutyric acid (GABA). After binding to the benzodiazepine receptor, lorazepam enhances the inhibitory effects of GABAergic transmission [Tavor 0.5 mg, 1.0 mg, 2.0 mg, 2.5 mg SmPC Pfizer Pharma 2019].
	Important information about its composition (e.g. origin of active substance for biologicals, relevant adjuvants or residues for vaccines) Active substance is chemically synthesized and provided by qualified active pharmaceutical ingredients (APIs) manufacturers. The quality of active substance is assured by specification presented in module 3.2.S.4.1 of Module 3. The finished drug product is manufactured by good manufacturing practice (GMP)-certified plants.
Hyperlink to the Product Information	[redacted] [redacted]
Indication(s) in the EEA	Current (if applicable): • Symptomatic short-term treatment of anxiety, tension and agitation, sleep disorders caused by these conditions • Premedication prior to diagnostic interventions, and before and after surgery
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): Treatment of anxiety, tension and agitation, as well as sleep disorders caused by these conditions The daily dose is generally 0.5 to 2.5 mg lorazepam, divided into 2 to 3 single doses or as a one-off dose in the evening. The daily dose can be increased to a maximum of 7.5 mg, taking into consideration all warnings and precautions, especially in a hospital setting. The daily dose (0.5 to 2.5 mg lorazepam) can be taken as a single administration about half an hour before going to bed if the focus is on sleep disorders that require treatment. Premedication prior to diagnostic interventions, as well as before and after surgery 1 to 2.5 mg lorazepam the evening before and/or 2 to 4 mg about 1 to 2 hours before the intervention. Postoperative, 1 to 2.5 mg at suitable intervals.
	Proposed (if applicable): Not applicable
	Current (if applicable):

[redacted]0.5 mg, 1 mg, 2.5 mg tablets

Pharmaceutical form(s) and strengths	*Pharmaceutical form*: tablets *Strength*: 0.5 mg, 1.0 mg, 2.5 mg
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

[redacted] 0.5 mg, 1 mg, 2.5 mg tablets

Part II: Safety specification

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

According to Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

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

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

Part II: Module SIII - Clinical trial exposure

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

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

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

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.

Part II: Module SV - Post-authorisation experience

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

SV.1 Post-authorisation exposure

Not applicable.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

Part II: Module SVII - Identified and potential risks

In line with algorithm harmonisation RMP domain for active substances for which there is no innovator or the innovator has no RMP, only those safety concerns should be listed that either:
1. have ongoing additional pharmacovigilance activity, or
2. have ongoing additional risk minimisation measure, or
3. have essential targeted questionnaires in place.

None of the above points are present, so all other safety concerns can be removed.

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

Not applicable.

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

Not applicable.

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

Not applicable.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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

Risks associated with [redacted] use are considered well-characterized and routine pharmacovigilance activities are considered sufficient.

III.2 Additional pharmacovigilance activities

None are planned.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable, efficacy of the concerned medicinal product in the proposed indication currently do not require further investigation.

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.

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.

[redacted] 0.5 mg, 1 mg, 2.5 mg tablets

Part VI: Summary of the risk management plan

Summary of risk management plan for [redacted] (Lorazepam)

This is a summary of the risk management plan (RMP) for [redacted]. The RMP details important risks of [redacted], how these risks can be minimised, and how more information will be obtained about [redacted] risks and uncertainties (missing information).

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

Important new concerns or changes to the current ones will be included in updates of [redacted] RMP.

I. The medicine and what it is used for

[redacted] is authorised for the treatment of:

- Symptomatic short-term treatment of anxiety, tension and agitation, sleep disorders caused by these conditions
- Premedication prior to diagnostic interventions, and before and after surgery

It contains lorazepam as the active substance and it is administered orally.

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

Important risks of [redacted] together with measures to minimise such risks and the proposed studies for learning more about [redacted] 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*.

[redacted] 0.5 mg, 1 mg, 2.5 mg tablets

II.A List of important risks and missing information

Important risks of medicinal product 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 medicinal product. 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).

Summary of safety concerns	
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 [redacted]

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

There are no studies required for [redacted]

[redacted] 0.5 mg, 1 mg, 2.5 mg tablets

Part VII: Annexes

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 (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

1. List of safety concerns per approved Risk Management Plan (RMP) of active substances per product (Doc. Ref: CMDh/330/2015, Rev. 30, 02.2021).
2. PubChem Substance: Lorazepam. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/lorazepam (last accessed 21.02.2021)
3. Tavor 0.5mg, 1.0 mg, 2.0 mg, 2.5 mg SmPC Pfizer Pharma 2019

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