VI.2 Elements for a public summary

For sake of completeness, with reference to article 11 of the Directive 2001/83, the applicant retains the option to carve out the patented indication in the national marketing authorisations, if carving is necessary to avoid infringement of national patents in certain countries. Carving out will not have any negative impact on risk assessment.

VI.2.1 Overview of disease epidemiology

Epilepsy

Epilepsy is among the most common of diseases that affect the nervous system in the human body. The number of newly diagnosed cases of epilepsy is estimated to be approximately 50 cases per 100,000 persons per year.

The proportion of the population affected by epilepsy is lowest for persons aged 65 years or older and highest for those aged 15 to 64 years, and males are slightly more likely to develop epilepsy than females.

Despite generally good outcome, epilepsy itself can be life threatening secondary to seizures (acute, prolonged etc.) it also carries an increase mortality independent of this. This increased risk was most notable among patients such as those with acute symptoms of epilepsy.

Neuropathic Pain

Neuropathic pain results, most notably, from dysfunction involving the nerve endings. Common causes include diabetes, acquired immune deficiency syndrome (AIDS), and cancer. Neuropathic pain is a complex diagnosis to make and quantify the extent of pain involved. Pain measurement procedures are difficult to obtain.

Data from the UK yielded the following estimates per 100,000 person years: 40 for pain after herpes infection, 27 for face pain after nerve damage, 1 for limb pain after amputation, and 15 for pain after nerve damage from diabetes.

Patients with nerve pain identified within UK family medical practices were more likely to be female, no longer married, living in council rented accommodations, unable to work, report no educational qualifications, and be smokers relative to respondents without nerve pain.

Death rates estimates regarding neuropathic pain are specific to the underlying disorder. In the case of diabetes, AIDS and cancer, death rates estimates are known to be considerably higher than in the general population.

Generalized Anxiety Disorder
While generalized anxiety had been described as early as 1894 , the diagnostic term generalized anxiety disorder (GAD) has currently been refined to include »excessive anxiety and worry about more than 1 life circumstances« in which a person finds it »difficult to control the worry«.

A study conducted in Norway found the combined estimate for panic and generalized anxiety disorder was 1.10 per 1,000 person-years.

Regardless of geography, women are approximately twice as likely to report GAD when compared with men. There also appears to be more cases of GAD among older people up until the age of 60, when estimates decline. The rates of anxiety disorders as a whole, decline with increasing income and education.

Persons with GAD report a high degree of professional help seeking, substantial medication use for GAD symptoms, and interference in their daily activities.

VI.2.2 Summary of treatment benefits
Pregabalin is currently approved by originator in the European Union (EU) for the treatment of nerve pain in adults, epilepsy, and generalized anxiety disorder in adults.

Epilepsy
Pregabalin has been compared with placebo for epilepsy by originator. There were three studies involving over 1,000 patients. The main measure of effectiveness was the change in the number of seizures after 11 to 12 weeks. Results showed that pregabalin reduced the number of seizures: about 45% of the patients taking 600 mg pregabalin a day and about 35% of those taking 300 mg pregabalin a day had a reduction in seizures of 50% or more. This compared with about 10% of the patients taking placebo.

Neuropatic pain
Pregabalin has been compared with placebo for peripheral nerve pain by originator. There were ten studies involving over 3,000 patients, about half of whom had diabetic neuropathy and half of whom had pain following shingles. A further study was carried out in 137 patients with central neuropathic pain due to a spinal cord injury. The studies lasted up to 12 weeks. The effectiveness of pregabalin was measured using a standard pain questionnaire.
Results showed that pregabalin was more effective than placebo in decreasing pain. 35% of patients with peripheral neuropathic pain treated with pregabalin had a decrease in pain scores of 50% or more, compared with 18% of the patients with peripheral neuropathic pain treated

with placebo. In another study, 22% of patients with central neuropathic pain treated with pregabalin had a decrease in pain scores of 50% or more, compared with 8% of the patients with central neuropathic pain treated with placebo.

Generalised Anxiety Disorder
Pregabalin has been compared with placebo for generalised anxiety disorder by originator. There were eight studies involving over 3,000 patients. Effectiveness was measured using a standard anxiety questionnaire after four to eight weeks. Results showed that pregabalin was more effective than placebo: 52% of the patients taking pregabalin had an improvement of 50% or more, compared with 38% of the patients taking placebo.

VI.2.3 Unknowns relating to treatment benefits
The safety and efficacy of pregabalin in children before the age of 12 years and in adolescents (12-17 years of age) have not been established. No data are available.

VI.2.4 Summary of safety concerns
Important identified risks

Risk	What is known	Preventability
Weight gain	Some patients gain weight while treated with pregabalin.	Some patients with diabetes who gain weight while taking pregabalin may need an alteration in their diabetic medicines.
Swelling of the body including extremities	Some patients develop swelling of the body including extremities.	Patients should inform their doctor if they develop swelling of their body.
Dizziness, sleepiness, loss of consciousness, fainting, and potential for accidental injury	Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in older people. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment.	Patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product. Patients should not drive, operate complex machinery or engage in other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.
Events after pregabalin discontinuation	After stopping short-term and long-term pregabalin treatment, patients may experience certain side effects. These include trouble sleeping, headache, nausea, feeling anxious, diarrhoea, flu-like syndrome, convulsions, nervousness, depression, pain, sweating, and dizziness, suggestive of physical dependence. Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.	Patients should not stop taking pregabalin unless their doctor tells them to do so. If treatment is stopped it should be done gradually over a minimum of 1 week.

Interactions with other medicines	Pregabalin and certain other medicines may influence each other (interaction). When taken with certain other medicines, pregabalin may potentiate the side effects seen with these medicines, including respiratory failure and coma. The degree of dizziness, sleepiness and decreased concentration may be increased if pregabalin is taken together with medicinal products containing: oxycodone – (used as a pain-killer), lorazepam – (used for treating anxiety), or alcohol.	Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.
Euphoria	Some patients treated with pregabalin has experienced elevated mood.	Before taking pregabalin, patients should tell their doctor if they have a history of alcoholism or drug dependence. Patients should not take more medicine than prescribed.
Hypersensitivity reactions and allergic reactions	Some patients taking pregabalin have reported symptoms suggesting an allergic reaction. These symptoms include swelling of the face, lips, tongue, and throat, as well as diffuse skin rash.	Should patients experience any of these reactions, they should contact their physician immediately.
Congestive heart failure	There have been reports of heart failure in some patients when taking pregabalin; these patients were mostly older with cardiovascular conditions.	Before taking this medicine patients should tell their doctor if they have a history of heart disease.
Vision-related events	Pregabalin may cause blurring or loss of vision, or other changes in eyesight, many of which are temporary.	Patients should immediately tell their doctor if they experience any changes in vision.

Abuse, misuse and drug dependence	Reports of abuse, misuse and drug dependence have been received from patients. This has not been observed during clinical studies performed by originator.	Before taking pregabalin patients should tell their doctor it they have a history of alcoholism or any drug abuse or dependence. Patients should not take more medicine than prescribed.

Important potential risks

Risk	What is known
Thoughts of harming or killing themselves	A small number of people being treated with anti-epileptics, including pregabalin, have shown a slightly increased risk of suicidal behaviour or ideation. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin. If at any time patients have these thoughts, they should immediately contact their doctor.
Cancer of the blood vessels	Cancer of the blood vessels has been observed in mice. This has not been observed in rat and humans. This is mouse specific and there is no evidence of an associated risk to humans.
Use in children	Pregabalin is not approved in patients less than 18 years of age.

Missing information

Risk	What is known
Pregnancy and breast-feeding	Pregabalin should not be taken during pregnancy, unless patients are told otherwise by your doctor. Effective contraception must be used by women of child-bearing potential. If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, patients should ask their doctor or pharmacist for advice before taking pregabalin. It is not recommended to breast-feed while using pregabalin as it is not known if pregabalin may be found in breast milk. Patients should ask their doctor or pharmacist for advice before taking any medicine while breast-feeding.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan
Not applicable. No postauthorisation studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time
Not applicable, this is the first Risk management plan.

Part VII- Annexes

Annex 1 – EudraVigilance Interface
Not applicable.

Annex 2 - SmPC & Package Leaflet
Please see attachment.

Annex 3 - Worldwide marketing authorisation by country (including EEA)
Not applicable yet.

Annex 4 - Synopsis of on-going and completed clinical trial programme
Not applicable.

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme
Not applicable.

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP part III
Not applicable.

Annex 7 - Specific adverse event follow-up forms
Not applicable.

Annex 8 - Protocols for proposed and on-going studies in RMP part IV
Not applicable.

Annex 9 - Newly available study reports for RMP parts III & IV
Not applicable.

Annex 10 - Details of proposed additional risk minimisation measures (if applicable)
Not applicable.