Oxycodone/Naloxone STADA 5 mg/2,5 mg prolonged-release tablet
Oxycodone/Naloxone STADA 10 mg/5 mg prolonged-release tablet
Oxycodone/Naloxone STADA 20 mg/10 mg prolonged-release tablet
Oxycodone/Naloxone STADA 40 mg/20 mg prolonged-release tablet

19.5.2015, Version 1.1

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pain has been associated with multiple underlying diseases, including skeletal, cancer, and autoimmune diseases. Estimates of the prevalence of chronic pain vary widely and typically range between 10 and 30% of the adult population, although prevalence rates ranging from 2 to 55% have been reported. This wide variation may reflect true differences between populations, but also the use of different definitions and classifications of chronic pain in epidemiological studies, for example duration of more than three or more than six months, and differences in assessment methods. Chronic pain is often reported to be more common among women and in older age groups (Bekkering, 2011). Cancer-related pain has become a major health concern as life-expectancy increases in developed countries. More than 3.5 million of patients worldwide experience cancer-related pain per day (Kumar, 2007).

VI.2.2 Summary of treatment benefits

The aim of the combination of prolonged-release (PR) oxycodone with PR naloxone in one tablet is to counteract opioid-induced constipation through the local antagonist effect of naloxone in the gut wall, while maintaining analgesia due to the low bioavailability of oral naloxone. Three trials in patients with pain demonstrated that oxycodone/naloxone PR improved gut function compared with oxycodone PR. Additionally, oxycodone/naloxone PR relieved pain more effectively than placebo and no less effectively than oxycodone PR after 12 weeks. Oxycodone/naloxone PR was generally well tolerated; the most frequently reported adverse events were of gut origin, consistent with those known to occur with opioid therapy. Of note, numerically lower rates of constipation were observed in the oxycodone/naloxone PR group compared with the oxycodone PR group. A cost-utility analysis predicted that oxycodone/naloxone PR would be a cost-effective option compared with oxycodone PR (Burness, 2014).

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns related to the treatment benefits.

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Respiratory depression	Slow and shallow breathing (respiratory depression) is the main danger of an opioid overdose. It mostly occurs in elderly and debilitated (weak) patients.	Oxycodone/Naloxoe should be avoided or used cautionsly in patients with reduced breathing capacity

Drug dependence and withdrawal	Abrupt withdrawal of opioids from persons with a dependency causes a withdrawal syndrome.	Long-term use should be avoided, because it can cause the development of tolerance and psychological dependence which leads to the use of higher doses in order to achieve the desired analgesic effect. If therapy with oxycodone is no longer required it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of a withdrawal syndrome.
Abuse, misuse and diversion	Abuse or misuse of the product can lead to overdose and even death. This risk is increased when the tablet is crushed, broken or chewed, since this could lead to the uncontrolled release and rapid absorption of a potentially fatal dose of oxycodone. Furthermore, chronic abusive use or prolonged use of opioids can lead to marked tolerance.	Oxycodone should be given cautiously to patients with risk factors for abuse/dependence like a history of drug dependence or alcoholism. To avoid damage to the prolonged-release properties of the tablets the tablets must not be chewed or crushed.
Constipation	Constipation is a common, predictable side effect of treatment with opioid painkillers. Most people who take the drug will develop some degree of constipation. If left untreated, constipation due to oxycodone can become very painful or, in some situations, could even lead to a dangerous intestinal blockage.	Naloxone in this product is used to counteract constipation.
Diarrhoea	The experience of diarrhoea may be due to the effect of naloxone at the start of treatment. It can occur within the first 3-5 days of treatment	If diarrhoea should persist after 3-5 days, or give cause for concern, a doctor should be contacted.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Ileus/bowel obstruction	Oxycodone decreases gastric mobility, prolonging gastric emptying. This increases oesophageal reflux and delays the passage of gastric contents through the duodenum. Oxycodone is clearly contraindicated in patients suffering from paralytic ileus (a type of bowel obstruction), since it

	may worsen the condition. The use of oxycodone is not recommended if the occurrence of a paralytic ileus is considered possible and if a paralytic ileus occurs treatment should be discontinued immediately.
Atrial fibrillation and other cardiac events	Cardiac events such as palpitations, tachycardia and even heart failure are associated with the use of oxycodone and naloxone. These side effects have been observed in primarily in patients with pre-existing cardiovascular disease.
Serotonin syndrome induced by interaction between oxycodone and serotoninergic drugs	The serotonin syndrome is caused by increased serotonin in the central nervous system. It is a potential symptom of any number of life-threatening drug interactions which may follow therapeutic drug use, combination, overdose or recreational use of particular drugs, especially those affecting serotonin in the central and/or peripheral nervous system such as opioids.[
Drug induced liver injury	Oxycodone is metabolised in the liver. Blood concentration of oxycodone and naloxone are elevated in patients with liver function impairment. Currently there is no known relationship for oxycodone related serious events affecting the liver.

Missing information	
Risk	**What is known**
Safety of use during pregnancy and lactation	There are no data from the use of the medicinal products under review in pregnant women and during childbirth. 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 exposed pregnancies are available. However, systemic exposure of the women to naloxone after use of the medicinal products under review is relatively low. Both oxycodone and naloxone pass into the placenta. Animal studies with oxycodone or naloxone administered as single drugs have not revealed any teratogenic or embryotoxic effects. Long-term administration of oxycodone during pregnancy may lead to withdrawal symptoms in the newborn. If administered during childbirth, oxycodone may evoke respiratory depression in the newborn.
Safety and efficacy of use in paediatric patients < 18 years	Studies have not been performed on the safety and efficacy of the medicinal products under discussion in children below the age of 18 years. Therefore, their use in children under 18 years of age is not recommended.
Safety and efficacy in patients with hepatic or renal impairment	In patients with hepatic or renal impairment, the breakdown of the active substances of the medicinal products under discussion can be reduced. This may lead to higher blood concentrations of the drug and thereby increases the risk for the occurrence of side effects. Dose adjustments might be necessary and caution should be exercised in these patients.
Safety and efficacy in long-	In patients under long-term opioid treatment with higher

term use	doses of opioids, the switch to the medicinal products under review can initially provoke withdrawal symptoms. Such patients may require specific attention.

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

Not applicable. No additional risk minimisation measures are planned.

VI.2.7 Planned post authorisation development plan

Not applicable.

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**
1.1	04.05.2015	Identified risks: • Respiratory depression • Drug dependence and withdrawal • Abuse, misuse and diversion, drug dependence • Constipation • Diarrhoea Potential risks: • Ileus/bowel obstruction • Atrial fibrillation and other cardiac events • Serotonin syndrome induced by interaction between oxycodone and serotoninergic drugs • Drug induced liver injury Missing information: • Safety and efficacy of use during pregnancy and lactation • Safety and efficacy of use in paediatric patients < 18 years • Safety and efficacy in patients with hepatic or renal impairment • Safety and efficacy in long-term use	None