VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pain is defined as an unpleasant feeling and emotional experience arising from actual or potential tissue damage or described in terms of such damage. Pain is a highly personal experience which can only be precisely described by the individual who is experiencing it.
If left untreated, pain can result in various negative physiologic and psychological sequelae to patients.
Pain is a common reason for patients to seek healthcare and be admitted to hospitals, and its severity is reported as moderate to severe by almost half of patients in the emergency department.
Persistent post-surgery pain is clearly a major cause of chronic pain and hence an important public health problem.
It is important to properly evaluate pain and optimize safe pain management for all patients.

Fever is a higher-than-normal body temperature (it exceeds 38). It usually occurs in response to an infection as with the flu virus or inflammation that occurs with tissue injury or disease.
Fever is a very common complaint and one of the most frequent causes of attendance at emergency departments worldwide.
Fever is seen as a strong alarm symptom in children, by parents and healthcare providers, and is a leading reason for medical consultation.
Fever can underline disorders from mild conditions to the most serious of bacterial and viral illnesses. If patients are not diagnosed and treated properly, fever can cause morbidity or mortality.
The epidemiology of fever differs per region and changes over time. Frequent epidemiological updates from different parts of the world are required for an adequate care management.

VI.2.2 Summary of treatment benefits

Paracetamol is a widely used and effective treatment for pain and fever in adults and children.

The mechanism of the analgesic and antipyretic effects of paracetamol is not well established. It may involve central and peripheral actions.

PARACETAMOL PANPHARMA 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 PANPHARMA reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

PARACETAMOL PANPHARMA is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever when intravenous administration is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

IMPORTANT IDENTIFIED RISKS

Risk	**What is known**	**Preventability**
PIL: Reactions at the injection site (SPC: Injection site reactions)	Pain or burning sensation at the injection site have been reported. Some cases may result from a high infusion rate. However, most of the cases have not been resolved following a decrease in infusion rate.	In some cases, respect of an administration rate of 15-minute may prevent the risk.
PIL: Medication errors (overdose) due to confusion between ml and mg in neonates, and overdose in underweight adult patients (SPC: Medication errors (overdose) due to confusion between ml and mg in neonates, and overdose in underweight adult patients)	The presentation used for paediatric population is the plastic bags at 500 mg/50 ml, which contains 10 mg of paracetamol per ml, like the product competitor. However the prescription is made per kg in this group category and the administration is based on ml of volume that the nurses have to extract from the plastic bag. So a conversion has to be performed before the administration and this is the point where confusions between mg of prescription and ml of administration occurred, leading to 10 times of concentration of paracetamol administrated to babies. Many cases of overdose occurred in underweight adult patients	Adherence to the educational materials developed for the health care professionals (HCP) such as: - a dosing guide which specifies the dosage and the volume to be administered depending on the patient's weight. - a letter was sent to health care professionals in order to better explain how to avoid medication errors. The use of Paracetamol Panpharma is well explained by a dosing table based on patient weight available in the proposed public information (PIL). A new presentation specific for full-term newborn infants and infants weighing less than 10 kg has been developed.

Risk	What is known	Preventability
	inadvertently treated with the maximale recommended dose (4 grams a day), and in the paediatric population resulting in the administration of a 10 times higher dose than the prescribed dose.	Caution should be exercided with underweight adult patients by adapting the dosage. The patient should also inform his doctor if symptoms like nausea, vomiting, pallor, abdominal pain and liver damage occurs because of the risk of irreversible liver damage in case of overdosage.
Gaz bubble in vascular system with glass vials (Air embolism with glass vials)	A small amount of air may gets into the blood circulation, which is stopped at the lungs and very rarely produces symptoms. Death may occur if a large bubble of gas becomes lodged in the heart.	As for all solutions for infusion presented in glass vials, a close monitoring is needed. This monitoring at the end of the perfusion applies particularly for central route infusion, in order to avoid air embolism.
PIL: Hepatobiliary disorders, abnormal liver function ((SPC: Hepatobiliary disorders, abnormal liver function	Paracetamol toxicity is caused by excessive use or overdose of paracetamol. Doses higher than those recommended entail the risk of very serious liver damage. Many patients with paracetamol toxicity may have no symptoms at all in the first 24 hours following overdose. Others may initially have nonspecific complaints such as vague abdominal pain and nausea or vomiting. Clinical symptoms and signs of liver damage are usually seen after two days and reach their maximum usually after 4 to 6 days. Progressive disease and signs of liver failure may develop; these include low blood sugar, low blood pH, easy bleeding, and hepatic encephalopathy (a liver disease causing confusion, tremor, decreased level of consciousness including coma), liver failure. Some signs will spontaneously resolve, although untreated cases may result in death. Risk factors for paracetamol toxicity include excessive chronic alcohol intake, fasting or anorexia nervosa, and the use of certain	To avoid the risk of overdose. It is recommended to check that other medicines administered do not contain paracetamol or propacetamol. The patient should inform health care professionals in case of concomitant medicine use (e.g. antiepileptics drugs, medicine used to reduce the amount of acid that stomach produces, medicines used to treat HIV-AIDS, medecines used to treat tuberculosis, medecines used to thin blood, etc.). Patients must be instructed to carefully read the labels of medications that may contain paracetamol in combination formulations. It is advised to use with caution Paracetamol Panpharma if the patient suffers from liver or severe kidney disease, chronic alcohol abuse or in case of nutrition problems and dehydratation.

Risk	What is known	Preventability
	drugs. The antidote N-acetylcysteine acts by helping the body to regenerate enough and so to prevent liver damage. A liver transplant is often required if damage to the liver becomes severe.	The toxic dose of acetaminophen in a single ingestion posing a significant risk of severe hepatotoxicity is about 7.5g or more in adults and 140 mg/kg of body weight in children. Specific information about these risks is included in the package leaflet.
PIL: Concomitant use of medecines used to thin blood (SPC: Drug interaction with anticoagulants)	Concomitant use of paracetamol with medecines used to thin blood (anticoagulants) may lead to slight variations of INR values (laboratory measurement of how long it takes blood to form a clot).	The patient should inform health care professionals in case of concomitant medicine use. Increased monitoring of INR values should be conducted during the period of concomitant use with paracetamol as well as for 1 week after paracetamol treatment has been discontinued.
PIL: Using other medicines (SPC: Drug interaction with enzyme inducers)	Paracetamol is transformed in the liver in a toxic substance which cause liver damage. Secondarly this toxic substance is transformed in non-toxic molecules. Some drugs such as antiepileptics medecines (e.g. phenytoin, carbamazepine), medicines used to treat HIV–AIDS (e.g.ritonavir) or tuberculosis (e.g.isoniazide, rifampicine), medicine used to reduce the amount of acid that stomach produces (e.g.omeprazole, lansoprazole), act on the enzymes responsible of the formation of toxic substance. Moreover, alcohol and St John wort may also induce a transformation of paracetamol, increasing toxic substance in liver. Consequently, a decrease in paracetamol effectiveness and an increase of the liver toxicity may be observed. The toxic substance is responsible of liver damage, including tender hepatic edge, hepatic necrosis (death of liver tissues) and dysfunction associated with	The patient should inform health care professionals in case of concomitant medicine use, even if it is a not prescribed drug. Particular care must be exercised when enzymatic inductors are administered concomitantly.

Risk	What is known	Preventability
	jaundice (yellowish pigmentation of the skin, tissues, and body fluids), coagulation disorders, low blood glucose, and hepatic encephalopathy (a liver disease causing confusion, tremor, decreased level of consciousness including coma), liver failure.	
PIL: allergic to paracetamol (SPC Hypersensitivity reactions (including severe cutaneous adverse reactions))	Very rare cases of serious skin reactions have been reported. Hypersensitivity reactions ranging from a simple skin rash or urticaria to anaphylactic shock, requiring discontinuation of treatment have been reported in very rare cases.	The patient should inform health care professionals in case of known hypersensitivity to paracetamol.
PIL: (SPC Severe hypotension)	In rare cases a drop in blood pressure may occur.	The patient should inform health care professionals in case of occurrence of drop in blood pressure.

IMPORTANT POTENTIAL RISKS

Risk	What is known (Including reason why it is considered a potential risk)
None	

MISSING INFORMATION

Risk	What is known
Neonates and premature neonates, Pregnant and lactating women	Clinical experience of the intravenous 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. No reproductive studies with the intravenous form of paracetamol have been performed in animals. However, studies with the oral route did not show any malformation or foetotoxic effects. After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effect on nursing infants have been reported. Consequently, PARACETAMOL PANPHARMA may be used in breast-feeding women.