Edipren 5 mg/2.5 mg prolonged-release tablet

Edipren 10 mg/5 mg prolonged-release tablet

Edipren 20 mg/10 mg prolonged-release tablet

Edipren 40 mg/20 mg prolonged-release tablet

12.2015, Version 2.0

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Table 14. Summary table of safety concerns

Important identified risks	• Respiratory depression • Severe gastrointestinal disorders
Important potential risks	• Tolerance and dependence after long-term administration • Opioid withdrawal symptoms • CNS-depressant effect • Abuse/misuse/diversion • Interactions • Increased plasma levels in patients with hepatic/renal impairment • Long-term treatment of restless legs syndrome beyond 12 months • Safety and efficacy in pregnant and lactating women and newborn
Missing information	• NA

VI.1.2 Table of on-going and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan (if applicable)

Not applicable.

VI.1.3 Summary of Post-authorisation efficacy development plan (if applicable)

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Table 15. Summary table of risk minimisation measures

VI.2 Elements for a public summary

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Respiratory depression	Contraindicated in section 4.3. Warning on the risk in section 4.4. Interactions with other medicinal products in section 4.5. Warning in section 4.6. Listed in section 4.8. Warning in section 4.9. Prescription only medicine.	Not applicable.
Severe gastrointestinal disorders	Contraindicated in section 4.3. Warning on the risk in section 4.4. Listed in section 4.8. Prescription only medicine.	Not applicable.
Tolerance and dependence after long-term administration	Warning in section 4.2. Warning on the risk in section 4.4. Warning in section 4.6. Listed in section 4.8. Prescription only medicine.	Not applicable.
Opioid withdrawal symptoms	Warning in section 4.2. Warning on the risk in section 4.4. Warning in section 4.6. Listen in section 4.8. Warning in section 4.9. Information in section 5.2. Prescription only medicine.	Not applicable.
CNS-depressant effect	Warning on the risk in section 4.4. Interactions with other medicinal products in section 4.5. Warning in section 4.7. Listed in section 4.8. Warning in section 4.9. Prescription only medicine.	Not applicable.
Abuse/misuse/diversion	Contraindicated in section 4.3. Warning on the risk in section 4.4. Warning in section 4.9. Information in section 5.2. Prescription only medicine.	Not applicable.

Interactions	Warning on the risk in section 4.4. Interactions with other medicinal products in section 4.5. Information in section 5.2. Prescription only medicine.	Not applicable.
Increased plasma levels in patients with hepatic/renal impairment	Warning in section 4.2. Contraindicated in section 4.3. Warning on the risk in section 4.4. Information in section 5.2. Prescription only medicine.	Not applicable.
Long-term treatment of restless legs syndrome beyond 12 months	Warning in section 4.2. Warning on the risk in section 4.4. Information in section 5.3. Prescription only medicine.	Not applicable
Safety and efficacy in pregnant and lactating women and newborn	Warning in section 4.6. Information in section 5.2. Information in section 5.3. Prescription only medicine.	Not applicable.

VI.2.1 Overview of disease epidemiology

Severe pain

Pain has become a major public health problem all around the world during the past decades. Moreover, the acute pain represents one of the most frequent complaints encountered by primary care physicians and accounts for nearly half of patient's visits. (1)

In a study conducted in the United Kingdom, France, Spain, Germany and Italy, 43.22% of respondents found the impact of pain on daily activities to be severely limiting and 22.63% found it to be moderately limiting. (2)

WHO has developed a three-step "ladder" for cancer pain relief for adults If pain occurs, there should be prompt administration of drugs in the following order: non-opioids (e.g. paracetamol, aspirin); mild opioids (e.g. codeine); strong opioids (e.g. morphine, oxycodone) until the patient is free of pain. Whenever necessary additional drugs – "adjuvants" – may be added to the treatment. (3)

Idiopathic (arising from unknown reason) restless legs syndrome (RLS) after failure of dopaminergic (affecting levels of dopamine) therapy

Restless legs syndrome is a common condition characterised by uncomfortable sensations deep in the legs developing at rest that compel the person to move, while the symptoms are commonly worse at night and also sleep disturbances are frequently present. The frequency of occurrence varies among the countries. In a large study conducted in France in 2005, involving 10 238 adults, the frequency of occurrence was 8.5%. The treatment of RLS is based on the drugs affecting levels of dopamine (substance which allows the transmission of nerve impulses in the certain areas), while oxycodone retains a role in the

treatment of episodes of RLS at which the standard treatment was evaluated as unsatisfactory or inefficient. (4)

VI.2.2 Summary of treatment benefits

Severe pain

Different studies have shown an improvement in bowel movements in patients with opioid-induced constipation after treatment with oxycodone/naloxone hydrochloride, compared to those patients receiving just oxycodone hydrochloride.

A 12-week study which included 322 patients who were treated with oxycodone/naloxone hydrochloride prolonged-release tablets, they had on average one extra complete spontaneous bowel movement in the last week of treatment, compared to patients who received only oxycodone hydrochloride prolonged release tablets.

Similar results were shown in a study with 265 patients with non-cancer pain given comparable daily doses of oxycodone hydrochloride/naloxone hydrochloride of 60 mg/30 mg to up to 80 mg/40 mg with oxycodone hydrochloride monotherapy in the same dose range.

Idiopathic (arising from unknown reason) restless legs syndrome (RLS) after failure of dopaminergic (affecting levels of dopamine) therapy

A 12 week study including 150 patients with severe to very severe idiopathic restless legs syndrome were treated with oxycodone hydrochloride/naloxone hydrochloride. The severity of the symptoms was measured with the International Restless Legs Syndrome Severity Scale (IRLS), considering 21-30 as severe and 31-40 as very severe. The study showed a clinically relevant improvement compared to placebo: IRLS score decreased in 5.9 points at week 12. Efficacy was evidenced from as early as week 1 of treatment.

VI.2.3 Unknowns relating to treatment benefits

None.

VI.2.4 Summary of safety concerns

Table 16. Important identified risks

Important Identified Risk	What is known	Preventability
Slow and shallow breathing or even breathing arrest. (Respiratory depression)	Slow and shallow breathing or even breathing arrest (respiratory depression) is well known undesirable effect of whole group of opioids. This safety concern may become life-threatening condition which could significantly impair the patient's health condition and it may contribute to development or worsening of concomitant diseases such as pulmonary disorders, cardiovascular disorders, etc.	The patient's medical history should be investigated by caregiving physician and in case of any concerns the physician should be consulted immediately. Patients should notify their treating physician as soon as they develop any worsening of breathing.
Severe gastrointestinal disorders.	The use of this medicinal product is contraindicated in patients with non-opioid induced paralytic obstruction of intestines (ileus). The paralytic ileus is defined as blockage of intestine due to group. Further, the caution must be also exercised when administering <Oxycodone/naloxone generic> loss of strength in the affected muscle to patients with opioid-induced ileus.	The patient's medical history should be investigated by caregiving physician and in case of any concerns the physician should be consulted immediately. Patients should notify their treating physician as soon as they develop any of their bowel worsening movement.

Table 17. Important potential risks

Important Potential Risk	**What is known (including reason why it is considered a potential risk)**
Tolerance and dependence after long-term administration	During long-term administration, the patient may develop tolerance to the medicinal product and higher doses may be required to maintain the desired effect. Chronic administration of <Oxycodone/naloxone generic> may lead to physical dependence, which is defined as physiological adaptation of the body to the presence of drug. Physical dependence is associated with development of withdrawal symptoms upon the abrupt cessation of therapy. Whereas, psychological dependence, which is sometimes called as "craving" is characterised by increased passion to reach the drug. If therapy with <Oxycodone/naloxone generic> is no longer required, it may be advisable to reduce the daily dose gradually to avoid the occurrence of withdrawal syndrome. The dependence and consequently withdrawal symptoms may have significant impact on patient's health condition. (5) If the treatment is no longer needed, the daily dose should be reduced gradually, in consultation with a physician.
Opioid withdrawal symptoms	The presence of opioid withdrawal symptoms is clearly associated with tolerance and dependence to opioid therapy. Withdrawal symptoms may occur if treatment is stopped too suddenly, like restlessness, bouts of sweating, and muscle pain. If therapy with <Oxycodone/naloxone generic> is no longer required, it may be advisable to reduce the daily dose gradually to avoid the occurrence of withdrawal syndrome. The dependence and consequently withdrawal symptoms may have significant impact on patient's health condition.(5)

Physiological depression of the central nervous system that can result in decreased rate of breathing, decreased heart rate, and loss of consciousness possibly leading to coma or death. (CNS-depressant effect)	Substances with a potential to cause physiological depression of the central nervous system that can result in decreased rate of breathing, decreased heart rate, and loss of consciousness possibly leading to coma or death.(CNS-depressant effect) (e.g. other opioids, sedatives, drugs used for treatment of insomnia, depression, psychosis, allergies, travel sickness and vomiting) may enhance the CNS- depressant effect (e.g. respiratory depression) of <Oxycodone/naloxone generic>. Further, concomitant use of alcohol and <Oxycodone/naloxone generic> may increase the undesirable effects of <Oxycodone/naloxone generic>. Concomitant use should be avoided.
Abuse/misuse/diversion	The opioids possess the ability to evoke euphoric mood and feelings, while this effect is very commonly one of the main reasons for abuse of these drugs. However, the overdose of opioids may end up with severe life-threatening conditions and in the worst case it may cause death, so particular caution is necessary.

Interactions	Relevant changes in the blood clotting test (International Normalized Ratio - INR) in both directions have been observed if oxycodone and coumarin anticoagulants were used concomitantly. INR is value which is used for monitoring of creation of blood clots and according to its values; the dose of anticoagulants is adjusted. Oxycodone is metabolised via specific liver enzymes (i.e. CYP3A4 and CYP2D6), while the concomitant use of medicines which affect these biologic structures should be administered with caution. There are 2 different groups of medicines affecting the above mentioned structures. The “inducers” accelerates the transformation of oxycodone/naloxone to components which are excreted from the body, thus the final amount of drug in body circulation is lowered and the dose must be re-adjusted in order to sustain the efficacy of the medicine. On the other hand, the “inhibitors” slows the transformation of oxycodone/naloxone which results in elevated levels of oxycodone/naloxone and the dose must be re-adjusted, due to the fact that the increased levels of oxycodone/naloxone may intensify the undesirable effects of this medicine. Examples of drugs, which can interact with oxycodone/naloxone, include coumarin anticoagulants (such as warfarin), antibiotics of the macrolide type (such as clarithromycin), antifungal medicines of the azole type (e.g. ketoconazole), ritonavir or other protease inhibitors (used to treat HIV), cimetidine (used to treat gastric and duodenal ulcer), rifampicin (used to treat tuberculosis), carbamazepine (used to treat seizures, fits or convulsions and certain pain conditions), phenytoin (used to treat seizures, fits or convulsions) and St. John’s Wort (medicinal herb with antidepressant activity and anti-inflammatory properties). Drinking alcohol or grapefruit juice should be avoided while taking <Oxycodone/naloxone generic>.

Increased plasma levels in patients with worsening of liver/kidney function (hepatic/renal impairment)	There is clear evidence that plasma levels of oxycodone/naloxone are elevated in patients with liver/kidney disease. The increased levels of oxycodone/naloxone may potentiate the undesirable effects of this medicinal product, therefore the particular caution in considered necessary. Moreover, this medicinal product must not be used in patients with moderate to severe liver disease.
Long-term treatment of restless legs syndrome beyond 12 months	During long-term (chronic) administration, the patient may develop tolerance to the medicinal product and higher doses may be required to maintain the desired effect. Chronic administration of <Oxycodone/naloxone generic> may lead to physical dependence, which is defined as physiological adaptation of the body to the presence of drug. Physical dependence is associated with development of withdrawal symptoms upon the abrupt cessation of therapy. Whereas, psychological dependence, which is sometimes called as “craving” is characterised by increased passion to reach the drug. Prior to continuation of restless legs syndrome treatment beyond 1 year a discharge regimen by gradually decreasing the <Oxycodone/naloxone generic> over a period of approximately one week should be considered to establish if continued treatment with <Oxycodone/naloxone generic> is indicated. At least every three months during therapy with <Oxycodone/naloxone generic> patients should be clinically evaluated.

Safety and efficacy in pregnant and lactating women and newborn	Use of <Oxycodone/naloxone generic> should be avoided as far as possible during pregnancy. If used over prolonged periods during pregnancy, oxycodone hydrochloride may lead to withdrawal symptoms in newborn infants. If oxycodone hydrochloride is given during childbirth, slow and shallow breathing (respiratory depression) may occur in the newborn infant. Limited data on the use of oxycodone during pregnancy in humans reveal no evidence of an increased risk of congenital abnormalities. For naloxone, insufficient clinical data on the use during pregnancy are available. Breastfeeding should be discontinued or interrupted during treatment with <Oxycodone/naloxone generic>. There is evidence that oxycodone passes into human milk. A milk-plasma concentration ratio of 3.4:1 was measured and it is therefore possible that the effects of oxycodone are seen in the breastfed infant. It is not known whether naloxone also passes into human milk. However, after use of <Oxycodone/naloxone generic> systemic naloxone levels are very low.

Table 18. Missing information

Missing Information	**What is known**
None	Not applicable

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 (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Version 1.0 of Oxycodone/Naloxone RMP submitted on 14-NOV-2014 was not approved by MPA, the Swedish competent authority (RMS). Following MPA's suggestion to modify the safety concerns of Oxycodone/Naloxone RMP, and considering this as a significant change of the RMP, version 1.1 has been prepared. Following additional MPA's comments to the wording of the proposed SmPC, version 2.0 has been prepared.

Table 19. Major changes to the Risk Management Plan over time

Version	Submission	Safety concerns	Comment
1.0	14-NOV-2014	**Important identified risks** • Respiratory depression • Severe GIT disorders (e.g. ileus) • Convulsion and increased risk of seizures **Important potential risks** • Tolerance and dependence after long-term administration • Opioid withdrawal symptoms • CNS-depressant effect • Abuse/misuse/diversion • Interaction with coumarin anti-coagulants • Interaction with drugs affecting either CYP3A4 or CYP2D6 • Increased plasma levels in patients with hepatic/renal impairment **Missing information** • Safety and efficacy in children and adolescents below 18 years • Long-term treatment of restless legs syndrome beyond 12 months • Safety and efficacy in pregnant or lactating women	Initially submitted version, never approved.

1.1	Not available.	**Important identified risks** • "Severe GIT disorders (e.g. ileus)" has been renamed: "Severe gastrointestinal disorders" • "Convulsion and increased risk of seizures" safety concern has been removed. **Important potential risks** • "Interaction with coumarin anti-coagulants" and "Interaction with drugs affecting either CYP3A4 or CYP2D6" safety concerns have been merged to a single one: "Interactions". • "Long-term treatment of restless legs syndrome beyond 12 months" and "Safety and efficacy in pregnant and lactating women and newborn" safety concerns have been reclassified as important potential risks. **Missing information** • "Safety and efficacy in children and adolescents below 18 years" safety concern has been removed.	Safety concerns update following MPA's request.
2.0	Not available.	No changes to safety concerns or other RMP content, only minor changes in SmPC wording due to MPA's comments and harmonisation with the reference product.	None.