VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Sudden pain is an unpleasant sensation resulting from physical hurt caused by injuries of the body, illness or emotional illness. Despite the fact that is uncomfortable, it has an useful purpose, to reduce spreading the wound, challenging the organism to keep off harmful stimulus.
Sudden pain is short-term pain, usually passing away when the injury heals. Wrong treatment or untreated pain can lead to changes in the entire body: rapid breathing, racing heartbeat, compromise of circulation and tissue metabolism, raised activity of nerves, decrease of the body's immune system.
Efficient treatment must consider the cause, duration and intensity of pain and heal pain in order to keep the patient as comfortable as possible. (1)
Sudden pain is an ordinary experience in the general population and has no specific cause.

VI.2.2 Summary of treatment benefits

The efficacy of paracetamol/codeine in the treatment of sudden pain due to different causes (multiple trauma, arthritis pain in the hip or knee, different surgical operations) combination (100/60mg or 500/30mg) was analysed in three studies versus ketorolac (10 mg, 60 patients), tramadol/paracetamol (37.5/325mg-122 patients) and buprenorphine (patches 5-25µm/h-220 patients). No differences concerning adverse reaction or efficacy were observed between paracetamol/codeine groups and the other drugs evaluated. (2)

One study was conducted in order to evaluate the efficacy of paracetamol/codeine (1mg/kg/dose) versus ibuprofen (10mg/kg) in the treatment of sudden pain in 336 children. There were not found significant differences between the efficacy of the used drugs, but children receiving ibuprofen reported fewer side effects.

Another two comparative studies were conducted to evaluate the efficacy of paracetamol/codeine (300/30mg) versus aspirin (1000mg) and placebo (inactive substance) in treatment of sudden pain. No significant differences were found between aspirin and paracetamol with codeine efficacy, but both drugc provided superior results versus placebo.

The efficacy of paracetamol/codeine (325/30 mg) was analyzed in patients with sudden pain compared to paracetamol/ibuprofen (1000/400mg) and paracetamol 1000mg. Paracetamol/ibuprofen had superior results compared to the other groups. (2)

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for acute moderate to severe pain, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Headache caused by use of medicines in higher doses than recommended and for longer periods of time (Medication overuse headache)	Where analgesics are used long-term (> 3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of painkillers (medication-overuse headache) should not be treated by dose increase. In such cases, the use of painkillers should be discontinued in consultation with the doctor.	The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients should seek doctor's advice.
Use of higher doses than recommended (Overdose)	Ingestion of 7.5 g or more of paracetamol in adults may result in abnormalities of glucose metabolism, sudden kidney damage, irreversible liver damage, coma and death. Use of higher doses of codeine than recommended may lead to reduced nervous activity, and breathing problems.	Recommended doses of paracetamol/codeine should not be overtaken.
Allergies (Hypersensitivity)	Allergy symptoms to paracetamol/codeine include rash and breathing problems, swelling of the legs, arms, face, throat or tongue.	Patients allergic to codeine or paracetamol, patients suffering from severe asthma attacks or severe breathing problems should not use this product.
Blood disorders: reduction in blood platelets, which increase the risk of bleeding or bruising and severe reduction in number of white blood cells which makes infections more likely (Blood dyscrasias (thrombocytopenia and agranulocytosis))	Paracetamol should be used with caution in patients with a medical history of red cell membrane and haemoglobin abnormalities, glucose-6 phosphate dehydrogenase deficiency and anaemia.	Paracetamol/codeine should be used with caution in patients with anaemia (reduced number of red blood cells which can make the skin pale and cause weekness and breathlessness)
Use in patients suffering from condition which causes sudden narrowing of the airways (Patients with acute asthma)	Codeine may allow accumulation of secretions in the lungs, blocking the airways.	Paracetamol/codeine should not be used in patients suffering from condition which causes sudden narrowing of the airways or breathing problems.
Use in patients with breathing problems	In patients suffering from tissue oxygen deficiency, ex-	Paracetamol/codeine should not be used in patients suf-

Risk	What is known	Preventability
(Patients with respiratory depression)	cess of carbon dioxide in the blood or blocked upper airways, normal therapeutic doses may decrease breathing capacity.	fering from condition which causes sudden narrowing of the airways or breathing problems.
Use in elderly	Codeine in older people may have several side effects as over-drowsiness, constipation, bowel blockage, fall and fracture, breathing problems, urine retention. Also, older patients may be taking more drugs that may act in such way as to have an effect on another.	Paracetamol/codeine should not be used in the elderly.
Patients who recently consumed alcohol (Patients with acute alcoholism)	Paracetamol and alcohol may interact on each other, because the substance produced by the liver (enzyme) processes both paracetamol and alcohol. Codeine and alcohol use at the same time can increase central nervous system depression.	Paracetamol/codeine should not be used in case of acute alcoholism.
Patients with head injuries	In patients with head trauma, adverse reactions of codeine like breathing problems (respiratory depression) and raising fluid relating to the brain and spinal cord may put out of sight the head diseases. Carbon dioxide retention caused by respiratory depression results in widening of the blood vessels in the brain.	Paracetamol/codeine should not be used in patients with head injuries.
Patients with raised pressure within the skull (Patients with raised intracranial pressure)	Signs of increased pressure in the head include headaches, being sick and blurred eyesight. In patients with head trauma, adverse reactions of codeine like breathing problems (respiratory depression) and raising fluid relating to the brain and spinal cord may put out of sight the head diseases. Carbon dioxide retention caused by respiratory depression results in widening of the blood vessels in the brain which may lead to	Paracetamol/codeine should not be used in patients whose have been told they have increased pressure in the head.

Risk	What is known	Preventability
	deadly alteration in the brain function.	
Patients suffering from bile or bile duct operation (Patients undergoing biliary surgery)	Codeine increases smooth muscle tone which may result in spasm, raised biliary tract pressure and biliary colic.	Paracetamol/codeine should not be used in patients which have recently had an operation on liver, gallbladder or bile duct (biliary tract).
Use in patients with under-active thyroid gland (Use in patients with hypothyroid disorders)	Patients with under-active thyroid gland suffer from typical symptoms like weight loss, mental or physical tiredness, cold intolerance, constipation, heavy menstrual periods and muscle aches. Codeine may lead to a decrease in the release of thyroid hormones.	Paracetamol/codeine should be used with caution in patients with under-active thyroid gland.
Use in patients with adrenal gland problems (Use in patients with adrenocortical insufficiency)	Long-term use of codeine in patients with adrenal gland problems may lead to diseases due to internal secretion of substances, decreasing the production and secretion of steroid hormones.	Paracetamol/codeine should be used with caution in patients with adrenal gland problems.
Use in patients with problems passing water or prostate problems (Use in patients with prostatic hypertrophy)	Codeine may inhibit the urine emptying reflex and increase the tone of the ring muscle which surrounds the bladder. Also, codeine may decrease the urine production through direct effects on the kidneys.	Paracetamol/codeine should be used with caution in patients with problems passing water or prostate problems.
Use in patients with kidney insufficiency (Use in patients with renal impairment)	Codeine use in patients with kidney insufficiency may supress the formation of urine and lead to urine retention. Paracetamol may lead to chronic kidney failure.	Paracetamol/codeine should be used with caution in patients with kidney insufficiency.
Use in patients with liver insufficiency (Use in patients with hepatic impairment)	Paracetamol is poisonous to liver cells causing cells' death. Codeine can cause abnormality in brain function and may worsen an existing brain disturbance associated with liver failure.	Paracetamol/codeine should be used with caution in patients with liver insufficiency. Paracetamol/codeine is contraindicated in patients with severe liver problems (liver failure).
Use in patients with more active liver enzymes (CYP2D6) (Use in CYP2D6 ultra-rapid metabolisers)	CYP2D6 is a substance produced by the liver (enzyme) facilitating the breakdown of codeine to morphine. People with ultra-high activity of this enzyme are at risk of developing side effects of opioid	Paracetamol/codeine should not be used in patients that metabolise codeine very rapidly to morphine.

Risk	What is known	Preventability
	toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in blood levels of morphine higher than expected. Between 1% and 29% of the population are CYP2D6 ultra-rapid metabolisers.	
Concomitant use with other products containing paracetamol or opiate derivatives	Concomitant use of paracetamol/codeine with other products containing paracetamol or opiate derivatives may lead to use of higher doses than recommended of paracetamol and/or codeine. Ingestion of 7.5 g or more of paracetamol in adults may result in abnormalities of glucose metabolism, sudden kidney damage, irreversible liver damage, coma and death. Use of higher doses than recommended of codeine may lead to reduced nervous activity, and breathing problems.	Paracetamol/codeine should not be used in patients that use other products containing paracetamol or opiate derivatives.
Concomitant or within 14 days use of antidepressive drugs called MAOIs (Patients who have taken monoamino oxidase inhibitors (MAOIs) within 14 days)	Antidepressive drugs called MAOIs may increase the action of morphine. Poisoning induces drowsiness, breathing problems and, finally, death.	Paracetamol/codeine should not be used in patients that use medicines to treat depression called MAOIs (monoamine oxidase inhibitors) or who have used them in the last 14 days.
Breastfeeding	At normal healing doses, codeine and morphine (metabolite-substance formed after codeine conversion) may be present in breast milk at very low doses. If the mother has more active liver enzymes (CYP2D6), then higher levels of codeine and morphine present in breast milk become poisonous to the baby.	Paracetamol/codeine should not be used in women during breastfeeding.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in children after operation	There have been reports in the published literature that codeine given in children after removal of tonsils and/or polyps

Risk	What is known (Including reason why it is considered a potential risk)
(Post-operative use in children)	for temporary pause in breathing during sleep, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine. Due to the limited information, the use of codeine in children after surgery is considered a potential risk. Due to an increased risk of developing serious and life-threatening adverse reactions, paracetamol/codeine is not indicated in paediatric patients (0-18 years of age) who undergo removal of tonsils and/or polyps due to temporary pause in breathing during sleep.
Use in children with breathing problems (Use in children with compromised respiratory function)	Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity, therefore the use in children with compromised respiratory function is a potential risk.
Driving and using machines	Effects of codeine use on ability to drive and use machines may appear as confusion, drowsiness, dizziness, hallucinations, blurred or double vision or convulsions.
Physical and psychological dependence (Addiction and drug dependence)	Regular prolonged use of codeine is known to lead to addiction (psychological dependence) and tolerance (capacity of the body to endure the effects of codeine). Symptoms of restlessness and irritability may result when treatment is stopped.
Excessive and incorrect use of drugs (Drug abuse misuse)	Excessive or incorrect use may be due to the fact that the drug modifies patients' perception of pain and the nature of the pain experience.
Serious skin reactions	Serious, possibly life-threatening skin reactions have rarely been reported with paracetamol use. Such reactions include Stevens-Johnson syndrome (SJS; severe form of skin flushing), toxic epidermal necrolysis (TEN; severe rash involving reddening, peeling and swelling of skin) or acute generalized exanthematous pustulosis (itching or burning painful eruption). SJS and TEN may be fatal in up to 25-35% of patients affected. These conditions may appear within a few days after paracetamol ingestion or may occur later on during therapy. Long-term complications may be present, such as narrowing of the throat and swallowing difficulties.

Missing information

Risk	What is known
Use in children under 12 years of age	Treatment with paracetamol/codeine is only approved for patients over 12 years of age, due to the lack of safety and efficacy data for treatment of younger patients. Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredicta-

Risk	What is known
	ble metabolism of codeine to morphine. Symptoms of codeine poisoning include drowsiness, breathing problems and coma.

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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for paracetamol/codeine.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	Submitted in January 2014	<u>Identified Risks</u> Medication overuse headache Use in CYP2D6 ultra-rapid metabolisers <u>Potential Risks</u> Post-operative use in children Use in children with compromised respiratory function <u>Missing information</u> Use in children under 12 years of age	
2.0	08-08-2014	<u>Identified Risks</u> Overdose Hypersensitivity Blood dyscrasias (thrombocytopenia and agranulocytosis) Patients with acute asthma Patients with respiratory depression Use in elderly Patients with acute alcoholism Patients with head injuries Patients with raised intracranial pressure Patients undergoing biliary surgery Use in patients with hypothyroid disorders Use in patients with prostatic hypertrophy Use in patients with adrenocortical insufficiency Use in patients with renal impairment Use in patients with hepatic impairment Concomitant use with other products containing paracetamol or opiate derivatives	The concerned tables displaying risk minimization measures for each added risk were updated. Characterization of the newly-added risks has been provided in *Part II: Module SVII - Identified and potential risks.* *Section SVII.5.1-Pharmacological class risks already included as important identified or potential risks* has been up-

Version	Date	Safety Concerns	Comment
		Patients who have taken monoamino oxidase inhibitors (MAOIs) within 14 days breastfeeding <u>Potential Risks</u> Driving and using machines Addiction and drug dependence Drug abuse misuse	dated to reflect newly-added important identified risks specifically related to phenylephrine. Lay language table *VI.2.4 Summary of safety concerns* was revised to include information relevant for the new risks presented in appropriate manner for a lay audience. *Annex 2 -Current or proposed SmPC/PIL* has been updated in order to reflect the revised PI *Annex 3- Worldwide marketing status by country* has been updated with latest changes.
3.0	18-02-2015	"Serious skin reactions" was added as important potential risk.	Subsection VI.2.4 was updated regarding the risk of abuse/misuse. Prescription-only status was added as routine RMM. Update of Annex 2: addition of latest proposed PI (Day 160). Update of Annex 3: change in product names and removal of 500/10 mg strength.