VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Epilepsy

Epilepsy is a long-term condition affecting the brain and is characterised by recurring seizures (or fits). It is one of the most common of diseases of the nervous system and every year about 50 new cases are diagnosed per 100,000 people in the population. For most patients there is no identifiable cause, though the condition can be caused by injury or damage to the brain as happens, for example, following strokes or in patients with brain tumours.

Generalised anxiety disorder

Generalised anxiety disorder is long-term anxiety or nervousness about everyday matters. The cause of generalised anxiety disorder is not clear although it is believed to be related to both genetic factors and life experiences. The number of people affected by this condition varies between different counties and cultures. Regardless of geography, however, women are more likely to be affected than men. There also appear to be more cases of generalised anxiety disorder among older people up until the age of 60, when the number of cases begins to decline. A study conducted in Norway found the combined estimate of the number of new cases of panic and generalised anxiety disorder to be 1.10 per 100,000 people per year.

VI.2.2 Summary of treatment benefits

In epilepsy, the benefits of pregabalin were evaluated in 3 studies involving over 1,000 patients that looked at how much the medicine reduced the number of seizures patients had after 11 to 12 weeks. 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. Pregabalin was more effective than placebo in generalised anxiety disorder: in 8 studies involving over 3,000 patients, 52% of the patients taking pregabalin had an improvement of 50% or more in their anxiety measured with a standard anxiety questionnaire, compared with 38% of the patients taking placebo.[1]

VI.2.3 Unknowns relating to treatment benefits

The efficacy of pregabalin has been studied in patients aged 18 years and older. However, there is not available information yet related with children and adolescents aged 12 to 17 years.

VI.2.4 Summary of safety concerns

Important identified risks of pregabalin:

Risk	What is known	Preventability
Weight gain	Weight gain is a common side effect of pregabalin.	Some patients with diabetes who gain weight while taking pregabalin may need to alter their diabetes treatment.
Soft-tissue swelling due to the accumulation of interstitial fluid (Peripheral oedema and oedema-related events)	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. Allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain) are rare adverse events. Swelling of the body including extremities are common adverse events.	Patients should inform their doctor if they develop swelling.
Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury mental impairment	Pregabalin has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in elderly patients. Dizziness, drowsiness and headache are very common.	Patients should be advised to exercise caution until they are familiar with the potential effects of the medicine. Patients should not drive, operate complex machinery or engage in other potentially hazardous activities until they know whether the medicine affects their ability to perform these activities.

Risk	What is known	Preventability
Discontinuation events	After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness. The patient should be informed about this at the start of the treatment. Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin. 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. If treatment is to be stopped, it should be done gradually over a minimum of 1 week.
Drug interactions (lorazepam, ethanol and CNS depressants)	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)* *Alcohol*	Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

Risk	What is known	Preventability
Euphoria	Feeling of elation is considered a common adverse effect related to pregabalin.	Before taking pregabalin, patients should tell their doctor if they have a history of alcoholism or drug dependence. Patients should let their doctor know if they think they need more of the medicine than has been prescribed for them.
Hypersensitivity 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. Allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain) are rare adverse effects.	Patients should avoid to take this medicine in case they are allergic to pregabalin or any of the other ingredients of this medicine. Should patients experience any of these reactions, they should contact their physician immediately.

Risk	What is known	Preventability
Inability of the heart to adequately meet the needs of organs and tissues for oxygen and nutrients (Congestive heart failure)	There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.	Before taking this medicine patients should tell their doctor if they have a history of heart disease.
Vision-related events	In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies	Patients should immediately tell their doctor if they experience any changes in vision.
Abuse, misuse and drug dependence	Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).	Reports of abuse, misuse and drug dependence have been received from patients. This has not been observed during clinical studies. However, before taking pregabalin patients should tell their doctor if they have a history of alcoholism or any drug abuse or dependence. The patient should not take more medicine than prescribed.

Important potential risks:

Risk	What is known
Suicidality	A small number of people being treated with anti-epileptics such as pregabalin have had thoughts of harming or killing themselves. If at any time patient have these thoughts, he/she should immediately contact his/her doctor.
Soft tissue tumor (Haemangiosarcoma)	Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.
Off-label use in paediatric patients	The safety and efficacy in children and adolescents (under 18 years of age) has not been established and therefore, pregabalin should not be used in this age group.

Missing information:

Risk	What is known
Pregnancy and Breast-feeding	Pregnancy and breast-feeding pregabalin should not be taken during pregnancy, unless you are told otherwise by your doctor. Effective contraception must be used by women of child-bearing potential. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

VI.2.5 Summary of additional 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.

The Summary of Product Characteristics and the Package leaflet for Pregabalin Medical Valley can be found on the web pages of the national competent authorities in the EU.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Neither planned studies nor studies imposed by the Committee for Medicinal Products for Human Use (CHMP)/National Competent Authorities (NCA) are foreseen for the aforementioned product. Therefore, there is no need to perform with post-authorisation efficacy studies (PAES) or post-authorisation safety studies (PASS).

List of studies in post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.1	May 2015	Identified Risks Potential Risks Missing information	The safety concerns should be updated according to the reference product (Lyrica)