VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pain is a highly subjective sensation, and can be broadly classified into cancer and non-cancer pain. Cancer pain is caused by this condition itself, as well as the bodily reactions to anticancer therapy and other associated treatment. Research estimates that one out of three people receiving anticancer treatment and two out of three people with advanced cancer will experience cancer pain.

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. Worldwide, research estimates that 12 to 25 out of 100 people are affected by non-cancer pain. In Europe, research suggests that 19 out of 100 adults will suffer from at least six months of moderate to severe chronic pain, and over half of those will have experienced the problem for 2 to 15 years. The number of people suffering from chronic non-cancer pain increases with age.

Restless legs syndrome (RLS) 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 RLS may range from 5 to14 out of 100 people. Globally, more people appear to suffer from RLS in Europe and North America compared to the rest of the world. Also, women appear to be more likely to suffer from RLS 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.

Targin®, Targinact® and Targiniq® (subsequently called “the products”) are the trade names of a product containing both oxycodone hydrochloride and naloxone hydrochloride as a prolonged-release formulation in a 2:1 ratio. 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 (20) studies generated efficacy and safety data on the products including one dose finding study.

The results of three main studies involving 1050 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 (Oxygesic®; subsequently called “OxyPR”) and improved bowel function compared to OxyPR. Furthermore, the results of supportive studies (excluding the dose finding study with 202 patients) involving 10080 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.

All clinical studies performed to support the efficacy claims of the products were conducted according to the current scientific standard and respective EU guideline (CPMP/EWP/612/00). The products were compared either to other active substances (e.g. OxyPR, 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 RLS 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 RLS 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 paediatric 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 RLS 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 RLS 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 RLS patients, the option to use the products as first line therapy or to use it in mild forms of RLS.

VI.2.4 Summary of safety concerns

Table VI-3: Summary of safety concerns – Important identified risks

Risk	What is known	Preventability
Slow or weak breathing (Respiratory depression)	The most serious side effect is a condition where you breathe more slowly or weakly than expected (respiratory depression). This condition can happen if you take too much of the drug.	Yes, by recognising the signs of respiratory depression or overdose, and calling your doctor or hospital straight away. If you suffer respiratory depression, you may need emergency treatment in hospital, where a drug that reverses the effects of oxycodone may be given.
Drug addiction (Drug dependence and drug withdrawal syndrome)	As with all strong painkillers, there is a risk that you may become addicted on oxycodone. Withdrawal symptoms such as agitation, anxiety, palpitations, shaking or sweating may occur if you suddenly stop taking the oxycodone naloxone product or if you decrease the dose abruptly. Withdrawal symptoms may also occur after you are switched from a different opioid-containing pain medication to oxycodone naloxone.	You should not suddenly stop administering oxycodone naloxone unless your doctor tells you to. If you want to stop using the oxycodone naloxone products, discuss this with your doctor first. They will tell you how to do this, usually by reducing the dose gradually so you do not experience unpleasant effects.
Deliberate or accidental intake of more drug than you should (Overdose)	If you take more oxycodone naloxone than you should, this may make you feel very sleepy, sick or dizzy. You may also have breathing difficulties leading to unconsciousness or even death and may need emergency treatment in hospital.	Yes, by adhering strictly to the instructions on how to take this medicine given by your doctor and described in the patient information leaflet.
Medication error	If you take oxycodone naloxone in a wrong way (such as crushing the tablet or taking it more or less frequently than instructed), you may experience serious side effects which may be fatal.	Yes, by adhering strictly to the instructions on how to take this medicine given by your doctor and described in the patient information leaflet.
Reduced frequency of bowel movements (Constipation)	Constipation is a common side effect of oxycodone naloxone.	Partly yes, by adequate food and drink intake.
Loose bowel movements (Diarrhoea)	If you have suffered from constipation with a different opioid pain killer, diarrhoea may occur after you are switched to oxycodone naloxone. It may also be due to an intolerance reaction to excipients or due to a number of non-medication specific reasons.	Preventability relies on treatment of the underlying disease, if any, and awareness of intolerance to excipients.

Table VI-4: Summary of safety concerns – Important potential risks

Risk	What is known
Intentional excessive and persistent or sporadic use of opioids which may be accompanied by harmful physical or psychological effects (Drug abuse, misuse and diversion)	Not taking your medication as instructed by your doctor can be dangerous, causing serious problems such as an overdose, which may be fatal. Oxycodone naloxone prolonged release tablets are designed to work properly over 12 hours. If the tablets are crushed, dissolved or chewed, the entire 12 or 24-hour dose may be absorbed rapidly into your body. The contents of this formulation should never be injected. This can be dangerous, causing serious problems such as an overdose, which may be fatal.
Liver problems (Hepatic disorders)	This medicine may sometimes cause mild and self-limited liver problems which are noticed in blood tests. At present oxycodone naloxone is not believed to cause a lasting damage to your liver or any specific serious liver disease.
Increased risk of withdrawal or overdose in patients with hepatic or renal failure	Whilst there is very limited data suggesting any higher risk in patients with hepatic or renal impairment, doctors prescribing this medication should advise these patients to seek medical attention if overdose or drug withdrawal are suspected. If you take more oxycodone naloxone than you should, this may make you feel very sleepy, sick or dizzy. You may also have breathing difficulties leading to unconsciousness or even death and may need emergency treatment in hospital. You should not suddenly stop taking oxycodone naloxone unless your doctor tells you to. If you want to stop using the oxycodone naloxone products, discuss this with your doctor first. They will tell you how to do this, usually by reducing the dose gradually so you do not experience unpleasant effects.

Table VI-5: Summary of safety concerns – Missing information

Missing information	What is known
Use in children (paediatric patients < 18 years)	There is limited data on the efficacy and safety of oxycodone naloxone use in children
Use in pregnant and breast feeding women	Do not use oxycodone naloxone products if you are pregnant or breastfeeding unless specifically advised by your doctor. There is limited data on the safety of use of oxycodone naloxone in pregnant women. Oxycodone passes into breast milk, and therefore breast feeding should be discontinued during treatment with oxycodone naloxone products.
Long term treatment in restless legs syndrome	There is limited data on the efficacy and safety of treatment of severe restless legs syndrome with oxycodone naloxone for more than 12 months.
Use for other conditions than allowed according to the product label (Off-label use)	As for any medicine, oxycodone naloxone should only be used to treat conditions listed in the product label because it is not known whether the 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. Therefore we kindly advise that you always read all of the PL carefully before you start taking this medicine.

This medicine has no special conditions and restrictions for its safe and effective use (no additional risk minimisation measures).

VI.2.6 Planned post authorisation development plan

There is no post authorisation development plan in place because none is required at this point in time.

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

Major changes to the Risk Management Plan over time are subsequently listed.

Table VI-6: Major changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
1.0	30 Nov 2007	Important identified risks Constipation Diarrhoea Physical dependence and drug withdrawal syndrome	First RMP for the OXN products
		Important potential risks Cardiac arrhythmias Drug abuse Psychological dependence	First RMP for the OXN products. Drug abuse and psychological dependence were discussed in general as opioid class effects
		Missing information Paediatric use Use in pregnant and breast feeding women	Statements at the time: OXN is not indicated in children under 12 years of age Contraindication in pregnancy and lactation
2.0	18 Mar 2008		Routine update No change in important risks or missing information elements other than that “Cardiac arrhythmias” term was replaced by “Cardiac events”, because all SAE terms from clinical trials had been depicted. The depiction took place without correlation to patient treatment duration.

Table VI-6: Major changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
3.0	21 Sep 2009		General comment The Targin DCP was closed in April 2009. As requested by the RMS at the time, all standard format tables were added in section 1.10 and all subsequent sections of version 3.0 of the EU-RMP. The risk of drug withdrawal syndrome was considered an identified safety concern and the risks of abuse, misuse, diversion, and dependence were considered potential safety concerns following discussions with European authorities during the DCP for OXN PR, as these are well known identified safety concerns for opioids in general. A commitment therefore arose from the DCP to perform a cumulative review of cases falling under the above categories at the time when future OXN Periodic Safety Update Reports (PSURs) were being compiled and also that such occurrences from the EU should be monitored. Accordingly such cumulative analyses have been included into all OXN PSURs since and lastly into the June 2012 OXN PSUR. The June 2013 OXN PSUR was written in the new format which entails risk tables for drug abuse (including misuse and diversion), psychological dependence and drug withdrawal syndrome / physical dependence as will any EU-RMPs from this point forwards. This will on a routine PV level fully account for the original DCP commitment.
		Missing information Paediatric use Use in pregnant and breast feeding women	Following the outcome of the DCP the children cut off age was changed from under 12 years of age to under 18 years of age. Both pregnancy and lactation were changed from a contraindication to a precaution based on standard EMA guidance on these populations.
4.0	10 Aug 2012	Important potential risk 1. Ileus / bowel obstruction added as important potential risk	Addition triggered by single case reports; close monitoring implemented
		2. Serious hepatic events added as important potential risk	Addition triggered by one small cluster of increased hepatic enzyme cases following perioperative Targin use; close monitoring implemented

Table VI-6: Major changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
		3. Cardiac events	Routine pharmacovigilance monitoring resumed for this “diverse group of events” instead of “close monitoring”; monitoring of atrial fibrillation ongoing pending need for updated full safety analysis
	21 Dec 2012	Other 1.CYP interactions text updated in section 1.6	Whilst the earlier text rated the clinical significance of the acknowledged interaction unclear, the new text states that OXN doses may need to be adjusted. In addition the text discriminates between CYP3A4 inhibitors, CYP3A4 inducers and CYP2D6 inhibitors.
		2.Tables in sections 1.10 and 2 were updated	The updates were made to discriminate better between routine and additional pharmacovigilance activities
5.0	13 Sep 2013	Important identified risks Respiratory depression added as important identified risk	This important risk is added to reflect a key opioid class effects.
		Important potential risks 1. Accidental overdose added as important potential risk	This important risk is added to reflect a key opioid class effect and due to the potentially serious consequences of overdosing a strong opioid product.
		2. Cardiac events	Table removed after availability of analysis showing no indication of risk for the product (for the first time using comparative treatment duration exposure data from interventional clinical trials as denominator); full safety analysis and BRA for atrial fibrillation also documented no indication of increased risk for the products
		3. Ileus / bowel obstruction	Table removed after availability of full safety analysis and benefit risk assessment report which documented no indication of an increased risk for the products
		Missing information 1. Paediatric use 2. Use in pregnant and breast feeding women	Complete set of tables added for these previously acknowledged items in line with EMA’s RMP integrated standard format
		3. Long term treatment (>12 months) in RLS 4. Off-label use in RLS	Added as important missing information items on request of a member state health authority received during the authorisation procedure for the indication severe RLS

Table VI-6: Major changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
6.0	23 Sep 2015	Newly added important identified risk: • Medication error Newly added important potential risks: • Panic attack/reaction • Aphasia Newly added missing information: • Use in patients with hepatic impairment • Use in patients with renal impairment	Update triggered by Variation Assessment Report for variation DE/H/XXXX/WS/220. Other changes: • Combination of previously included risks "Physical dependence and drug withdrawal syndrome" and "Psychological dependence" to Important identified risk:" Drug dependence and drug withdrawal syndrome" • Previously listed risk "Accidental overdose" expanded to include all overdose concepts; reclassified from "potential" to "identified" risk • Previously listed topic "Off-label use in RLS" expanded to include any off-label use • Removal of serious in the potential risk "Hepatic disorders (formerly Hepatic events) • Removal of the educational materials that had been in use in some EU countries, because based on the experience with OXN products those materials were no longer deemed appropriate or necessary. Editorial changes in the names of several risks
7.0	01 Apr 2016	Removal of important potential risks: • Panic attack/reaction • Aphasia Removal of missing information: • Use in patients with hepatic impairment • Use in patients with renal impairment	Update as requested by MHRA and agreed by BfArM after review of updated MAH data in context of variation DE/H/XXXX/WS/290.
7.1	20.Jun 2016	Addition of important potential risk: Increased risk or withdrawal and overdose in patients with renal or hepatic failure.	Update as requested by BfArM after review of updated text in the context of DE/H/xxxx/WS/290 - Targin/Oxynal (oxycodone+naloxone) - DE - FVAR/re-start procedure