PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Pregabalin

This is a summary of the RMP for pregabalin. The RMP details important risks of pregabalin, how these risks can be minimised, and how more information will be obtained about pregabalin's risks and uncertainties (missing information).

Pregabalin's SmPC and its PL give essential information to healthcare professionals and patients on how pregabalin should be used.

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

I. The Medicine and What It Is Used For

In the EU, pregabalin is authorised for the treatment of Neuropathic Pain, Epilepsy, and Generalised Anxiety Disorder and (see SmPC for the full indication). It contains pregabalin as the active substance and it is given by orally.

Further information about the evaluation of pregabalin's benefits can be found in pregabalin's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage.

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

Important risks of pregabalin, together with measures to minimise such risks and the proposed studies for learning more about pregabalin'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 public (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 events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of pregabalin is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of pregabalin 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 pregabalin. 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).

As requested by PRAC in the final assessment report adopted with recommendation on 11 September 2014, the MAH has changed abuse, misuse and dependence from a potential risk to an identified risk in the pregabalin RMP (version 11.3, dated 18 February 2015).

Based on the pregabalin PRAC PSUR Assessment Report (EMEA/H/C/PSUSA/00002511/201701), the MAH has renamed the important identified risk Abuse, Misuse, and Drug dependence to "Abuse and Drug dependence" and removed the important risk "misuse" from both the RMP and PSUR. The Preferred Term (PT) "Misuse" refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information but still for therapeutic purposes. An example for misuse could be that a patient deliberately took the medication once daily instead of spreading the daily dose over the day. The MAH agrees with the PRAC statement (Pregabalin PSUR Single Assessment procedure (EMEA/H/C/PSUSA/00002511/201701) that the majority of cases of the risk "abuse, misuse and dependence" concerned misuse and lumping these reports together is not informative in further characterising the cases of abuse. Moreover, in line with the PSUR Single Assessment procedure (EMEA/H/C/PSUSA/00002511/201701), the MAH has revised the Targeted Questionnaire to focus on abuse and has removed questions relating to misuse. In the RMP, since there is no specific safety issue related to misuse that requires regulatory action, the deletion of misuse from the list of safety concerns (as proposed by the MAH in the ongoing type II variation to update the RMP (EMEA/H/C/WS1364) was agreed by the PRAC in the Rapporteur's preliminary assessment report for procedure no. PSUSA/00002511/201801, dated 4 July 2018). Consistently, the MAH proposes not to re-include "misuse" in the important identified risk of "abuse and dependence" and to accordingly update the search criteria (i.e. removing Misuse PTs: Intentional product use issue, and Intentional product misuse) also in the RMP. Please see PART II.SVII.2.1.1.

Table 1. List of Important Risks and Missing Information

Important identified risks	Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury
	Discontinuation Events
	Drug interactions (lorazepam, ethanol, and CNS depressants)
	Euphoria
	Congestive Heart Failure
	Vision-related events
	Abuse and Drug Dependence[a]
Important potential risks	Suicidality
	Off-label use in paediatric patients
Missing information	Pregnancy and lactating women

a. Abuse and Drug Dependence is an identified risk in the EU only.

II.B. Summary of Important Risks

Table 2. Summary of Important Identified and Potential Risks

Important Identified Risk: Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall), especially in the elderly population.
Risk minimisation measures	<u>Routine risk communication</u> SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions SmPC Section 4.7 Effects on ability to drive and use machines SmPC Section 4.8 Undesirable effects. <u>Other routine risk minimisation measures beyond the Product Information:</u> None.
Important Identified Risk: Discontinuation Events	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	Patients using pregabalin.

Table 2. Summary of Important Identified and Potential Risks

Risk minimisation measures	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects. Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Drug interactions (lorazepam, ethanol, and CNS depressants)	
Evidence for linking the risk to the medicine	Post-marketing data.
Risk factors and risk groups	Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, PK interactions. Accordingly, in in-vivo studies, no clinically relevant PK interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone, or ethanol. Population PK analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine, and topiramate had no clinically significant effect on pregabalin clearance. Drug interactions with CNS depressants are identified safety concerns with pregabalin that emerged in clinical development and in the postmarketing experience. These AEs are monitored and reviewed in the PSUR under the heading "Drug interactions (lorazepam, ethanol, and CNS depressants)".
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 (Interaction with other medicinal products and other forms of interactions). Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Euphoria	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	Known drug abusers.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 (Undesirable Effects) Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Congestive Heart Failure	

Table 2. Summary of Important Identified and Potential Risks

Evidence for linking the risk to the medicine	Non-clinical and clinical data, and cumulative review, and postmarketing database.
Risk factors and risk groups	Patients with diabetes.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, (special warnings and precautions for use) SmPC section 4.8 (undesirable effects). Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Vision-related Events	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 (Special warnings and Precautions) SmPC section 4.8, (Undesirable Effects) SmPC section 5.1(Pharmacodynamic properties). Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Abuse and Drug Dependence	
Evidence for linking the risk to the medicine	Postmarketing safety database.
Risk factors and risk groups	Patients with a history of substance abuse.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, (Special warnings and Precautions). Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk: Suicidality	
Evidence for linking the risk to the medicine	Clinical data, cumulative reviews, postmarketing safety database.

Table 2. Summary of Important Identified and Potential Risks

Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 (Special warnings and Precautions). Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk: Off Label Use in paediatric patients	
Evidence for linking the risk to the medicine	Postmarketing safety database.
Risk factors and risk groups	No specific group within the paediatric population.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.1 (Therapeutic indications) SmPC section 4.2 (Posology and method of administration). SmPC Section 5.1 Pharmacodynamic properties. Other routine risk minimisation measures beyond the Product Information: None.

Table 3. Summary of Missing Information

Missing Information: Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 (Fertility, pregnancy, and lactation). SmPC Section 5.2 Pharmacokinetic properties. Other routine risk minimisation measures beyond the Product Information: None.

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 pregabalin.

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

Table 4. Required Additional Pharmacovigilance Activities (Category 3)

Study Name / Status	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
Category 3 - Required additional pharmacovigilance activities					
Pregabalin Ophthalmological Safety Study (A0081096) Ongoing	Study A0081096: A Prospective Randomised 12-Week Controlled Study of Visual Field Change in Subjects with Partial Seizures Receiving Pregabalin or Placebo.	Vision-related events emerged as an identified risk in clinical development and in the postmarketing period. To increase understanding of potential underlying mechanism(s) leading to the occurrence of vision related events.	Prospective Randomised Double Blind Placebo Controlled	Male and Females Ages 18 to 65 Years of Age	Final Report: 29 July 2020 (planned)[a]
Pregabalin Pregnancy Outcomes Study (A0081359)	Study A0081359: A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes.	The study objectives are to describe the use of pregabalin exposure in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations and neurodevelop mental outcomes with the use of pregabalin.	Population based cohort study based on routinely collected data from four Nordic countries: Denmark, Finland, Norway, and Sweden.	Study population for the main analysis will include pregnancies ending in live or still birth in Denmark, Finland, Norway, and Sweden	Final Report: November 2019 (planned)

a. This study is a post-marketing commitment to the US FDA.