Part VI: Summary of the risk management plan

Summary of risk management plan for Kevesy solution for infusion (Levetiracetam)

This is a summary of the risk management plan (RMP) for Kevesy solution for infusion. The RMP details important risks of Kevesy solution for infusion, how these risks can be minimised, and how more information will be obtained about Kevesy solution for infusion 's risks and uncertainties (missing information).

Kevesy solution for infusion 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kevesy solution for infusion should be used.

I. The medicine and what it is used for

Kevesy solution for infusion is authorised in patients from 16 years of age with newly diagnosed epilepsy, to treat partial-onset seizures (fits) with or without secondary generalisation (see SmPC for the full indication).

It can also be used as an add-on to other anti-epileptic medicines to treat:

- partial-onset seizures with or without generalisation in patients from one month of age;
- myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in patients from 12 years of age with juvenile myoclonic epilepsy;
- primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in patients from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause)

It contains levetiracetam as the active substance and it is given by intravenous route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kevesy solution for infusion, together with measures to minimise such risks and the proposed studies for learning more about Kevesy solution for infusion, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Kevesy solution for infusion is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kevesy solution for infusion are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kevesy solution for infusion. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 5: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Blood dyscrasias, with cytopenias Suicidal behavior, including suicide attempt, suicidal ideation, psychotic disorder, and completed suicide Severe cutaneous adverse reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiform Abnormal behavior including restlessness, aggression, agitation, irritability and insomnia DRESS syndrome Renal failure Encephalopathy Rhabdomyolysis Hypersensitivity (including angioedema and anaphylaxis) Interaction with methotrexate
Important potential risks	Seizure worsening including convulsion, epilepsy and complex partial seizure Electrolyte disturbance Haemorrhage in association with levetiracetam
Missing information	Long term effects on intelligence, growth, endocrine function, puberty and childbearing potential in children

II.B Summary of important risks

Table 6: Summary of important risks

Important Identified Risk: Blood dyscrasias, with cytopenias	
Evidence for linking the risk to the medicine	The risk of blood dyscrasias related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Not identified
Risk minimisation measures	Routine risk communication: • SmPC sections 4.4 and 4.8 • Package leaflet section 4 Additional risk minimisation measures: none

Important Identified Risk: Suicidal behavior, including suicide attempt, suicidal ideation, psychotic disorder, and completed suicide	
Evidence for linking the risk to the medicine	The risk of suicidal behavior related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Increased risk for behavioural and psychiatric adverse reactions in the paediatric patient population.
Risk minimisation measures	Routine risk communication: • SmPC sections 4.4 and 4.8 • Package leaflet sections 2; 4 Additional risk minimisation measures: none

Important Identified Risk: Severe cutaneous adverse reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiform	
Evidence for linking the risk to the medicine	The risk of severe cutaneous adverse reactions related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Not known
Risk minimisation measures	Routine risk communication: • SmPC section 4.8 • Package leaflet section 4 Additional risk minimisation measures: none

Important Identified Risk: Abnormal behavior including restlessness, aggression, agitation, irritability and insomnia	
Evidence for linking the risk to the medicine	The risk of abnormal behavior reactions related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Paediatric patient population
Risk minimisation measures	Routine risk communication: • SmPC section 4.8 • Package leaflet section 4 Additional risk minimisation measures: none

Important Identified Risk: DRESS syndrome	
Evidence for linking the risk to the medicine	The risk of DRESS syndrome related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	None known
Risk minimisation measures	Routine risk communication: • SmPC section 4.8 • Package leaflet section 4 Additional risk minimisation measures: none

Important Identified Risk: Renal failure	
Evidence for linking the risk to the medicine	The risk of renal failure related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Not available
Risk minimisation measures	Routine risk communication: • SmPC section 4.4 and 4.8 • Package leaflet sections 2; 4 Additional risk minimisation measures: none

Important Identified Risk: Encephalopathy	
Evidence for linking the risk to the medicine	The risk of encephalopathy related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Not identified
Risk minimisation measures	Routine risk communication: • SmPC section 4.8 • Package leaflet section 4 Additional risk minimisation measures: none

Important Identified Risk: Rhabdomyolysis	
Evidence for linking the risk to the medicine	The risk of rhabdomyolysis related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Not identified
Risk minimisation measures	Routine risk communication: • SmPC section 4.8 • Package leaflet section 4 Additional risk minimisation measures: none

Important Identified Risk: Hypersensitivity (including angioedema and anaphylaxis)	
Evidence for linking the risk to the medicine	The risk of hypersensitivity related to levetiracetam is well-known and described in the literature.
Risk factors and risk groups	Not identified
Risk minimisation measures	Routine risk communication: • SmPC sections 4.3 and 4.8 • Package leaflet sections 2; 4 Additional risk minimisation measures: none

Important Identified Risk: Interaction with methotrexate	
Evidence for linking the risk to the medicine	Coadministration of levetiracetam and Methotrexate may result in delayed elimination of Methotrexate, increasing the likelihood of toxicity
Risk factors and risk groups	Not identified
Risk minimisation measures	Routine risk communication: SmPC section 4.5 Additional risk minimisation measures: none

Important potential risk: Seizure worsening including convulsion, epilepsy and complex partial seizure	
Evidence for linking the risk to the medicine	Seizure worsening could potentially be experienced by all epileptic patients. It has been suggested that worsening of seizures after withdrawal of anticonvulsivants may reflect loss of efficacy rather than an abstinence phenomenon. However risk of seizure worsening is known for levetiracetam, and is therefore described in the product information.
Risk factors and risk groups	Sudden withdrawal of the treatment
Risk minimisation measures	Routine risk communication: SmPC section 4.8 Additional risk minimisation measures: none

Important potential risk: Electrolyte disturbance	
Evidence for linking the risk to the medicine	Current evidence of hypomagnesaemia and hypokalaemia in association with levetiracetam is considered weak. However, as hyponatraemia has already been demonstrated for levetiracetam, and that levetiracetam may impact on renal function, it is considered that "Hypokalaemia and hypomagnesaemia" should be kept under close monitoring in the context of a new safety Signal for levetiracetam.
Risk factors and risk groups	Unidentified
Risk minimisation measures	Routine risk communication: None Other routine risk minimisation measures beyond the Product Information: potential risk subject to close monitoring Additional risk minimisation measures: none

Important potential risk: Haemorrhage in association with levetiracetam	
Evidence for linking the risk to the medicine	Seizure worsening could potentially be experienced by all epileptic patients. It has been suggested that worsening of seizures after withdrawal of anticonvulsivants may reflect loss of efficacy rather than an abstinence phenomenon. However risk of seizure worsening is known for levetiracetam, and is therefore described in the product information.
Risk factors and risk groups	Patients treated with anticoagulant drugs and anti-platelet drugs
Risk minimisation measures	Routine risk communication: None Other routine risk minimisation measures beyond the Product Information: potential risk subject to close monitoring Additional risk minimisation measures: none

Missing information: Long term effects on intelligence, growth, endocrine function and childbearing potential in children	
Risk minimisation measures	Routine risk communication: SmPC section 4.4

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Kevesy solution for infusion.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Kevesy solution for infusion.