Pregabalin STADA 25 mg hard capsules
Pregabalin STADA 75 mg hard capsules
Pregabalin STADA 150 mg hard capsules
Pregabalin STADA 225 mg hard capsules
Pregabalin STADA 300 mg hard capsules

1.6.2015, V 1.3

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Pregabalin is a drug intended for the treatment of neuropathic pain, epilepsy and generalised anxiety disorder.

Epilepsy

Reference 1 - Kotsopoulos I, et al. Systematic Review and Meta-analysis of Incidence Studies of Epilepsy and Unprovoked Seizures. Epilepsia 2002; 43(11):1402-9.

Reference 2 - Bell G, Sander J. The epidemiology of epilepsy: the size of the problem. Seizure 2001; 10:306-16.

Reference 3 - Lhatoo S, et al. Mortality in epilepsy in the first 11 to 14 years after diagnosis: Multivariate analysis of long-term, prospective, population-based cohort. Ann Neurol 2001; 49:336-344.

Reference 4 - Rafnsson V, et al. Cause-specific mortality in adults with unprovoked seizures. A population-based incidence cohort study. Neuroepidemiology 2001; 20(4): 232-6.

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 (reference 1 and 2)

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 (reference 1)

Despite generally good outcome, epilepsy itself can be life threatening secondary to seizures (acute, prolonged etc.) It also carries an increased mortality independent of this (reference 2, 3 and 4). This increased risk was most notable among patients such as those with acute symptoms of epilepsy.

Neuropathic Pain

Reference 5 - Torrance N, et al. The epidemiology of chronic pain of predominantely neuropathic origin. Results from a general population survey. Journal of Pain 2006; 7(4): 281-9.

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 (reference 5)

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 the general population.

Generalized Anxiety Disorder

Reference 6 - Freud S. Collected Papers, Vol. 1. 1957, London, England: Hogarth Press.

Reference 7 - American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. 1987, Washington, DC: American Psychiatric Association.

Reference 8 - American Psychiatric Association, Diagnostic and Statistical Manual, Fourth Edition. 1994, Washington, DC: American Psychiatric Association.

Reference 9 - ESEMeD/MHEDEA 2000 Investigators. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand 2004; 109(Suppl. 420): 21-7

Reference 10 - Kessler R, et al. Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States, Results from the National Comorbidity Study. Arch Gen Psychiatry 1994;51:8-19.

Reference 11 - Wittchen H, et al. DSM-III-R Generalized Anxiety Disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:355-364.

Reference 12 - Kessler R, et al. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:593-602

While generalized anxiety had been described as early as 1894 (reference 6), 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" (reference 7 and 8)

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 (reference 9, 10 and 11)

There also appears to be more cases of GAD among older people up until the age of 60, when estimates decline (reference 12). The rates of anxiety disorders as a whole, decline with increasing income and education (reference 10).

Persons with GAD report a high degree of professional help seeking, substantial medication use for GAD symptoms, and interference in their daily activities (reference 11).

VI.2.2 Summary of treatment benefits

Pregabalin has been compared with placebo (a dummy treatment) in 22 studies.

In neuropathic pain, the benefits of Pregabalin were evaluated for up to 12 weeks using a standard pain questionnaire. In 10 studies involving over 3,000 patients with peripheral neuropathic pain (either diabetic pain or shingles), 35% of the patients treated with Pregabalin had a decrease in pain scores of 50% or more, compared with 18% of the patients treated with placebo. In a smaller study involving 137 patients with central neuropathic pain due to a spinal cord injury, 22% of patients treated with Pregabalin had a decrease in pain scores of 50% or more, compared with 8% of the patients treated with placebo.

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.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, pregabalin can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

However as stated in the proposed SmPC, long term safety and outcomes for fertility, pregnancy and lactation and use in the paediatric population has not yet been established.

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 diabetes medication.
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	Pregabalin treatment has been associated with dizziness and	Patients should be advised to exercise caution until they are

Risk	What is known	Preventability
Potential for Accidental Injury	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.	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 long- and short-term pregabalin treatment, patients may experience certain side effects. These include, trouble sleeping, headache, nausea, feeling anxious, diarrhoea, flu-like symptoms, convulsions, nervousness, depression, pain, sweating, and dizziness. It is not clear at this time whether these symptoms occur more commonly or severely if patients have been taking pregabalin for a longer period of time.	Patients should not stop taking pregabalin unless their doctor tells them to. If treatment is stopped it should be done gradually over a minimum of 1 week.
Interactions with other medications	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 let their doctor know if they think they need 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	Should patients experience any of these reactions, they should contact their physician immediately.

Risk	What is known	Preventability
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Congestive Heart Failure	There have been reports of heart failure in some patients when taking pregabalin; these patients were mostly elderly 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.	Before taking pregabalin patients should tell their doctor if they have a history of alcoholism or drug dependence. Patients should also let their doctor know if **they** think they need more medicine than prescribed.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Thoughts of harming or killing themselves	A small number of patients being treated with anti-epileptics, including pregabalin, have shown a slightly increased risk of suicidal behavior or ideation. The mechanism is unknown but a causal association with pregabalin has not been suggested. 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 rats, monkeys and humans. This is mouse specific and there is no evidence of an associated risk to humans.
Off-label use in paediatric patients	Pregabalin is not approved in patients less than 18 years of age as data about the efficacy and safety in this subgroup of patients is lacking.

Missing information

Risk	What is known
Pregnant and breastfeeding women(lactation)	Pregabalin should not be taken during pregnancy or when breast feeding, 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.

VI.2.5 Summary of additional risk minimisation measures by safety concern

No additional risk minimisation activities are required. Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

VI.2.6 Planned post authorisation development plan (if applicable)

There are no studies in the post authorisation development plan.

VI.2.7 Summary of changes to the risk management plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	**Date**	**Safety Concerns**	**Comment**
Version 1	Under Review	Important Identified Risk • Weight gain • Peripheral Oedema and Oedema –related events • Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental injury • Discontinuation Events • Drug interactions (lorazepam, ethanol, and CNS depressants) • Euphoria • Hypersensitivity and Allergic Reactions • Congestive heart failure • Vision-related events Important Potential Risks • Suicidality • Haemangiosarcoma • Abuse, Misuse, and Drug Dependence • Off-label use in paediatric patients Missing information • Use in pregnancy • Use in lactation	N/A
Version 1.1	Under Review	Important Identified Risks • Abuse, misuse and drug dependence updated to an important identified risk Important potential risks • Suicidality updated to suicidal ideation and	Updated in line with authority comments

Version	Date	Safety Concerns	Comment
		behaviour Missing information • 'Use in pregnancy' and 'use in lactation' updated to 'pregnant and lactating women'	
Version 1.2	Under Review	Not updated	Updated with day 160 PI
Version 1.3	Under Review	Not updated	Updated with day 200 PI