VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Apotel 10mg/ml Solution for Infusion is indicated for adults, adolescents and children weighing more than 33 kg in the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

Paracetamol is a well know active substance with established efficacy and tolerability. Paracetamol is a para-aminophenol derivative with analgesic and antipyretic properties and weak anti-inflammatory activity. The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions1.Paracetamol provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours. Paracetamol reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

VI.2.2 Summary of treatment benefits

Not Applicable.

VI.2.3 Unknowns relating to treatment benefits

None identified.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hepatobiliary disorders (cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers);	There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism.	The medicine is contraindicated in patients who suffer from a severe liver disease. Patient will inform their HCP if they suffer from a liver or kidney disease, from alcohol abuse, or cases of nutrition problems (malnutrition) or dehydration. The medicine will be prescribed and administered by a HCP.

Risk	What is known	Preventability
Abnormal liver function (cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers),	There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism.	The medicine is contraindicated in patients who suffer from a severe liver disease. Patient will inform their HCP if they suffer from a liver or kidney disease, from alcohol abuse, or cases of nutrition problems (malnutrition) or dehydration. The medicine will be prescribed and administered by a HCP.
Drug interaction with enzyme inducers	There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of patients receiving enzyme inducers.	Caution is advised during the concomitant treatment with enzyme inducers. The medicine will be prescribed and administered by a HCP.
Drug interaction with anticoagulants	Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.	Closer check-ups of the effect of the anticoagulant might be necessary. The medicine will be prescribed and administered by a HCP.
Medication errors (overdose due to confusion between mL and mg in neonates, and overdose in underweight adult patients).	Cases of accidental overdose have been reported during treatment with intravenous paracetamol 10mg/ml solution for infusion. In most cases, this occurred in infants and neonates due to confusion between the prescription of paracetamol solution for infusion being issued in mg and then administered in ml; in more of these cases, a 10-fold overdose was reported.	Warnings and precautions in section 4.2 and 4.4 of the SmPC, relevant warnings and precautions in PIL. Prescription only medicine 100ml bag is restricted to adults, adolescents and children weighing more than 33 kg. Medicine will be administered by a HCP. Education materials for HCPs

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
N/A	

Missing information

Risk	What is known
Neonates and premature neonates, pregnant and lactating women	Pregnancy Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus / newborn infant. Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk. Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects. Nevertheless, Apotel 10mg/ml Solution for Infusion should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed. Breastfeeding: After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Apotel 10mg/ml Solution for Infusion may be used in breast-feeding women. The 100 ml bag is restricted to adults, adolescents and children weighing more than 33 kg.

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 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 Apotel10mg/ml Solution for Infusion can be found in the Netherland's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in Netherland's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Overdose in underweight patients (≤50kgs)

Professional education material
Objective and rationale Healthcare professionals need to understand the risk of overdose during treatment with intravenous paracetamol 10 mg/mL solution for infusion in patients weighing less than 50 kg. For these patients, the prescribed dose must be based on the patient's weight, taking into account individual risk factors for hepatotoxicity which includes: "hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione) and dehydration".
Summary description of main additional risk minimisation measures Development of educational material for healthcare professional, such as a poster and a dosing guide strip (increments starts from 33kg to 50kg and correspondences between mg and ml). Active surveillance of cases of overdose.

Safety concern in lay terms (medical term)

Not Applicable.

VI.2.6 Planned post authorisation development plan

There are no studies in the post authorisation development plan.

Studies which are a condition of the marketing authorisation

Not Applicable.

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

Not applicable for the initial RMP.