Elements for a public summary

VI.2.1 Overview of disease epidemiology

Oxycodone/naloxon prolonged release is indicated for treatment of severe pain requiring treatment with opioids; a low dose of naloxone added to the fixed-dose combination antagonizes opioid receptors in the gastrointestinal tract, providing relief of opioid-induced constipation. Oxycodone/naloxon is the first product with a dual mechanism for achieving opioid analgesia while targeting the underlying cause of opioid-induced constipation, thus proactively addressing constipation symptoms.

Pain is a highly subjective sensation, and can be broadly classified into cancer and non-cancer (non-malignant) pain. ***Cancer pain*** is caused by this condition itself, as well as the bodily reactions to anticancer therapy and other associated treatment. ***Chronic non-cancer*** pain is usually defined as continuous, long-lasting pain of at least 12 weeks, or pain which continues after an injury would have been expected to have healed. The number of people suffering from chronic non-cancer pain increases with age.
Chronic non-malignant pain is experienced by 20 to 40% of adults, and cancer pain by up to 70% of oncology patients. Opioids are routinely employed in pain treatment for both etiologies, despite a lack of data to characterize potential implications of long-term use for nonmalignant pain. The United States ranks 3rd for opioid consumption per capita, with hydrocodone and oxycodone most commonly prescribed. Despite increasing use of opioid analgesics, pain is still frequently undertreated in the US and around the world.

Restless legs syndrome is a relatively common disorder of the nervous system. The most common symptoms are a distressing urge to move the legs or other limbs, as we all other uncomfortable sensations such as crawling or creeping feelings. The symptoms are usually worse at night, and can result in sleep disturbances. Restless legs syndrome symptoms range from mild to very severe; this is linked to how often they occur and how much distress they cause. Studies have suggested that the number of people suffering from Restless legs syndrome may range from 5 to14 out of 100 people. Globally, more people appear to suffer from Restless legs syndrome in Europe and North America compared to the rest of the world. Also, women appear to be more likely to suffer from Restless legs syndrome than men.

VI.2.2 Summary of treatment benefits

The World Health Organisation has developed a three-step “ladder”, which is used for the treatment of pain: non-opioids (e.g. Aspirin and paracetamol); then, as necessary, mild opioids (e.g. tramadol, codeine); then strong opioids such as oxycodone, hydromorphone, and morphine. This approach is 80-90 % effective. Opioid therapy is therefore a mainstay in the management of chronic pain, however dose increase can be limited by side effects. According to the evidence-based recommendations from a European Pain Association, morphine, oxycodone and hydromorphone can be used as the first choice strong opioids.

The oxycodone component provides pain relief and the naloxone component reduces constipation produced by oxycodone’s action on the digestive tract and therewith improves bowel function. The clinical benefit of addition of naloxone to oxycodone was clearly demonstrated throughout the clinical studies conducted to prove the efficacy and safety of the products. Twenty studies generated efficacy and safety data on the products including one dose finding study. The results of three main studies involving 1.050 patients suffering from moderate to severe pain overall demonstrated that the products provided superior pain relief compared to placebo, comparable pain relief compared to oxycodone

hydrochloride prolonged-release and improved bowel function compared to oxycodone hydrochloride prolonged-release. Furthermore, the results of supportive studies (excluding the dose finding study with 202 patients) involving 10.080 patients were in line with the results gathered in the pivotal studies. All studies enrolled patients suffering from moderate to severe pain such as cancer pain, severe non-cancer pain, e.g. post-operative pain, pain due musculoskeletal pain conditions (e.g. low back pain), pain due to damage to nerves caused by diabetes and other inadequately treated severe pain conditions. The products were compared either to other active substances (e.g. oxycodone hydrochloride prolonged-release, morphine prolonged-release, pregabalin) or compared to placebo. Demographic characteristics (age, race, and sex) and baseline characteristics were balanced across different treatments and study designs. The patient population included in the clinical studies is representative for the patient population in clinical practice and clearly demonstrate that the products are efficacious and safe for the treatment of moderate to severe pain. Due to the extensive clinical development programme and the availability of the products in the market since many years, a huge amount of experience exists.

In addition to pain studies (19 studies), one study was performed to investigate the efficacy and safety of the products for the treatment of severe to very severe Restless Legs Syndrome of unknown origin in patients where the previous treatment did not show benefit any longer. The results of this study demonstrated that the products were efficacious for the treatment of Restless Legs Syndrome related symptoms.

VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies nearly all patients were white Caucasians aged between 21 and 95 years suffering from moderate to severe pain of different origin. There is no evidence to suggest that results would be any different in non-white patients. No information about pain treatment of the pediatric population or pregnant or breast feeding women is available.

A treatment benefit of the products was shown in one trial with patients suffering from severe to very severe Restless Legs Syndrome of unknown origin after previous treatment didn't show benefit any longer. Demographic characteristics (age, race, and sex) and baseline characteristics were balanced across the treatment groups. This was the first confirmatory trial which provided the evidence about the efficacy of the products in patients suffering from severe to very severe Restless Legs Syndrome of unknown origin. At this point in time the study does not allow for a full assessment of a potential long term benefit of the products therapy in Restless Legs Syndrome patients, the option to use the products as first line therapy or to use it in mild forms of Restless Legs Syndrome.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
A decrease in the ability to exhale and inhale (Respiratory depression)	***Respiratory depression*** = ***respiratory failure*** = ***a slowing respiratioon*** is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination. Opiates and opioids (including oxycodone) do create a slowing of	Routine pharmacovigilance by monitoring for early symptoms is sufficient. <Invented name> should not be taken in cases if patient has breathing problems, such as breathing more slowly or weakly than expected (respiratory depression).

	respiration, breathing, and if it slows too much it creates severe respiratory depression. The risk of side effects is increased if patients take these tablets at the same time as medicines which affect the way the brain works. For example, they may feel very sleepy, or breathing problems may get worse. Drinking alcohol whilst taking <Invented name> may make patients feel more sleepy or increase the risk of serious side effects such as shallow breathing with a risk of stopping breathing, and loss of consciousness. If oxycodone is given during childbirth, the baby may have breathing problems (respiratory depression). An overdose may result in breathing more slowly or weakly than expected (respiratory depression). The most serious side effect is a condition where patients breathe more slowly or weakly than expected (respiratory depression).	Doctor or pharmacist should be informed if patients have severe lung problems (i.e. reduced breathing capacity). Doctor or pharmacist should also be informed, if patients suffer with a condition characterised by frequent breathing stops during the night which may make them feel very sleepy during the daytime (sleep apnoea).
An inability to stop using a drug **(Drug dependence and drug withdrawal syndrome)**	***Drug dependence*** develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug. When the drug is withdrawn, several physiologic reactions occur. These can be mild or even life threatening. This is known as the ***withdrawal syndrome***, also called ***a discontinuation syndrome***. The risk of a discontinuation syndrome occurring increases with dosage and length of use. If patients have been taking this medicine for a long time, they may become tolerant. This means they may need a higher dose to achieve the desired effect. Long-term use of this	Routine pharmacovigilance by monitoring for early symptoms is sufficient. If patients experience withdrawal symptoms, they may need to be specially monitored by a doctor. Withdrawal symptoms may occur if treatment is stopped too suddenly. If patients no longer need treatment, they should reduce daily dose gradually, in consultation with a doctor. These tablets are not suitable for withdrawal treatment. *Pregnancy* Use of these tablets during pregnancy should be avoided

	medicine may also lead to addiction. As with other strong opioid painkillers, there is a risk that patients may develop a psychological dependence to oxycodone. If patients have been using high doses of another opioid, withdrawal symptoms (such as restlessness, bouts of sweating or muscle pain) may occur when they initially switch to taking this medicine. *Pregnancy* Prolonged use of opioid analgesics during pregnancy can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. *Lactation* Oxycodone is excreted into human breast milk. It is unknown if naloxone is distributed in human breast milk. Withdrawal signs can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped or when breastfeeding is stopped.	unless a doctor thinks treatment with this medicine is essential. If opioid use is required for a prolonged period in a pregnant woman, the patient should be advised of the risk of neonatal opioid withdrawal syndrome. *Lactation* Breastfeeding should be stopped during treatment with this medicine.
The ingestion or application of a drug in quantities greater than are recommended (Overdose)	***Drug overdose*** occurs when a person takes more than the medically recommended dose. An overdose may result in mild, moderate or serious, harmful symptoms, or even in death. Symptoms, treatment, and recovery depend on the specific drug involved. The cause of a drug overdose is either by accidental overuse or by intentional misuse. If the overdose happens by mistake, it is called an *accidental overdose*. For example, a young child may accidentally take an adult's heart medicine. If a patient takes too much drug on purpose, it is called an *intentional overdose*. However, some people may be more sensitive to certain	Routine pharmacovigilance by monitoring for early symptoms is sufficient. Doctor will decide how much patients should take every day and how to divide a total daily dosage into morning and evening doses. Doctor will also decide on any necessary dose adjustments during treatment. A dose will be adjusted according to an individual sensitivity. Patients should not take more than one dose within any 8 hour period. Patients should not take a double dose to make up for a forgotten dose.

	medications, so the low (more dangerous) end of a drug may be toxic for them; a dose that is still within the range of acceptable medical use may be too much for their bodies to handle. An overdose may result in breathing more slowly or weakly than expected.	If patients have taken more than the prescribed dose, they must inform the doctor immediately. An overdose may result in: - a reduction in size of pupils in the eye; - breathing more slowly or weakly than expected (respiratory depression); - drowsiness or loss of consciousness; - low muscle tone (hypotonia); - reduced pulse rate; - a fall in blood pressure. Patients should avoid situations which require they to be alert, e.g. driving.
An unintended failure in the drug treatment process (Medication error)	A ***medication error*** is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine are the most common preventable cause of undesired adverse events in medication practice. Errors can happen in the hospital, at the doctor's office, at the pharmacy, or at home. Taking broken, chewed or crushed tablets may result in body absorbing a potentially fatal dose of oxycodone.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. To avoid medication error this medicine should be taken exactly as doctor or pharmacist has prescribed. Prolonged-release tablets must be swallowed whole so as not to affect the slow release of oxycodone from the tablets.
Bowel movements that are infrequent or hard to pass (Constipation)	Being constipated means the bowel movements are difficult or happen less often than normal. The normal length of time between bowel movements varies widely from person to person. Some people have bowel movements three times a day. Others have them only once or twice a week. Going longer than three or more days without one is usually too long. After three days, the stool or feces become harder and tougher to pass. Constipation is a typical side	Routine pharmacovigilance by monitoring for early symptoms is sufficient. Prolonged-released tablets should be taken exactly as doctor or pharmacist has prescribed.

	effect of treatment with strong painkillers. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.	
Frequent passing of watery and unformed faeces (Diarrhoea)	***Diarrhoea*** is defined as the abnormal passage of loose or liquid stools more than three times daily and/or a volume of stool greater than 200 g/day. A bout of diarrhoea can be caused by a wide range of disorders, infections and events including many drugs. Diarrhoea may be considered as a possible side effect of naloxone.	Routine pharmacovigilance by monitoring for early symptoms is sufficient. If diarrhoea persists after 3 to 5 days, or it gives a patient cause for concern, a doctor should be informed immediately.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
(Drug abuse, misuse and diversion)	***Drug abuse*** is the use of a legend drug in a way not intended by an authorized prescriber of the medication. The intent of prescription drug abuse is to obtain an altered state of mood or behavior. Prescription drug abuse frequently involves circumventing the intended route of drug administration. Drug abuse can lead to drug dependence or addiction. People who use drugs for pain relief may become dependent, although this is rare in those who don't have a history of addiction. ***Drug misuse*** is the voluntary administration of legend drugs for medical indications other than the indication and dosage intended by the authorized practitioner for the defined recipient of the prescription. This often includes administration of doses that exceed the directions of the prescription. Misuse of drugs also includes use of a legend drug for an appropriate indication but not prescribed by an authorized practitioner. Drug misuse predominately involves "self-medication" with legend drugs, although administration of prescription drugs to children by adults is included in prescription drug misuse. ***Drug diversion*** is the illegal transfer of legend medications to recipients outside the legal pathways as defined by the drug enforcement agencies and state agencies. Opioids (including oxycodone) are powerful pain killers that are highly addictive. <Invented name> should not be taken in cases if patient has a history of opioid abuse. Doctor or pharmacist should be informed if patients ever have been addicted to alcohol or drugs, or have previously suffered from withdrawal symptoms such as agitation, anxiety, shaking or sweating upon stopping alcohol or drugs. Long-term use of this medicine may also lead to addiction.
Liver problems (Hepatic disorders)	***Liver disease*** is any disturbance of liver function that causes illness. The liver is responsible for many critical functions within the body and should

	it become diseased or injured, the loss of those functions can cause significant damage to the body. Liver disease is also referred to as hepatic disease. This medicine should not be taken in cases of moderate to severe liver problems. Doctor or pharmacist should be informed if patients have mild liver problems. In cases of mild liver impairment may be prescribed a lower dose. Patients should not take these tablets for any longer than they need to. If patients have been taking them for a long time a doctor should regularly check that they still need them.
Increased risk of withdrawal or overdose in patients with hepatic or renal failure	Doctor or pharmacist should be informed if patients have kidney or liver problems. In cases of renal or mild liver impairment may be prescribed a lower dose. This medicine should not be taken in cases of moderate to severe liver problems. Patients should not take these tablets for any longer than they need to. Patients should not stop taking these tablets without first speaking with a doctor. Doctor will advise them how to reduce the daily dose gradually. In this way, patients will avoid withdrawal symptoms, such as restlessness, bouts of sweating and muscle pain. Patients should not take more than one dose within any 8 hour period. Patients should not take a double dose to make up for a forgotten dose.

Missing information

Risk	What is known
Use in paediatric patients < 18 years	No studies have been carried out to show that these tablets work properly in children and adolescents, or are safe for them to take. They are therefore not recommended for use in patients under 18 years of age.
Use in pregnant women and breastfeeding mother	*Pregnancy* Use of these tablets during pregnancy should be avoided unless the doctor thinks treatment with this medicine is essential. If used over prolonged periods during pregnancy, oxycodone may lead to withdrawal symptoms in the newborn baby. If oxycodone is given during childbirth, the baby may have breathing problems (respiratory depression). *Breastfeeding* Breastfeeding should be stopped during treatment with these tablets as oxycodone (one of the active ingredients of the medicine) passes into breast milk.
(Long term treatment (< 12 months) in restless leg syndrome)	There is limited data on the efficacy and safety of treatment of severe restless legs syndrome (a disorder of the part of the nervous system that causes a strong urge to move the legs; because it usually interferes with sleep, it also is considered a sleep disorder) with oxycodone/naloxone for more than 12 months.
Use a product for an indication not in the approved labeling (Off-label use)	***»Off-label use«*** means the medication is being used in an unapproved age group, dosage, or route of administration or in a manner not specified in the approved packaging label or insert. As for any medicine, oxycodone/naloxone should only be used to conditions listed in the product label because it is not known whether drug will work and will be safe if used for other conditions or in manners not in line with the product label.

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.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the agency's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

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

Not applicable, this is the first Risk management plan.