VI.2. Elements for a Public Summary

VI.2.1. Overview of disease epidemiology

Paracetamol is used in all age groups. The indication of this analgesic is short-term treatment of moderate pain and fever. Paracetamol is the most commonly used drug for the treatment of mild to moderate pain in children. As with adults, the primary area for concern is that of overdosage. In children even moderate overdose can have serious or even fatal sequelae. On the basis of the kinetic data, adjustment of the paracetamol dosage for the elderly is generally not necessary. Precautions relating to renal or hepatic insufficiency may be appropriate in elderly patients. Specific geriatric problems that would limit the usefulness of paracetamol in the elderly have not been demonstrated by the studies performed.

VI.2.2. Summary of treatment benefits

Paracetamol by the oral route may be considered the drug of choice when a mild pain reliever is indicated. Indications include the treatment of mild and moderate pain arising from headache, musculoskeletal conditions, toothache and mild menstrual cycle related pains [US-monograph 2008, Martindale 2008]. The use of direct in vein paracetamol is however confined to use for short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever, when there is an urgent need to treat pain or hyperthermia and/or when other routes of administration such as oral are not possible [Boghossian 2007].

The i.v. formulation of paracetamol will potentially reduce dose-related side effects that occur when using certain agents, such as the adverse effects of high opiate doses (e.g. nausea, vomiting). The i.v. formulation is also a useful choice for patients who have a prolonged nil-by-mouth status, for those who are unable to receive other pain killers or for those in whom opiate doses should be kept to a minimum [Boghossian 2007].

Intravenous paracetamol has been shown to offer increased dosing accuracy, and avoid absorption from the stomach and effect variability particularly in children for whom unfortunately, the drug effect knowledge of pain killer agents remains neglected and is usually extrapolated from adult counterparts [Anderson & Palmer 2006].

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VI.2.3. Unknowns relating to treatment benefits

Given the long-term experience with paracetamol plenty of data regarding its treatment benefits are available today. However, clinical experience of the i.v. administration of paracetamol in pregnant / lactating women as well as in preterm neonates is limited. This is therefore included as missing information in this RMP.

VI.2.4. Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Overdose / Error while administering the drug (due to confusion between ml and mg in neonates, and overdose in underweight adults)	A national health service (NHS) evaluation on accidental i.v. overdose in children within the time period from November 2004 to 31 December 2009 was performed [NHS, 2010]. The search produced a total of 439 incidents. A sample of 250 incidents was manually reviewed of which 177 appeared directly related to unintentional overdose in children (age distribution was as followed: up to 1 year (13%), 2-4 years (12%), 5-11 years (33%), 12-17 years (28%), 18 years (1%)). In 79% of the cases no harm occurred, in 12% low harm was caused, 8% were affected with moderate harm and in 1% severe harm occurred. The main errors were prescribing errors (31%), administration or infusion errors (25%), incidents in which the patients received i.v. as well as the oral dose (21%), wrong frequency (13%) and incidents with an oral dose administered *via* i.v. (10%). A World Health Organisation (WHO) request on i.v. overdose of paracetamol from July 2011 resulted in 27 cases in all countries with no age restriction [WHO 2011]. Following acute overdose with paracetamol there is a serious risk of hepatotoxicity.	• making physicians and nurses aware of the risk of overdose and confusion between ml and mg • providing educational material with detailed dosing information to facilitate dosing of paracetamol based on the patient's weight • providing the new paediatric container (10 ml ampoule) restricted to term newborn infants, infants and toddlers weighing up to 10 kg.

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Hepatobiliary Disorders and Abnormal Liver Function	In cases of paracetamol overdose there is a risk of liver injury including hepatitis, and liver failure particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving drugs classified as 'enzyme inducers'. Over-dosing may be fatal in these cases. Increased levels of hepatic function tests are observed together with decreased prothrombin levels that may appear 12 to 48 hours after paracetamol overdose [Bray 1992].	The risk of hepatobiliary disorders and abnormal liver function can be mitigated by monitoring for early symptoms.
Drug Interaction with substance that prevent clotting of blood and with substances that can induce hepatic enzyme activity	Concomitant use of paracetamol with agents reducing blood coagulation has been reported to increase anticoagulation effect leading to haemorrhage. Data on severity, seriousness and outcomes of risk are not systematically available. However, such events are potentially serious, depending upon the extent and location of the haemorrhage. Concomitant intake of drugs that induce hepatic enzyme activity can lead to increased metabolism of paracetamol to the reactive metabolite resulting in increased liver toxicity of paracetamol.	Yes, by avoiding concomitant treatment with anticoagulants or enzyme inducing drugs.
Important potential risks		
None	-	-
Missing information		
Limited information on the use in neonates and pre-mature neonates	No safety and efficacy data are available for premature newborn infants.	
Use in Pregnancy and lactation	Clinical experience of the i.v. administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects in pregnancy or on the health of the foetus / newborn infant. Prospective data on pregnancies exposed to overdoses did not show any increase in the risk of malformation.	

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	No reproductive studies with the i.v. form of paracetamol have been performed in animals. However, studies with the oral route did not show any malformation or foetotoxic effects. Nevertheless, Paracetamol B. Braun 10 mg/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. After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported.

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

The additional risk minimisation activities are for following risk:

Overdose / Error while administering the drug (due to confusion between ml and mg in newborns, and overdose in underweight adults)
Risk minimisation measure(s): **1) Direct Healthcare Professional Communication** **2) Posters dedicated to the nurses' offices** **3) Dose calculator**
Objective and rationale
• To draw the attention of HCPs to the risk of accidental overdose particular in children • To inform the HCPs of the risk of confusion between mg and ml • To give detailed instructions on the dosing of Paracetamol B. Braun 10 mg/ml solution for infusion in particular in children • To highlight that the dose depends only on the patients weight • To highlight that the volume to be administered may be very small • Facilitation and acceleration of proper dose calculation

VI.2.6. Planned post authorisation development plan

Not applicable. No additional post-authorisation development plan is proposed.

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

1. Major changes to the Risk Management Plan over time			
Version	**Date**	**Safety Concerns**	**Comment**
4	31-Aug-2014		Previous safety concerns stay unchanged. The RMP was updated to incorporate the information regarding the new formulation and the consequent new compatible mixing solution.
3 (version number mentioned in this RMP itself, page 1, was 2.1)	15-Oct-2013	• Overdose / Medication error (due to confusion between ml and mg in neonates, and overdose in underweight adults) • Hepatobiliary disorders • Abnormal liver function • Drug interaction with anticoagulants • Drug interaction with Enzyme inducers	No new safety concern was identified, however the RMP was updated to incorporate the information about development of new pack size (10 ml ampoules) mentioned as a part of risk minimisation activity in previous RMP, and to update the format in-line with new template proposed by Good pharmacovigilance practices (GVP) module V.
2 (former version number 2.0)	20-Dec-2012	• Overdose / Medication error (due to confusion between ml and mg in neonates, and overdose in underweight adults) • Hepatobiliary disorders • Abnormal liver function • Drug interaction with anticoagulants • Drug interaction with Enzyme inducers	