VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Tyrosinaemia is an inborn error of metabolism, in which the body is unable to break down the amino acid (building blocks of proteins in our body) tyrosine. There are three types of tyrosinaemia, each with distinctive symptoms and caused by the deficiency of a different enzyme (a protein that can trigger a chemical reaction in the body). Patients with tyrosinaemia type 1 are born with a defective gene coding for an enzyme called 4-hydroxyphenylpyruvate oxidase. Normally this enzyme breaks down tyrosine. In this disease, the body is unable to completely break down the amino acid tyrosine, forming harmful substances. These substances are accumulated in the body with the result of damage to the liver and kidneys. Untreated, tyrosinaemia type 1 is chronically debilitating and life threatening.

Birth incidence is 1/100,000 in most areas but is more common is some regions, notably in Québec, Canada [**Orphanet**].

Tyrosinemia I is an autosomal recessive disorder, therefore, the sex distribution is equal, with a 25% risk of recurrence within a family. Even the severity of onset and the subsequent course does not differ between the sexes.

VI.2.2 Summary of Treatment Benefits

Nitisinone is used for treatment of the rare disease called hereditary tyrosinemia type 1 in adults, adolescents and children (in any age range) by blocking the breakdown of tyrosine and the harmful substances are not formed.

A special diet must be followed while taking this medicine, because tyrosine will remain in the body. This special diet is based on low tyrosine and phenylalanine (another amino acid) content.

When compared to data for historical controls, it can be seen that treatment with nitisinone together with dietary restriction results in a higher survival probability in all HT-1 phenotypes [van Spronsen et al (1994)]. The probability of survival seems to have improved, especially in patients who began the treatment before the age of 6 months; in this population, higher mortality is seen if dietary restrictions are the only measure introduced. Treatment with nitisinone was also found to result in reduced risk for the development of hepatocellular carcinoma (2.3 to 3.7-fold) compared to historical data on treatment with dietary restriction alone. It was found that the early initiation of treatment resulted in a further reduced risk for the development of hepatocellular carcinoma (13.5-fold when initiated prior to the age of 12 months). Moreover, the treatment seems to effectively prevent renal complications (renal tubular disease) and acute neurological events (polyneuritis, pseudo-Guillain-Barré syndrome, dystonic pain crises) often observed in these patients. The costs of all forms of health care resource utilization for type 1 hereditary tyrosinaemia (HT-1) resulted to be reduced with the introduction of nitisinone: survival have been improved, liver transplants were almost eliminated, and morbidity was reduced, particularly when nitisinone was initiated in the first weeks after birth, thus preventing early damage to the liver and kidneys.

VI.2.3 Unknowns Relating to Treatment Benefits

No relevant unknowns related to treatment benefits were identified.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What Is Known	Preventability
Increased tyrosine levels	Hypertyrosinaemia is a direct adverse effect of nitisinone therapy. Elevated tyrosine levels have been associated with toxicity to eyes, skin, and the nervous system.	Hypertyrosinaemia is preventable by monitoring for early symptoms. Nitisinone treatment should be initiated and supervised by a physician experienced in the treatment of HT-1 patients. It should be established that the patient is adhering to his/her dietary regimen and the plasma tyrosine concentration and other biochemical parameters should be measured and, if the case, a more restricted tyrosine and phenylalanine diet should be implemented.
Hypertyrosinemia related eye disorders	Eye disorders and corneal opacities are a potential consequence of NTBC treatment for HHT-I. The lesions probably result from elevated serum and ocular tyrosine levels due to inhibition of the tyrosine catabolic pathway and poor dietary compliance.	Eye disorders are preventable by monitoring for early symptoms. It is recommended that a slit-lamp examination of the eyes is performed before initiation of nitisinone treatment. An ophthalmologist should immediately examine a patient, of who is displaying visual disorders during nitisinone treatment.
Leukopenia/Granulocytopenia	Leucopenia, and granulocytopenia have been reported with niisinone treatment. Granulocytopenia was not associated with infections.	Leukopenia/ Granulocytopenia are both preventable by monitoring for early symptoms. It is recommended that the patient's WBC count be regularly monitored.

Important Potential Risks

Risk	What is Known (Including Reason Why It Is Considered a Potential risk)
Lack of efficacy	As the dose of nitisinone should be adjusted individually, it may result in a too low dose and the consequent lack of efficacy may result in deterioration of the patient's clinical condition caused by original metabolic defect.
Development and cognitive disorders	Recent concerns about cognitive performance have also been raised in patients on nitisinone. During nitisinone treatment, tyrosine concentrations increase even without liver failure, leading to the hypothesis that high tyrosine concentrations may be associated with impaired neurocognitive functioning. High tyrosine concentrations could have a direct toxic effect on the brain.
Embryo-fetal toxicity	There are no adequate data from the use of nitisinone in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Nitisinone should not be used during pregnancy unless the clinical condition of the woman requires treatment with nitisinone.
Exposure to nitisinone during breast-feeding	It is unknown whether nitisinone is excreted in human breast milk. Animal studies have shown adverse postnatal effects via exposure of nitisinone in milk. Therefore, mothers receiving nitisinone must not breast-feed, since a risk to the suckling child cannot be excluded.

Missing information

Risk	What is Known
Interactions with substances known to induce or inhibit CYP3A4	No formal interaction studies with other medicinal products have been conducted. Nitisinone is metabolised *in vitro* by CYP 3A4 and dose-adjustment may therefore be needed when nitisinone is co-administered with inhibitors or inducers of this enzyme.
Use in elderly	There are no specific dose recommendations for elderly but more information are necessary reflecting the greater frequency of concomitant diseases or other drug therapy in this patient population.
Use in pregnant women	There are no adequate data from the use of nitisinone in pregnant women. Studies in animals have shown

	reproductive toxicity. The potential risk for humans is unknown. Nitisinone should not be used during pregnancy unless the clinical condition of the woman requires treatment with nitisinone.

VI.2.5 Summary of Risk Minimization 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 minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.
Nitisinone is subjected to restricted medical prescription. Therefore, nitisinone treatment should be initiated and supervised by a physician experienced in the treatment of HT-1 patients.

This medicine has no additional risk minimization measures.

VI.2.6 Planned Post-Authorization Development Plan

No post-authorisation studies are planned and therefore this section is not applicable.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Not applicable, since this is the first RMP of nitisinone.