

## 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 [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Scientific\\_Discussion/human/000546/WC500046600.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000546/WC500046600.pdf).

### 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).

**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 <sup>a</sup>
Important potential risks	Suicidality
	Off-label use in paediatric patients
Missing information	None.

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**

<b>Important Identified Risk: Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury</b>	
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.

**Table 2. Summary of Important Identified and Potential Risks**

<p>Risk minimisation measures</p>	<p><u>Routine risk communication</u></p> <p>SmPC Section 4.4 Special warnings and precautions for use</p> <p>SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions</p> <p>SmPC Section 4.7 Effects on ability to drive and use machines</p> <p>SmPC Section 4.8 Undesirable effects.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>
<p><b>Important Identified Risk: Discontinuation Events</b></p>	
<p>Evidence for linking the risk to the medicine</p>	<p>Clinical trials, literature articles, and post-marketing data.</p>
<p>Risk factors and risk groups</p>	<p>Patients using pregabalin.</p>
<p>Risk minimisation measures</p>	<p><u>Routine risk communication</u></p> <p>SmPC Section 4.4 Special warnings and precautions for use</p> <p>SmPC Section 4.8 Undesirable effects.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>
<p><b>Important Identified Risk: Drug interactions (lorazepam, ethanol, and CNS depressants)</b></p>	
<p>Evidence for linking the risk to the medicine</p>	<p>Post-marketing data.</p>
<p>Risk factors and risk groups</p>	<p>Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (&lt;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.</p> <p>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.</p> <p>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)”.</p>

**Table 2. Summary of Important Identified and Potential Risks**

Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.5 (Interaction with other medicinal products and other forms of interactions).</p> <p>SmPC Section 4.4 (Special warnings and precautions for use)</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>
<b>Important Identified Risk: Euphoria</b>	
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	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.8 (Undesirable Effects)</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>
<b>Important Identified Risk: Congestive Heart Failure</b>	
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	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Sections 4.4 (special warnings and precautions for use)</p> <p>SmPC section 4.8 (undesirable effects).</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>
<b>Important Identified Risk: Vision-related Events</b>	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	None identified.

**Table 2. Summary of Important Identified and Potential Risks**

Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.4 (Special warnings and Precautions)</p> <p>SmPC section 4.8, (Undesirable Effects)</p> <p>SmPC section 5.1 (Pharmacodynamic properties).</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>None.</p>
<b>Important Identified Risk: Abuse and Drug Dependence</b>	
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	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.4 (Special warnings and Precautions).</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>None.</p>
<b>Important Potential Risk: Suicidality</b>	
Evidence for linking the risk to the medicine	Clinical data, cumulative reviews, postmarketing safety database.
Risk factors and risk groups	None identified.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.4 (Special warnings and Precautions).</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>None.</p>
<b>Important Potential Risk: Off Label Use in paediatric patients</b>	
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	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Sections 4.1 (Therapeutic indications)</p> <p>SmPC section 4.2 (Posology and method of administration).</p> <p>SmPC Section 5.1 Pharmacodynamic properties.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>None.</p>

## 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 3. Required Additional Pharmacovigilance Activities (Category 3)**

Study Name / Status	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
<b>Category 3 - Required additional pharmacovigilance activities</b>					
Pregabalin Evaluating the Abuse Potential of Lyrica When Taken Orally Concomitantly with Oxycodone Hydrochloride in Healthy Non-drug Dependent, Recreational Opioid Users (A0081365)  Ongoing	Study A0081365: A Phase 4, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Single-Dose, Six-Way Crossover Study	To determine the abuse potential of orally administered pregabalin taken concomitantly with oxycodone HCl in non-dependent, recreational opioid users under a fasted condition.  To evaluate additional pharmacodynamic (PD) effect and PK of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a fasted condition.  To evaluate safety of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a fasted condition	Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Single-Dose, Six-Way Crossover Study	Male and Females Ages 18 to 65 Years of Age	Final Report: August 2022 (planned)