VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Epilepsy is caused by excessive electrical activity in the brain. Levetiracetam Krka film-coated tablets are an antiepileptic medicine. This is a medicine used to treat seizures in epilepsy.

Levetiracetam Krka is used to treat partial onset seizures with or without secondary generalisation. This is a type of epilepsy where too much electrical activity in one side of the brain causes symptoms such as sudden, jerky movements of one part of the body, distorted hearing, sense of smell or vision, numbness, or a sudden sense of fear. Secondary generalisation occurs when the overactivity later reaches the whole brain. Levetiracetam Krka can also be used to treat myoclonic seizures (short, shock-like jerks of a muscle or group of muscles), and primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in patients with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

Around 50 million people worldwide have epilepsy. Nearly 80% of the people with epilepsy are found in developing regions.

VI.2.2 Summary of treatment benefits

Levetiracetam Krka is used:

- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation.
- as an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age,
  - myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy,
  - primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Levetiracetam (by innovator) has been used on its own or as an add-on treatment. In all of these studies, the main measure of effectiveness was the change in the number of seizures before and during treatment.

Levetiracetam (by innovator) used on its own has been studied in 579 patients with partial-onset seizures aged 16 years and over, who received either levetiracetam or carbamazepine (another anti-epileptic medicine) for up to two years. The study measured how many patients remained free of seizures for six months once they had reached their effective dose. Levetiracetam (by innovator) was as effective as carbamazepine in keeping patients free of seizures when taken on its own for partial onset seizures. In both groups, 73% of the patients experienced no seizures for six months once on an adequate dose.

Levetiracetam (by innovator) has also been studied as an add-on treatment:

- in partial-onset seizures, it has been studied in three main studies in a total of 904 patients aged 16 years and over. In these studies, levetiracetam at doses of 1,000, 2,000 or 3,000 mg per day, was compared with placebo (a dummy treatment) over 12 to 14 weeks. All of the patients were taking at least one other anti-epileptic medicine. Levetiracetam has also been compared with placebo in 314 patients aged between one month and 17 years. Placebo treatment reduced the weekly number of seizures by 6 to 7%, while the reduction with levetiracetam at a dose of 1,000 mg per day was between 18 and 33%, depending on the study. With levetiracetam at a dose of 2,000 mg, the reduction was 27%, and with 3,000 mg, it was around 39%. Levetiracetam was also more effective than placebo in children.
- in myoclonic seizures, levetiracetam was studied in 122 patients aged 12 years and over, who received either levetiracetam or placebo in addition to their normal anti-epileptic medicine for up to 30 weeks. The number of seizure days per week was halved in 58% of the patients receiving levetiracetam and in 23% of the patients receiving placebo.
- in primary generalised tonic-clonic seizures, levetiracetam was compared with placebo in 164 patients aged four years or over. The patient's treatment was continued for 20 weeks once they were taking their full dose. The number of seizures fell by an average of 28% in the patients receiving placebo, compared with 57% in those receiving levetiracetam. However, there were too few patients aged below 12 years to support the use of levetiracetam for this type of seizure in this age group.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of Levetiracetam Krka in children and adolescents below 16 years as monotherapy treatment have not been established. There are no data available.

VI.2.4 Summary of safety concerns

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
A behaviour that departs from the norm and harms the affected individual (Abnormal behaviour)	A small number of people being treated with anti-epileptics such as Levetiracetam Krka have had thoughts of harming or killing themselves. The mechanism of this risk is not known. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years abnormal behaviour was reported more frequently than in other age ranges or in the overall safety profile. A paediatric safety study has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. Results related to behavioral and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behavior as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioral and emotional functioning; in particular measures of aggressive behavior were not worse than baseline.
The pathologic disorders in which the constituents of the blood are abnormal or are present in abnormal quantity (Blood dyscrasias)	Decreased number of blood platelets and decreased number of white blood cells are uncommon ADRs. Decreased number of neutrophils (neutrophils are type of white blood cells) and decreased number of all blood cell types are rare ADRs.
Increase in frequency and severity of seizures (Seizure worsening)	Levetiracetam Krka is indicated in the treatment of seizures (convulsions) with newly diagnosed epilepsy. However, convulsions are common adverse drug reaction of levetiracetam.

Important missing information:

Risk	What is known
Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children	Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.
Limited data are available on safety of levetiracetam in infants younger than 12 months with different epilepsy syndromes	The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.

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 this product can be found at the national agency's EPAR page.

This medicine has no additional risk minimisation measures.

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

Not applicable. No postauthorisation studies are planned.

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

From version 1.1 to version 1.2 there were no major changes to the Risk Management Plan.