VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Oxycodone hydrochloride is a strong pain killer used for treatment of moderate to severe pain.

It is believed that globally 1 in 5 adults suffer from pain and one in five Europeans suffer from moderate to severe chronic pain. Pain can be broadly classified in non-cancer and cancer pain. In Europe, 12 to 25 out of 100 individuals suffer from non-cancer related pain.

Pain is one of the most common symptoms of cancer and affects an estimated third of patients receiving cancer treatment. A survey conducted in 15 European countries and Israel, found that on the country level, cancer types with the highest pain were reported to be the in Switzerland, Israel, Italy, UK, France and Ireland.

With regards to demographics, 18 out of 100 young adults experience non-cancer pain which increases to 30 to 65 out of 100 adults aged 55-65 years and 25 to 55 of 100 adults over 85 years. A classification of the age groups in cancer pain depends on the type of the cancer an individual experiences.

Pain can be treated by selecting proper drugs and pain-killers. The selection of the drugs depends on how severe the pain is. For example for pain caused by the swelling of joints drugs that reduce the swelling and a pain-killer are used. For moderate to severe cancer and non-cancer pain an opioid pain reliever (strong pain killer) is used.

People affected by pain generally use a number of other drugs related to their conditions such as back pain, joint pain and pain caused by cancer. Often drugs to treat cancer or drugs that are used to treat unwanted effects of cancer treatment are used.

VI.2.2 Summary of treatment benefits

The World Health Organisation (WHO) has developed a three-step “ladder”, which is used for the treatment of pain: nonopioids (e.g. aspirin and paracetamol); then, as necessary, mild opioids (e.g. tramadol, codeine); then strong opioids such as 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.

They are widely used and are now well established in pain management and are considered to be opioids of choice by many clinicians. They provide simple but highly effective therapy which is favoured by both patients and medical staff. Although morphine is a widely respected and efficacious drug there are sometimes problems with its use. Oxycodone is an effective alternative to morphine. It has been used for many years in a number of countries including Germany, France, Finland, USA, Canada and Australia. When administered orally, oxycodone may be up to twice as potent as morphine. OxyContin is a prolonged-release tablet of oxycodone, allowing a twice daily intake for 24 hours pain relief. A range of tablet strengths is proposed (5, 10, 20, 40 and 80mg) to facilitate individualised dose adjustment. Furthermore immediate release formulations have also been approved (OxyNorm capsules and liquids). In addition there are situations in which oral administration is not possible, e.g. patients with difficulty in swallowing, nausea, vomiting, gastrointestinal obstruction, or in post-operative patients. For these patients, an injectable formulation of oxycodone (OxyNorm Injection) has been developed.

The clinical efficacy and s afety development study programme involved more than 1500 subjects treated with oxycodone. The studies have been performed in both cancer (n = 723 patients) and non-cancer pain (n = 884 patients), with the latter including arthritis of the joints and back pain (n = 455 patients), post-operative pain (n = 356 patients) and pain due to damage of nerves (e.g. due to diabetes mellitus or pain due to herpes zoster virus infections, n = 51 patients). Overall 1048 patients (n = 640 non-cancer, n = 408 cancer) in the age of 18 – 65 years and 552 patients (n = 240 non-cancer, n = 312 cancer) above 65 years have been enrolled in the studies being part of analysis. In addition 7 paediatric patients with a mean age of 14 (range 9 – 17 years) have been enrolled in the clinical studies. In the cancer pain studies 3.2 % of patients received a daily dose less than 10 mg oxycodone, 61.6 % of patients received a daily dose of 10 up to 80 mg oxycodone and 34,9 % of patients received more than 80 mg per day. In the non-cancer pain studies 5.1 % of patients received a daily dose less than 10 mg oxycodone, 91.2 % of patients received a daily dose of 10 up to 80 mg oxycodone and 3.7 % of patients received more than 80 mg per day.

Arthrosis of the joint and back pain were selected as pain type in several of the non cancer pain studies since they are common chronic conditions, and similar to many other painful conditions.

The majority of studies were comparing oxycodone to other active drugs (morphine, immediate release oxycodone, a combination of acetaminophen and oxycodone, or hydromorphone) and 3 studies were comparing to placebo. The measurement of pain was following the current scientific standards and respective EU guideline (CPMP/EWP/612/00).

It was demonstrated that prolonged-release (PR) oxycodone was superior to placebo and equivalent to immediate-release oxycodone and morphine PR in analgesic effectiveness. Patients could be converted easily from morphine, hydromorphone with a different dosage or immediate release oxycodone. Oxycodone PR was safely and ef fectively used in patients receiving opioids for the first time. Therefore, the results of the clinical studies demonstrated a clinically meaningful efficacy of oxycodone PR tablets in the relief of cancer and non-cancer pain.

The patient population included in the clinical studies are representative for the patient population in clinical practice and clearly demonstrate that oxycodone is efficacious and safe for the treatment of pain independent of the origin.

As oxycodone has been available for many years and t here is a substantial amount of experience with oxycodone, no post-authorisation efficacy studies have been performed to address a specific efficacy concern.

VI.2.4 Summary of safety concerns

Important identified risks

Part VI. Table 4 – Summary of safety concerns – Important identified risks

Risk	What is known	Preventability
A condition where you breathe more slowly and weakly than expected (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 hydrochloride may be given.
A condition where the bowel does not work properly (ileus)	Ileus can be caused by a number of other factors, including pain, emotional stress, other medications, anaesthetics and surgery (especially bowel operations).	Avoid taking the drug before having a surgery or 12-24h after the surgery, as the chances that the bowels do not work properly are higher. You also should not take the drug if you are currently suffering from ileus.
Not taking your medication as recommended by your doctor (drug abuse)	Not taking your medication as instructed by your doctor can be dangerous, causing serious problems such as an overdose, which may be fatal. Oxycodone hydrochloride tablets are designed to work properly over 12 hours when swallowed whole. If a tablet is broken, crushed, dissolved or chewed, the entire 12-hour dose may be absorbed rapidly into your body. This can be dangerous, causing serious problems such as an overdose, which may be fatal. The tablets should never be crushed or injected as this may lead to serious side effects, which may be fatal.	Always take your medication exactly as your doctor has told you. The label on your medicine will tell you how much to take and how often.
Becoming addicted or reliant on oxycodone hydrochloride (psychological dependence)	As with all strong painkillers, there is a risk that you may become addicted or reliant on oxycodone hydrochloride.	Yes, by avoiding use in patients with a history of or present alcohol or drug abuse.
Accidentally taking too much drug (accidental overdose)	If you take more oxycodone hydrochloride than you should, this may make you feel very sleepy, sick or dizzy, or have hallucinations. You may also have breathing difficulties leading to unconsciousness or even	Yes, by recognising the side effects of overdose, and calling your doctor or hospital straight away. If you suffer an overdose, you may need emergency treatment in hospital, where a drug that reverses the effects of oxycodone

Intentionally taking too much drug (intentional overdose)	death and may need emergency treatment in hospital.	hydrochloride may be given. Always take oxycodone hydrochloride exactly as your doctor has told you. The label on your medicine will tell you how much to take and how often. Do not exceed the dose recommended by your doctor.
Drug withdrawal syndrome (physical dependence)	Withdrawal symptoms such as agitation, anxiety, palpitations, shaking or sweating may occur if you suddenly stop taking oxycodone hydrochloride	You should not suddenly stop taking oxycodone hydrochloride unless your doctor tells you to. If you want to stop taking your oxycodone hydrochloride, 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.
Use of oxycodone hydrochloride if you have liver problems (Use of oxycodone hydrochloride in patients with hepatic impairment)	If you have liver problems you should only take oxycodone hydrochloride at a dose and dosing frequency as prescribed by your doctor and you may require additional monitoring of your drug blood levels.	Always take oxycodone hydrochloride exactly as your doctor has told you
Use of oxycodone hydrochloride if you have kidney problems (Use of oxycodone hydrochloride in patients with renal impairment)	If you have liver problems you should only take oxycodone hydrochloride at a dose and dosing frequency as prescribed by your doctor and you may require additional monitoring of your drug blood levels.	Always take oxycodone hydrochloride exactly as your doctor has told you
Allergy (hypersensitivity)	All medicines can cause allergic reactions, although serious allergic reactions are rare. Do not take oxycodone hydrochloride if you are allergic (hypersensitive) to oxycodone hydrochloride, or any of the other ingredients	Tell your doctor immediately if you get any sudden wheeziness, difficulties in breathing, swelling of the eyelids, face or lips, rash or itching especially those covering your whole body
Use in patients with head injury	If you have a head injury that causes a severe headache or makes you feel sick do not take oxycodone hydrochloride because the drug may make these symptoms worse or hide the extent of the head injury.	Do not take oxycodone hydrochloride if you have a head injury
Use of oxycodone hydrochloride in patients taking MAO inhibitors (examples include tranylcypromide, phenelzine, isocarboxazid, moclobemide and	Do not take oxycodone hydrochloride if you are taking a type of medicine known as a monoamine oxidase inhibitor (examples include tranylcypromide, phenelzine, isocarboxazid, moclobemide and linezolid), or you have taken this type of medicine in the last two weeks	Oxycodone hydrochloride must not be used together with a monoamine oxidase inhibitor, or if you have taken this type of medicine in the last two weeks

linezolid),		
Concomitant use with other medicines such as tranquillisers, hypnotics, benzodiazepines or sedatives or alcohol (Interactions with CNS	If you take oxycodone hydrochloride with other medicines that affect the central nervous system, the side effects from oxycodone hydrochloride may worsen.	Tell your doctor or pharmacist if you are taking medicines to help you sleep (tranquillisers, hypnotics, benzodiazepines or sedatives) or to treat depression
depressants)		It is recommended not to drink
	Drinking alcohol whilst taking	while you're taking oxycodone
	oxycodone hydrochloride may	hydrochloride
	you feel more sleepy or increase	
	risk of serious side effects such as	
	shallow breathing with a risk of	
	stopping breathing, and loss of	
	consciousness.	

Important potential risks

Part VI. Table 5 – Summary of safety concerns – Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Drug mistakes (medication errors)	The causes of drug mistakes can be due t o a m istake in prescribing the drug, dispensing the drug, or may be due to wrong dose given to patients with certain conditions. Always take oxycodone hydrochloride exactly as your doctor has told you. The label on your medicine will tell you how much to take and how often. Do not exceed the dose recommended by your doctor.
Abnormal heart rythmn (Prolongation of QTc)	There is currently no evidence that oxycodone hydrochloride use causes an abnormal heart rhythm. (prolongation of QTc).

Important missing information

Part VI. Table 6 – Summary of safety concerns – Important missing information

Risk	What is known
Use in pregnant and breast-feeding women	Use of oxycodone hydrochloride should be avoided as much as possible in pregnant or breast-feeding women. There is limited data on the safety of use of oxycodone hydrochloride in pregnant women. Use of oxycodone hydrochloride during the last 3 to 4 weeks before giving birth may lead to respiratory depression and drug withdrawal syndrome (see explanations under 'Important identified risks' above. Oxycodone hydrochloride may enter breast milk, where it may cause respiratory depression.

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

There are no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan;

Part VI. Table 7 – List of studies in post authorisation development plan

Study / activity	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of interim or final results
Non-interventional observational study	Characterise the demographics, and incidence of oxycodone hydrochloride abuse in Europe	Oxycodone hydrochloride abuse in Europe	Ongoing	The final study report was submitted to BfArM on 19 December 2016

The above study is not a condition of the marketing authorisation.

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

Major changes to the Risk Management Plan over time;

Part VI. Table 8 – Major changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
1.0	21 /12/009	-	First RMP that amalgamates all oxycodone hydrochloride formulations
2.0	13/08/2010	Routine update	
3.0	14/06/ 2011	**Important identified risks** 1.Use of oxycodone hydrochloride in patients with renal failure- classified as important identified risks	-
		2. Use of oxycodone hydrochloride in patients with hepatic impairment- classified as important identified risks	-
		3. Abuse, drug assisted crime- classified as important identified risks	Classified as important potential risk in the previous version of the

			RMP
		4. Overdose	Classified as important potential risk in the previous version of the RMP
		5. Drug withdrawal syndrome and physical dependence	Classified as important potential risk in the previous version of the RMP
		6. Interaction with alcohol- classified as important identified risks	-
		Important potential risk 1.Injection site reactions	Classified as important identified risk in the previous version of the RMP
		2. Prolongation of QTc	Classified as important identified risk in version 2 of the RMP
		3.Interaction with Gabapentin/ pregabalin	Removed from the important potential risks
		Important missing information Use in elderly population (for immediate release capsules, immediate release solution, orodispersible tablets and parenteral formulations)- was added as important missing information	-
4.0	21/12/ 2012	**Important identified risks** 1.Pre and post-operative oxycodone hydrochloride administration	Pre and post-operative oxycodone hydrochloride administration now included as risk factor of respiratory depression and ileus
		2.Hepatic enzyme elevation – removed as important identified risk	Doesn't meet definition of important for inclusion in RMP
		3.Use of oxycodone hydrochloride in patients with renal failure- removed as important identified risk	No risk meeting definition of important identified
		4.Use of oxycodone hydrochloride hydrochloride in patients with	Not considered important missing

		renal failure- removed as important identified risk	information, and no risk meeting definition of important identified
		5.Interaction with alcohol- removed as important identified risk	Not considered to meet definition of important risk for inclusion in RMP
		6.Overdose- separated in Accidental overdose and Intentional overdose	Separated to differentiate accidental and intentional overdose.
		7.Phenylketonuria - removed as important identified risk for oxycodone hydrochloride orodispersible tablets	Not considered to meet definition of important risk for inclusion in RMP
		8.Inborn errors of sugar Metabolism- removed as important identified risk	Not considered to meet definition of important risk for inclusion in RMP
		9.Respiratory depression in opioid naïve patients- included under the general term of respiratory depression	Not an important risk in its own right, but a risk factor for respiratory depression
		10. Psychological dependence included as an important identified risk	-
		Important potential risk 1.Tooth damage and Xerostomia- removed as important potential risk	Classified as important potential risk in version 3.0 of oxycodone hydrochloride RMP
		2.Prolongation of QTc - removed as important potential risk	Classified as important potential risk in version 3.0 of oxycodone hydrochloride RMP
		3.Injection site reactions- removed as important potential risk	Classified as important potential risk in version 3.0 of oxycodone hydrochloride RMP for oxycodone hydrochloride parenteral
		4.Off label use- removed as important potential risk	Classified as important potential risk in version 3.0 of oxycodone hydrochloride RMP
	21/12/ 2012	**Important missing information** 1.Use in children and adolescents- removed as important missing information	Not considered important missing information
		2.Use in the elderly population- removed as important missing information	Not considered important missing information
5.0	23/04/2013	**Important identified risks** 1.Use in patients with hepatic impairment 2.Use in patients with renal	Added as important risks in version 5.0 of oxycodone hydrochloride RMP

		impairment 3. Hypersensitivity 4. Use in patients with head injury (due to increased intracranial pressure) 5. Use of oxycodone in patients taking MAO inhibitors 6. Interactions with CNS depressants	
		Important identified risks 1.Prolongation of QTc	Added as important potential risk in version 5.0 of oxycodone hydrochloride RMP
6.0	30 July 2013	Updated the RMP to incorporate data on the ONF formulation and improve formatting. The following sections have been updated to incorporate ONF data: - Part I (Table1, Tables 3) Part II (SIII.1, SV.1, SV.5, SV.3.2.1, SVI.3.I)	
7.0	01 September 2014	The details of the non-interventional observational study have been updated to reflect the most current study title and timelines. The following sections have been updated: - Part III (Table 17 and Table 18) - Part V (Section V.1 and Section V.3) - Part VI (Section VI.1.2 Table 2, Section VI.1.4 Table 3 and Section VI.2.6 Table 7) - Annex X	
8.0	16 February 2015	The proposed additional risk minimisation activity of 'Opioid Aware' has been deemed not necessary by the MEB (Netherlands Regulatory Authority) as there has been no change in the parameters of the risk to which it applied and therefore additional risk minimisation activites are not considered appropriate.	
9.0	12 April 2017	The details of the non-interventional PASS study looking at oxycodone abuse in Europe in particularly UK and Germany.	