VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Epilepsy
Epilepsy is one of the most common chronic diseases that there are: 0.5% of all human beings suffer from epilepsy, which means that in the U.K. alone around 300,000 to 600,000 people are affected. When someone repeatedly has epileptic seizures then that person is suffering from epilepsy. An epileptic seizure itself is one of the many pathological forms of reaction which can take place in the brain; it is the brain's "response" or reaction to a disturbing, irritating or damaging stimulus. This reaction to the stimulus is accompanied by abnormal electro-chemical excitatory processes in the cerebral nerve cells. If epileptic patients have mental abnormalities, e.g. mental retardation, behavioral or speech disorders, these are not usually caused by the epilepsy but by the brain disorder which itself is the cause of the epilepsy.

Neuropathic pain
Neuropathic pain is a chronic pain resulting from injury to the nervous system and it differs from other more common types of pain. The injury can be to the central nervous system (brain and spinal cord) or the peripheral nervous system (nerves outside the brain and spinal cord). Neuropathic pain can occur after trauma and many diseases such as multiple sclerosis and stroke. It is common and affects more than 2 million people in the US alone. This type of pain is notoriously difficult to treat.

Generalized anxiety disorder
Generalized anxiety disorder (GAD) is a severe, ongoing anxiety that interferes with day-to-day activities. It's possible to develop GAD as a child or as an adult. GAD has similar symptoms as panic disorder, obsessive-compulsive disorder and other types of anxiety, but they're all different conditions. Living with GAD can be a long-term challenge. In many cases, it occurs along with other anxiety or mood disorders. GAD affects about 3.1% American adults age 18 years and older (about 18%) in a given year, causing them to be filled with fearfulness and uncertainty. The average age of onset is 31 years old. GAD affects about 6.8 million American adults, including twice as many women as men. The disorder develops gradually and can begin at any point in the life cycle, although the years of highest risk are between childhood and middle age.

VI.2.2 Summary of treatment benefits

Pregabalin belongs to a group of medicines used to treat Epilepsy, Neuropathic pain and Generalised Anxiety Disorder (GAD) in adults.

Peripheral and central neuropathic pain
Pregabalin benefits have been evaluated for up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period. In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo (a dummy treatment) had a 50% improvement in pain score. In the

controlled clinical trial in central neuropathic pain 22% of the pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

Epilepsy
In epilepsy pregabalin benefits have been studied in 3 controlled clinical trials involving over 1,000 patients. A reduction in seizure frequency was observed by Week 1.
As a monotherapy (newly diagnosed patients) pregabalin has been studied in 1 controlled clinical trial of 56 week duration with twice a day dosing.

Generalised Anxiety Disorder
Pregabalin has been studied in 6 controlled trials. Relief of the symptoms of GAD was observed by Week 1. 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. No data are available.

For control of epilepsy, pregabalin is normally used together with another antiepileptic agent. There are currently no data available suggesting that the other agents may be stopped and that treatment with pregabalin alone is possible.

There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity. Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

VI.2.4 Summary of safety concerns

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Weight increased *(Weight gain)*	In all clinical studies lasting up to 14 weeks, 9% of patients	In accordance with current clinical practice, some

	who were taking pregabalin gained weight, compared with 2% of patients taking a placebo (dummy treatment).	diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.
Hypersensitivity or allergy to pregabalin *(Hypersensitivity and allergic reactions)*	Hypersensitivity and allergic reactions (which may include swollen face, swollen tongue, difficulty breathing, itchiness, inflammation of the eyes (keratitis), vision loss and a serious skin reaction characterized by rash, blisters, peeling skin and pain) have been reported in the post-marketing experience.	Patients experience any of these reactions, should ask immediately for medical advice.
Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury *(Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury)*	Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Pregabalin may influence the ability to drive or use machines.	Patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.
Problems with the eyes *(Vision-related events)*	Pregabalin may cause blurring or loss of vision, or other changes of visual acuity many of which are transient.	Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.
Events after pregabalin discontinuation *(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. Data suggest that the incidence and severity of withdrawal symptoms may be dose-related.	The patients should be informed about the aforementioned adverse reactions at the start of the treatment. Pregabalin should not be stopped unless the treating physician tells so. Discontinuation of pregabalin should be done gradually over a minimum of 1 week.

When the heart fails to maintain an adequate circulation of blood around the body owing to a defect in the heart's pumping action *(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.	Before taking this medicine patients should tell their physician if they have a history of heart disease. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.
Elevated mood *(Euphoria)*	Elevated mood is an uncommon psychiatric disorder and some patients may experience this adverse reaction during pregabalin treatment.	Before taking pregabalin, patients should tell their doctor if they have a history of alcoholism or drug dependence. Euphoria has been reported during the first 10–15 minutes of alcohol consumption.
Taking other medicines along with pregabalin (e.g. lorazepam, ethanol and CNS depressants) *(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) and alcohol.	Patients should always tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines especially oxycodone, lorazepam and alcohol use.
Swelling of tissues, usually in the lower limbs, due to the accumulation of fluids (*Peripheral oedema and oedema-related events)*	Pregabalin treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of	Patients should inform their doctor if they develop swelling. The prescriber should exercise caution when co-administering pregabalin and thiazolidinedione antidiabetic agents.

	deterioration in renal or hepatic function. Higher frequencies of weight gain and peripheral edema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone.	
Malpractice, misusage and drug addiction *(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. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea, consistent with physical dependence. In the post-marketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.	As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g., development of tolerance, dose escalation, and drug-seeking behavior). Before taking pregabalin patients should tell their doctor if they have a history of alcoholism or any drug abuse or dependence.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
A rare, malignant tumor related to blood vessels (*Haemangiosarcoma*)	Cancer of the blood vessels has been observed in mice, but not in rats, monkeys or humans. This risk is mouse specific and there is no evidence of a similar risk in humans.
Thoughts of self-harming or suicide (*Suicidality*)	Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients

	(and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Pregabalin use in unapproved populations (*Off-label use in paediatric patients*)	The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. No data are available; therefore its use in this population should not be encouraged.

Missing information	
Risk	**What is known**
Use in pregnancy and lactation	There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pregabalin should not be used during pregnancy unless clearly necessary. Effective contraception must be used in women of child bearing potential. Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Withdrawal of concomitant antiepileptic medicinal products	For control of epilepsy, pregabalin is normally used together with another antiepileptic agent. There are currently no data available suggesting that the other agents may be stopped and that treatment with pregabalin alone is possible.

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 healthcare professionals with details on how to use the medicine, the risks and recommendations for 6uthorizat 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 authorization development plan

Not applicable