Oxycodone hydrochloride formulations risk management plan (RMP) in the EU

Active substance(s) (INN or common name):	Oxycodone hydrochloride
Pharmaco-therapeutic group (ATC Code):	Natural opium alkaloids N02A A05
Name of Marketing Authorisation Holder or Applicant:	[redacted] Napp Pharmaceuticals Ltd (UK) [redacted]
Number of medicinal products to which this RMP refers:	Five (5)
Product(s) concerned (brand name(s)):	[redacted]

Data lock point for this RMP	12 April 2017	Version number	9.0
Date of final sign off	07 July 2017		

Part I: Product(s) Overview

Part I. Table 1 -Administrative information on the RMP

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	14 Dec 2012	Version 4.0
	SII Non-clinical part of the safety specification	07 Jul 2017	Version 9.0
	SIII Clinical trial exposure	14 Dec 2012	Version 4.0
	SIV Populations not studied in clinical trials	30 Jul 2013	Version 6.0
	SV Post-authorisation experience	07 Jul 2017	Version 9.0
	SVI Additional EU requirements for the safety specification	07 Jul 2017	Version 9.0
	SVII Identified and potential risks	07 Jul 2017	Version 9.0
	SVIII Summary of the safety concerns	02 May 2013	Version 5.0
Part III Pharmacovigilance Plan		07 Jul 2017	Version 9.0
Part IV Plan for post-authorisation efficacy studies		30 Jul 2013	Version 6.0
Part V Risk Minimisation Measures		07 Jul 2017	Version 9.0
Part VI		07 Jul 2017	Version 9.0

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Summary of RMP			
Part VII Annexes	**ANNEX 2** Proposed Core Safety Profile (CSP)	07 Jul 2017	Version 9.0
	ANNEX 3 Worldwide marketing status by country	14 Dec 2012	Version 9.0
	ANNEX 4 Synopsis of clinical trial programme	Not applicable	
	ANNEX S Synopsis of pharmacoepidemiological study programme	Not applicable	
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	
	ANNEX 7 Specific adverse event follow-up forms	14 Dec 2012	Version 4.0
	ANNEX 8 Protocols for studies in Part IV	Not applicable	
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	
	ANNEX 10 Details of proposed additional risk minimisation activities	16 February 2015 (Opioid Aware removed)	Version 8.0
	ANNEX 11 Mock up examples	Not applicable	
	ANNEX 12	Not applicable	

QPPV name

QPPV signature

Contact person for this RMP

E-mailaddress or telephone number of contact person

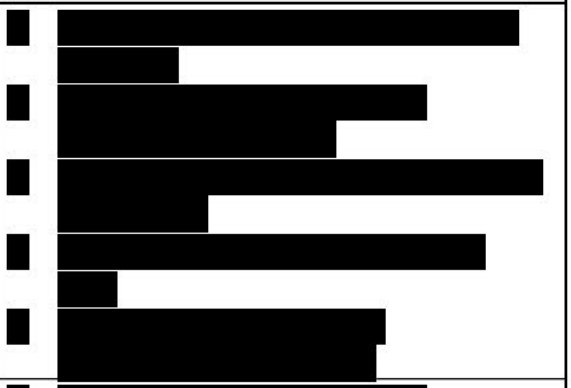
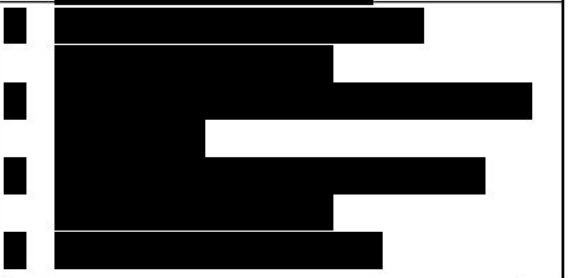
Overview of versions:

Version number of last agreed RMP:

Version number	8.0
Agreed within	Mutual Recognition Procedure / Decentralised

Current RMP versions under evaluation:

Part I. Table 2 - Current RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
4.0	1. 17 Dec 2012 2. 19 Feb 2013 3. 28 Feb 2013 4. 5 Feb 2013 5. 13 Mar 2013	
5.0	1. 7 May 2013 2. 14 May 2013 3. 22 May 2013 4. 26 Apr 2013	
6.0	1. 19 Nov 2013 2. 19 Nov 2013 3. 19 Nov 2013 4. 19 Nov 2013 5. 22 Jan 2014 6. 14 Oct 2013 7. 20 May 2014 21 May 2014 6 May 2014 Mar 2014 8. 5 May 2014 Mar 2014 12 May 2014 9. 5 Feb 2014 June 2014 Mar 2014 10.19 May 2014 11.30 June 2014	

7.0	1. 11 September 2014 (initial submission) 17 October 2014 (resubmission due to validation comments)	1. Type II variation to introduce (or update) RMP in EU via work sharing procedure: DE/H/XXXX/WS/0219 RMS – DE [redacted] UK
8.0	1. 1 April 2015	1. Type II variation to update RMP in EU via work sharing procedure: DE/H/XXXX/WS/0219 RMS – DE [redacted] UK

Part I. Tables 3 - Product information

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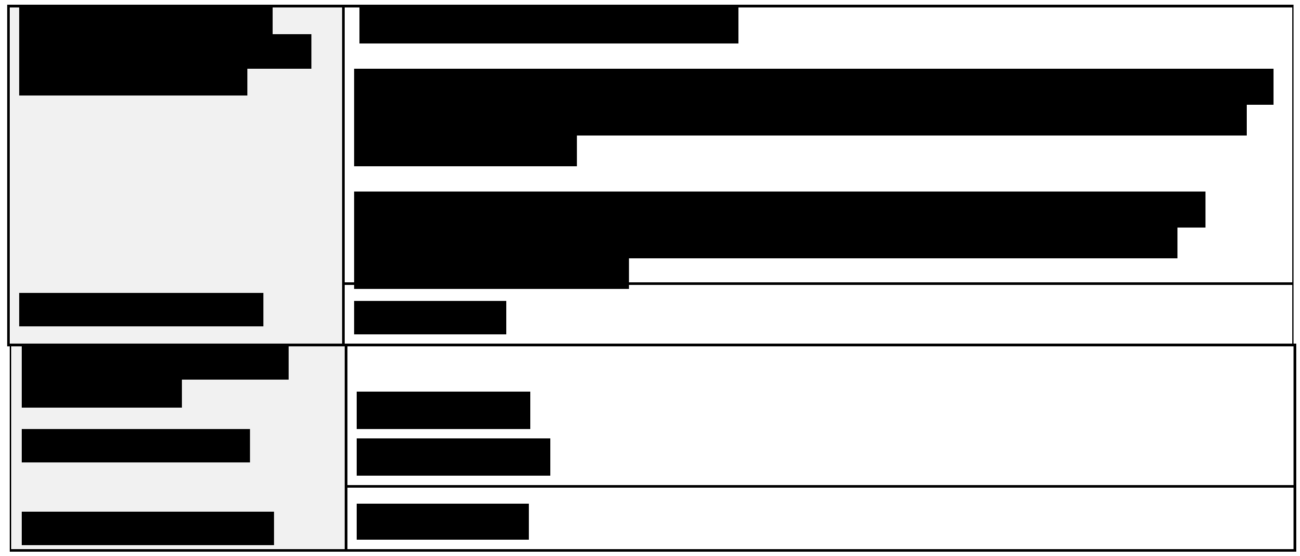

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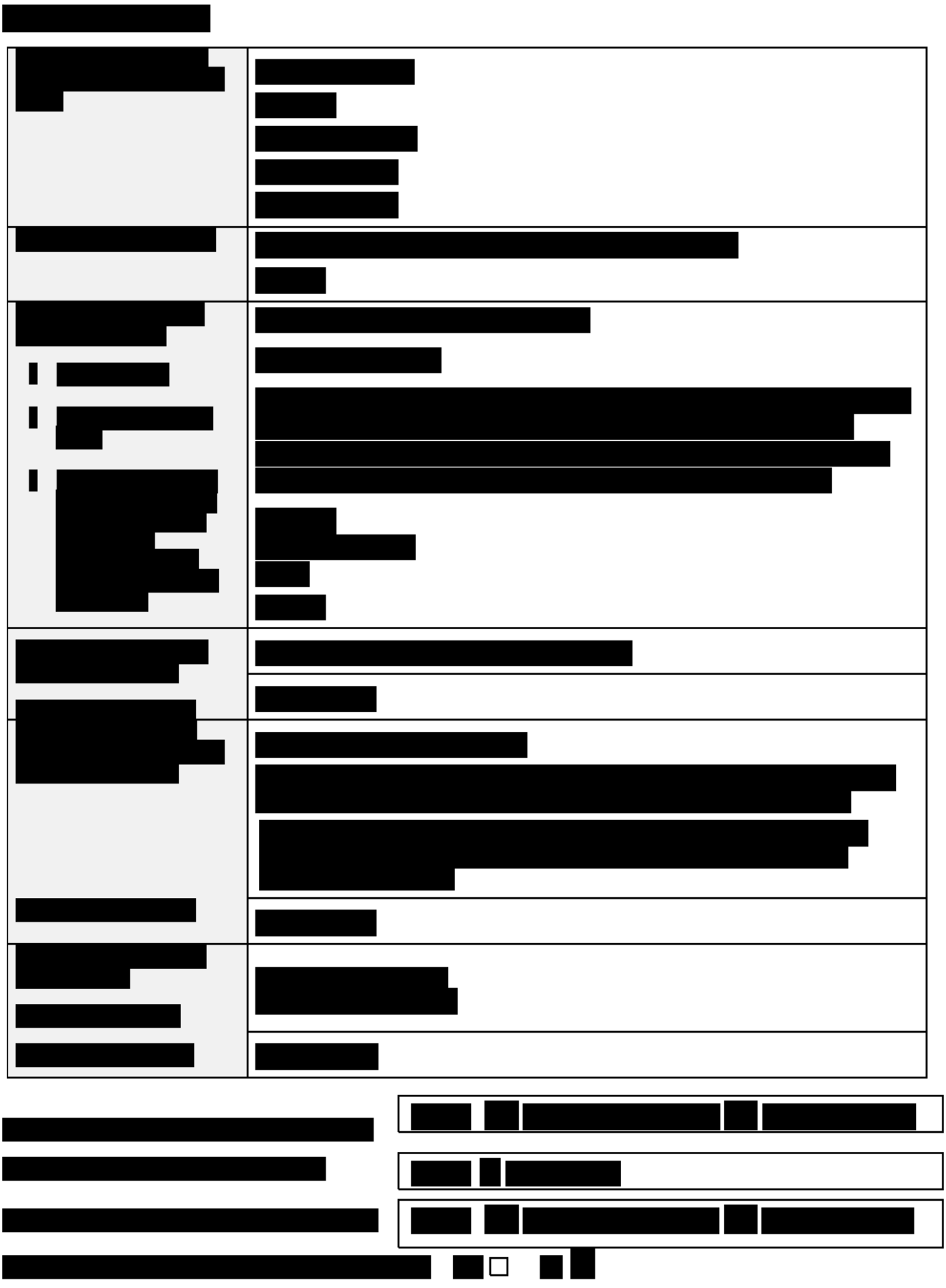

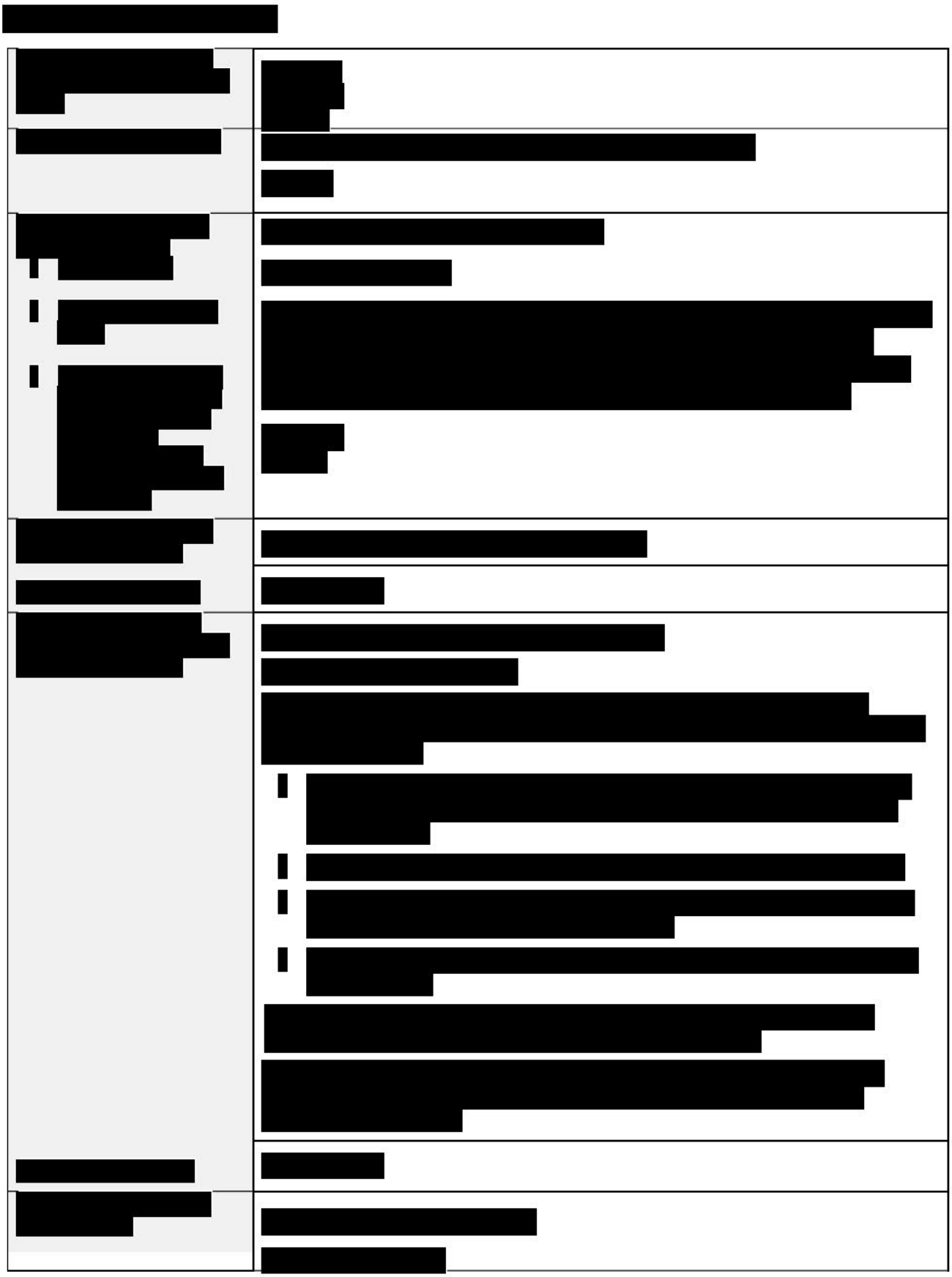

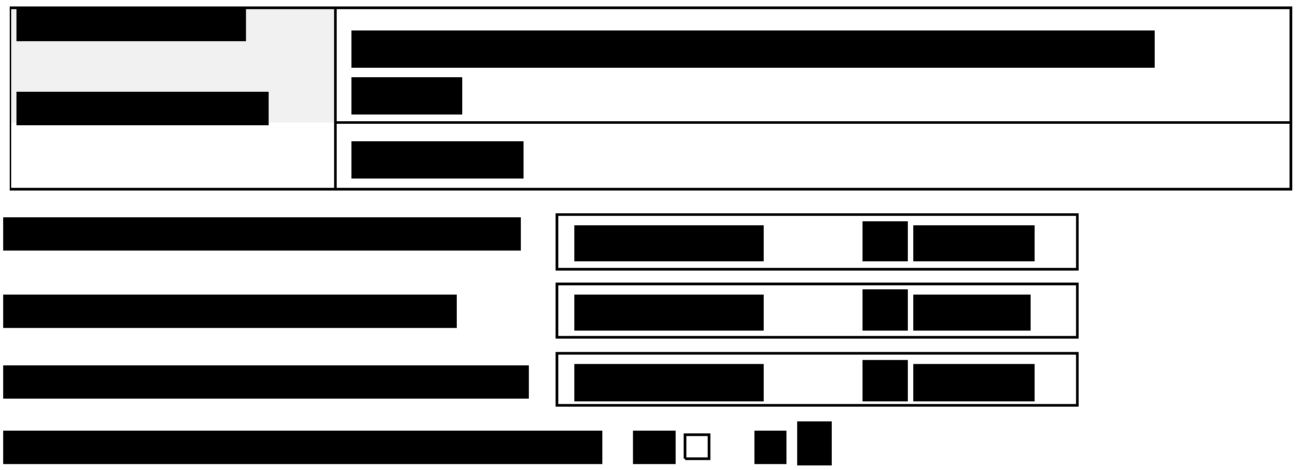

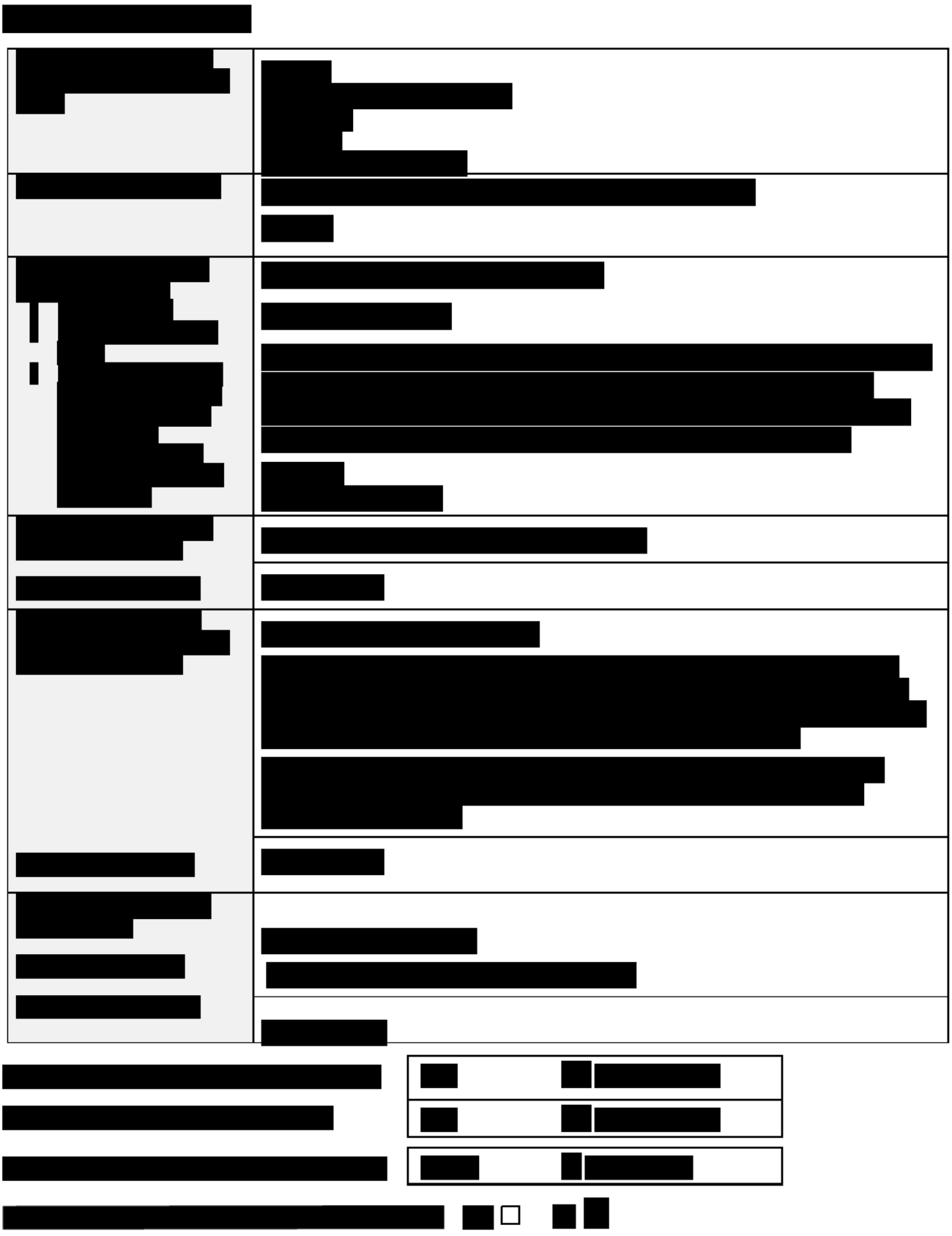

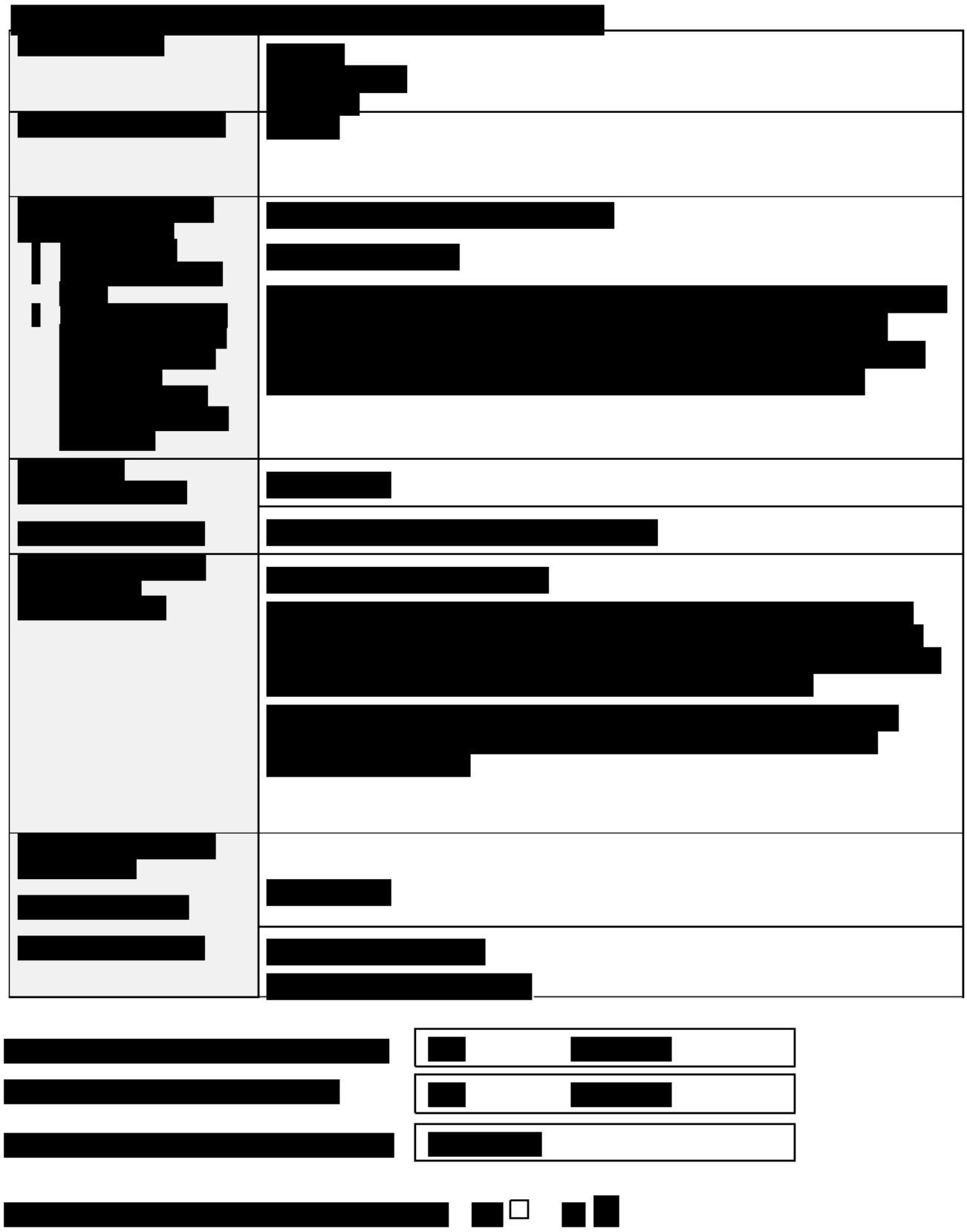

Part II: Module SI - Epidemiology of the indication(s) and target population

Oxycodone is a semi-synthetic opioid derived from the opium alkaloid thebaine, and shares certain physicochemical characteristics and opioid receptor agonist activity with morphine and other similar opioids. The principal pharmacological actions are analgesia and effects on the central nervous system and smooth muscle. Oxycodone-containing products are currently used clinically in many countries for treatment of moderate to severe pain.

Pain is a subjective symptom and is affected by various psychological factors[1]. It is estimated globally that 1 in 5 adults suffer from pain and 10% of the world's population are newly diagnosed with chronic pain each year [2]. Like the global incidence, one in five Europeans suffers from moderate to severe chronic pain [3, 4] and many of the affected are elderly [5].

Due to the differences in the target population, the epidemiology of non-malignant and cancer pain are described separately below. Broadly pain can be classified as nociceptive and neuropathic. The nociceptive pain can be somatic and visceral [6].

Non-Malignant Pain

SI.1 Epidemiology of the disease

The prevalence of chronic non-malignant pain is estimated to be between 12-25% and varies across regions: 12-25% in the US and 20% in Europe [2]. The available data on moderate-to-severe chronic non-malignant pain suggests a one month prevalence estimate of 19% [3].Chronic non-cancer pain can include both nociceptive and neuropathic pain, typical locations being upper and lower back, head and neck, and joints [7,8]. The lifetime prevalence of chronic pain in Europe based on specific pain conditions is 6-9% for upper and lower chronic back pain, 5% for chronic neck pain [9]. Across Europe the reported prevalence of chronic non-malignant pain is highest in Norway, Poland and Italy and lowest in Spain. The most common source of pain reported was chronic back pain (24%) [10].

- Demographics of the target population – age, sex, race/ethnic origin.

It is estimated that about 18% of young adults experience non-malignant pain which increases to 30-65% in adults aged 55-65 years and 25-55% in adults over 85 years [13].

It is difficult to establish a correlation between gender and the occurrence of non-malignant pain as this varies depending on the medical condition. However, a survey conducted amongst individuals with non-malignant chronic pain revealed that women experienced more multiple localizations of pain and reported pain in the neck, shoulder, arm, and thigh to a greater extent than men [14].

- Main treatment options

Paracetamol is the first line analgesic for mild to moderate long-term and osteoarthritic non-malignant pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are used generally in rheumatoid arthritis, followed by opioid analgesics in severe pain, or when other analgesics fail to relieve pain. The most common opioids used in the elderly are: morphine, codeine and oxycodone [13].

- Mortality and morbidity (natural history)

Chronic non-cancer pain is a significant burden on public health. The impact of uncontrolled chronic pain is substantial both for the patient and society and often leads to a decline in the quality of life and disability [16]. In the adult population, the experience of pain represents a substantial burden both for the afflicted individual and society [17] with negative impacts on quality of life [18], healthcare resource utilization [18], workforce status and productivity [19].

SI.2 Concomitant medication(s) in the target population

The majority of chronic pain patients are aged 65 and over and will have co-morbid medical conditions requiring multiple different concomitant medications.

SI.3 Important co-morbidities found in the target population

Patients with chronic pain present with depression, anxiety, and somatisation disorder more often than in the general population. Studies evaluate that the co-morbidity of major depression in chronic pain population ranged from 15% to 56%, which is higher than the occurrence of major depression within the general population which ranged from 5% to 10%. Likewise, the occurrence of somatisation disorder ranged from 20% to 31% in chronic pain population compared to the 1-4% in the general population[16].

Cancer Pain

SI.4 Epidemiology of the disease

- Incidence and prevalence

The aetiology of pain in cancer patients varies: pain can be caused directly by tumour involvement, related to the cancer, related to anticancer treatment or can be caused by a concurrent disorder [11]. Pain is one of the most common symptoms of cancer and affects an estimated third of patients receiving anti-cancer treatment, increasing to two-thirds in patients with advanced disease [12] with higher prevalence in the following types of tumours: head and neck (67-91%), prostate (56-94%), uterine (30-90%), genitourinary (58-90%), breast (40-98%) and pancreatic (72-85%) [13]. A large–scale computer-assisted telephone survey was undertaken to explore the prevalence, severity, treatment and impact of chronic cancer pain. The survey, was conducted in 15 European countries and Israel, and found that, on the country level, cancer types with the highest pain prevalence were reported in Switzerland, Israel, Italy, UK, France and Ireland [3].

- Demographics of the target population – age, sex, race/ethnic origin.

Stratification of the incidence of cancer by ethnicity and age groups was performed by Cancer Research UK and the National Cancer Intelligence Network. The results showed that liver cancer was between 1.5 and 3 times more likely in Asians than in Whites for all ages. For cervical cancer, the risk was significantly higher in Asian females aged 65 and over but lower for individuals under the age of 65 compared with the white ethnic group. Black males of all ages were more likely to have a diagnosis of prostate cancer (ratios between 1.1 and 3.4) compared to White males. The report also shows that females with breast cancer under 65 years of age from Asian and Black ethnic groups have a lower survival rate than those from White ethnic groups [15].

- Risk factors for the disease

Since pain is a subjective symptom the risk factors associated with the occurrence of pain rely on the underlying medical condition of the patient.

- Main treatment options

For cancer pain, the WHO three step analgesic ladder guideline is the mainstay in pain management [11]. The first step consists of Non-opioids (paracetamol, aspirin, NSAIDs) with or without an adjuvant, step 2 consists of a weak opioid (codeine, dihydrocodeine, dextropropoxyphene) with or without an adjuvant and step 3 consists of a strong opioid (morphine, diamorphine, fentanyl, hydromorphone, methadone and oxycodone) with or without an adjuvant.

- Mortality and morbidity (natural history)

The major cause of morbidity and mortality is bone metastases due the tumour that induces significant skeletal remodelling, fractures, pain, and anaemia [20].

SI.5 Concomitant medication(s) in the target population

Adjuvant analgesics are drugs used in combination with opioids. Examples of adjuvants include; NSAIDs (ibuprofen, diclofenac), steroids (dexamethasone), antidepressants and anticonvulsants (carbamazepine, nortriptyline, gabapentin) [21].

Treatment for the particular type of cancer such as chemotherapy, radiotherapy, biologics and immunotherapy are used, as well as various treatments for the side effects of the cancer therapy.

SI.6 Important co-morbidities found in the target population

Co-morbidities in cancer pain patients can be related to the malignancy itself, to the effects of cancer treatment or to an unrelated underlying condition such as osteoarthritis.

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[10.] *Pain in Europe- a Report, last updated May 2011. http://www.paineurope.com/healthcare-professional/pain-surveys/pain-in-europe-survey/publication-for-download.html*

[11.] *Cancer pain relief, second edition- WHO 1996*

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Part II: Module SII - Non-clinical part of the safety specification

Part II. SII. Table 1 - Non-Clinical part of the safety specification

Key Safety findings (from non-clinical studies)	Relevance to human usage
General Toxicology: Although formal acute lethality toxicity studies have not been conducted in animals, the profile of acute adverse effects associated with sub lethal doses of oxycodone in animals has been observed in conjunction with the initiation of other, single- and multiple-dose studies. These studies have shown that oxycodone hydrochloride exhibits similar pharmacotoxic effects to those found with other opioids, including respiratory and CNS depression. The published information on oxycodone hydrochloride toxicity after administration to animals is limited to acute studies using parenteral dosing routes. The median lethal dose (LD_{50}) of oxycodone hydrochloride ranged from 275 to 340 mg/kg after subcutaneous administration in mice[1,2]. The lowest lethal dose has been reported to be 200 mg/kg after subcutaneous administration in mice[1]. Repeat dose toxicity studies in rats, dogs and rabbits with orally administered oxycodone hydrochloride revealed pharmacotoxic effects similar to those expected of an opioid. There were no drug-related histopathological effects in the liver, any other organ, or serum chemistry changes indicative of organ toxicity. The Maximum Tolerated Doses (MTD) of 25 mg/kg/day in rats and 8 mg/kg/day in dogs caused significant pharmacological effects but no drug-related organ toxicity has been identified to date. [1] Aubry P., Claude P., Lebel M, Leblanc M and Truchaud M. Étude pharmacologique clinique humaine et vétérinaire d'un nouvel analgésique le pectinate de dihydrone. Anesth. Anal., 1951;8:663-672. [2] Oelkers H.A. Vergleichende untersuchungen über die Wirkungsstärke des morphins seiner derivate. I Mitteilung Naunyn-Schmiedebergs Archiv. fur experiment Path. u Pharmakol., 1940; 194:296-307.	There is substantial therapeutic experience with the different formulations of oxycodone hydrochloride. Oxycodone hydrochloride has a similar side effect and toxicity profile to other opioid analgesics and there is no special health hazard for humans based on conventional studies of acute and repeated dose toxicity.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mutagenicity: As with other opioids, oxycodone hydrochloride has been associated with genotoxicity in some *in vitro* assays (the mouse lymphoma and human lymphocyte chromosomal aberration, although this latter finding was not replicable with oxycodone hydrochloride) at high concentrations but, was without effects in the bacterial mutagenicity assay with and without metabolic activation or in an *in vivo* mouse micronucleus study, even at lethal doses. Further, oxycodone hydrochloride was genotoxic in the *in vitro* mouse lymphoma assay after incubation with microsomes obtained from rats. However, *in vitro* mouse lymphoma studies with the closely related opioid, hydrocodone, and the opioid antagonist, naltrexone, utilizing human S9 did not result in genotoxic effects[1,2,4,4,5]. Finally, it is observed that other opioids and related drugs, that have long clinical experience, have been reported in the literature or found in studies conducted by the sponsor to be positive in *in vitro* mammalian genotoxicity assays, including morphine[6.7 8 9.10.11], codeine[12], hydrocodone[13], hydromorphone[14], naloxone[15,16,17], naltrexone[3,4,5], and meperidine [pethidine][7,11]. In studies conducted by the sponsor, codeine, hydrocodone, hydromorphone, and naltrexone each were associated with genotoxicity in the mouse lymphoma assay after incubation with rat S9. [redacted] [3]Hew, K. W., Cifone, M. A. and Lawlor, T. Differential S-9 Activation of Hydrocodone Bitartrate and Naltrexone Hydrochloride with Human Liver S-9 and Rat Liver S-9 in the Mouse Lymphoma Forward Mutation Assay. Toxicologist 84 (S-1):454, 2005. [redacted] [6]Badr, F. M. & Rabouh, S.A. Effects of Morphine Sulfate on the Germ Cells of Male Mice. Teratogenesis, Carcinogenesis, and Mutagenesis, 1983, 3:19-26. [7]Das R.K. & Swain, N. Mutagenic evaluation of morphine sulfate and pethidine hydrochloride in mice by the micronucleus test. Indian J. Med. Res., 1982, 75:112-117. [8]Kabarity A. et al. Effect of morphine sulphate on mitosis of allium cepa l. root tips. Biologia Plantarum (Praha), 1974, 16:275-282. [9]Sawant S.G. & Couch, D.B. Induction of micronuclei in murine lymphocytes by morphine. Envir. Molec. Muta., 1995, 25: 279-283. [10]Shafer D.A., Yiping, X., and Falek, A. Detection of opiate-enhanced increases in dna damage, hprt mutants, and mutation frequency in human hut-78 cells. Envir. Molec. Muta., 1994, 23:37-44. [11]Swain N. et al., Cytogenetic assay of potential mutagenicity in vivo of two narcotic analgesics. Mut. Res., 1980, 78:97-100. [redacted]	In all assays doses/exposure concentrations used in these studies were beyond those likely to be attained in humans, even for patients receiving very large doses. The metabolism of oxycodone hydrochloride is similar in mice and humans. The lack of genotoxicity in mice, despite plasma concentrations of oxycodone hydrochloride and its metabolites that were hundreds of times the concentrations which would likely be found in human patients (~1400-, 1300-, and 2700-times the C_{max} values for oxycodone, noroxycodone, and oxymorphone, respectively, in humans given a 20 mg dose) suggests that oral administration of this drug to humans is unlikely to pose a genotoxic risk. Overall, the findings suggest that *in vitro* mammalian cell genotoxic responses may reflect a class effect of opioids which are of minimal, if any, relevance to humans.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenicity: Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats1. Oxycodone did not increase the incidence of tumors in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone. [redacted]	Overall the data indicates that oxycodone poses minimal, if any, risk for human carcinogenicity.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Developmental Toxicity:	
Oxycodone hydrochloride had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone hydrochloride did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual foetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual foetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/d group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the foetal findings were considered likely a secondary consequence of severe maternal toxicity.	On a body weight basis, the maternal MTD which was without early embryonic effect in the rat, 8 mg/kg, is equivalent to a human (70 kg) dose of 560 mg; and for the maternal rabbit 125 mg/kg MTD, the human dose equivalent is 9375 mg.
In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses ≥ 2 mg/kg/d compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/d dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/d based on body weight effects seen at 6 mg/kg/d). There were no effects on the F2 generation at any dose in the study.	On a body weight basis, the human (70 kg) equivalent dose for the maternal dose that caused a reduction in the F_1 offspring body weight is 420 mg. The human equivalent dose for the maternal dose in this study that resulted in no effect on offspring is 140 mg.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Local Tolerance: Parenteral Formulations Local tolerance was examined using 10 mg/mL, 25 mg/mL, and 50 mg/mL formulations in rats and rabbits. This included intravenous, paravenous, intra-arterial, subcutaneous, intramuscular acute, single dose, regimens as well continuous sub chronic infusion by the clinically indicated intravenous and subcutaneous routes. Rats were used for continuous infusion of the 10 mg/mL formulation; however, rabbits were used to assess the local tolerance after continuous infusion for the higher strength formulations due to anticipated toxicity in rats given the higher strengths (i.e. the formulations were fixed concentrations and dose therefore had to be adjusted by adjusting infusion rate; however the infusion rates could not be reduced low enough for use in rats because of practical concerns, such as clogged cannulas/infusion tubing and, at higher rates the resultant mg/kg dose to a small animal such as the rat would have been too high for the animals to tolerate). At the doses used in the acute injection studies, no indication of local injection site irritation due to oxycodone hydrochloride formulation treatment was evident except at the two highest doses (~2-4 mg/kg) in the acute rat intramuscular study, using the 10 mg/mL formulation and a dilution at 5 mg/mL, but not in rabbits with the higher the concentration formulations. However, it is noted that the intramuscular dose is not a clinically-indicated route of administration. At the doses used in the 4-hr to 7-day infusion studies in rats, no indication of local injection site irritation was evident using the 10 mg/mL formulation. In rabbit studies assessing 25 and 50 mg/mL formulations, no irritation was found after acute dosing or after 24 hours of infusion. At 96 hours after dosing, there was an indication of some irritative effects; whereas there appeared to be greater local irritative effects after 14 days of continuous infusion, particularly by the intravenous route. The maximum doses administered in the studies were considered the maximum dose that could be administered for each dose route to each species. The highest dosage used in the 14-day infusion study in rabbits was about 12 mg/kg/day (minor dosage variance was related to body weight variance of animals in treatment groups). Oral Formulations Studies of oral oxycodone hydrochloride in animals to specifically evaluate its local gastrointestinal tolerance have not been conducted owing to the length of clinical experience with the drug substance. However, general toxicity studies of varying duration in mice, rats, rabbits, and dogs revealed no evidence of local injury associated with oral ingestion of oxycodone solutions of varying concentrations (mice, rats, rabbits) or oxycodone in gelatin capsules (dogs).	Local venous or subcutaneous irritation is not expected from oxycodone hydrochloride parenteral formulations when administered as indicated. The starting doses for human use as an infusion are 48 mg/day (2 mg/hr) and 7.5 mg/day for the intravenous and subcutaneous routes, respectively. Assuming a 70 kg reference person, this equates to 0.7 and 0.1 mg/kg/day for the i.v. and subcutaneous routes, respectively. Thus, the mg/kg/day doses used in the infusion studies in rabbits are approximately 17- (i.v.) and 120- (subcutaneous) times the starting daily human dose. The pattern of metabolites was similar to that found after oral dosing, where noroxycodone was detected at much higher concentrations than oxymorphone. Oral administration of oxycodone hydrochloride is not expected to cause local gastrointestinal intolerance.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Safety Pharmacology: The qualitative primary pharmacodynamic profile of oxycodone hydrochloride is the same as similar opioid analgesics on a variety of physiological parameters and is a more potent analgesic than morphine in a variety of models that are recognized as indicators of analgesic activity[1,2,3]. Specific areas investigated in the published literature are discussed in the sections that follow. [1]Doteuchi M., Sato H, Otani K, Koshida H, Hirono S, Hirose F, Koyabu K, Ryu T, Takemoto Y and Yoshimura K. Pharmacological studies of oxycodone hydrochloride 1. antinociceptive effect and general pharmacology. Pharmacometrics. 1995; 49:257-273 [2]Swedberg M.D.B. The mouse grid-shock analgesia test: pharmacological characterization of latency to vocalization threshold as an index of antinociception. J Pharmacol. Exper. Ther., 1994; 269; 1021-1028. [3]Reynoldson J.A. and Bentley G.A. The effect of narcotic analgesics and their antagonists on conditioned avoidance in the rat. Clin. & Exper. Pharmacol. and Physiol., 1974; 1:503-518.	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Addiction Liability: In a rat assay of drug discrimination, oxycodone hydrochloride had similar subjective effects to the training drug fentanyl and the dose of oxcycodone resulting in 50% of the maximum response (ED_{50}) to fentanyl was below the analgesic dose[1]. In addition rats that are trained to self-administer a strong narcotic[2] will self administer oxycodone hydrochloride as a substitute. Data from studies using monkeys[2] indicate that oxycodone hydrochloride has the potential for physical dependence. In the first of these studies, a dose of 1 mg/kg was administered to monkeys every 4 hours for 21 days. Abrupt withdrawal resulted in an abstinence syndrome resembling that of morphine, but of intermediate intensity only. Administration of oxycodone at 1 mg/kg suppressed the signs of morphine abstinence for 4 hours. Finally, this work found that fairly complete morphine substitution was obtained with an oxycodone dose of 1.33 mg/kg administered every 3 hours in morphine-dependent monkeys. A previous report (Coop, 2002) provides data showing complete substitution for morphine by 0.3 mg/kg of oxycodone hydrochloride. In the second study by Beardsley and colleagues (2004) oxycodone administered at 3 or 0.75 mg/kg completely suppressed signs indicative of dependence (retching, restlessness, rigid abdominal muscles and vocalization when palpated). [1]Meert T.F. and Vermeirsch, H.A. A preclinical comparison between different opioids: antinociceptive versus adverse effects. Pharmacology Biochemistry and Behavior 2005;80(2):309-326. [2] Beardsley P.M. et al. Discriminative stimulus, reinforcing, physical dependence, and antinociceptive effects of oxycodone in mice, rats, and rhesus monkeys. Experimental and Clinical Psychopharmacology, 2004;12(3):163-172. [3]Coop A. Biological evaluation of compounds for their physical dependence potential and abuse liability. XXXL. In Dewey, W.L. and Harris, L.S. Problems of Drug Dependence, 2002: Proceedings of the 64th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc., NIDA Research Monograph 183, pp. 152-226.	Oxycodone hydrochloride has an abuse and addiction profile similar to other strong opioids[1]. [1] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies.

Key Safety findings (from non-clinical studies)	Relevance to human usage
aPostural Muscle Rigidity: Oxycodone hydrochloride causes postural rigidity in rodents[1,2,3,4,5,6,7]. Like other opioids, oxycodone hydrochloride increases sensitivity of *in vitro* muscle preparations to acetylcholine, this effect may be mediated by alteration of cholinesterase activity[7,8]. [1]Biberfeld J. Zur Kenntnis der Gewöhnung. IV. Über gewöhnung an kodeinderivate (Eukodal u. Parakodin). Biochem. Ztschr, 1920; 111:91-104. [2]Small L.F., Eddy N.B., Mosettig E and Himmelsbach C.K. Studies on drug addiction with special reference to chemical structure of opium derivatives and allied synthetic substances and their physiological action. Pub. Health Rep., 1938; Supplement 138:22-31. [3]Oelkers H.A. Vergleichende untersuchungen über die Wirkungsstärke des morphins seiner derivate. I Mitteilung Naunyn-Schmiedebergs Archiv. fur experiment Path. u Pharmakol., 1940; 194:296-307. [4]Kreuger H., Eddy, N.B., and Sunwalt, M. Pharmacology of opium alkaloids. Federal Security Agency, Public Health Reports, USPHS Supplement 165, US Government Printing Office, 1943:969-975. [5]Roesch, E. Über den antagonismus von n-allynormorphin zu morphin und eukodal am Kreislauf von wachen Hunden. Arch. exper. Path. u Pharmakol., 1955; 226:518-526. [6]Meert T.F., Vermeirsch H.A. A preclinical comparison between different opioids: antinociceptive versus adverse effects. Pharmacol Biochem Behav. 2005 Feb;80(2):309-26. 2005. [7]Dastugue G., Bresson A., and Gandour M. Recherches sur le mécanisme de l'action sensibilisante de la dihydro-oxycodéinone vis-à-vis de l'acétylcholine. Bull. Soc. Pharmacol. 1940; 47: 144-154. [8]Sollmann T. A Manual of Pharmacology And Its Application To Therapeutics and Toxicology. Philadelphia: WB Saunders, 1957, pp. 285-294.	Opioids can cause muscle rigidity in man as well as animals.[1,1a] The clinical implications of *in vitro* alteration in cholinesterase activity are unknown since the effect appears to be minor *in vivo*[2]. [1]Reisine, T. and Pasternak, G. Opioid Analgesics and Antagonists. In Hardman, J.G. et al., Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th Edition. NY: McGraw Hill, 1996. pp. 521-555. [1a] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies. [2]Hazard R and Delga J. Action de la dihydro-oxycodéinone (Eucadol) sur la cholinésterase du singe et du cérveau chez le cobaye normal ou intoxiqué par le diisopropyl-fluorophosphonate (D.F.P.). Arch. Int. Pharmacodyn., 1951; XC: 116-123.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Respiratory Depression: The published literature indicates that oxycodone hydrochloride has effects qualitatively similar to those of other opioids including morphine on respiration[1, 2, 3, 4, 5, 6]. Biberfeld et al[1] observed respiratory depression in a variety of species following administration of many opioids including oxycodone hydrochloride. Symptoms of respiratory depression were decreased inspiratory ventilation, reduced breathing frequency, and diminished tidal volume[7,8] that can lead to death by anoxia. However, severe opioid induced respiratory depression usually occurred at doses that are higher than needed for adequate analgesia[9]. Myers et al[10] reported that oxycodone hydrochloride caused bradypnea in cats. Doteuchi et al[11] observed decreased respiratory rate in anaesthetised rats following intraduodenal administration of 3 or 10 mg/kg of oxycodone hydrochloride but not at 1 mg/kg. In the same model, morphine decreased the respiratory rate at 10 mg/kg, but not at lower doses. Additionally, Doteuchi et al[11] showed that both drugs decreased the respiratory rate and minute volume in the anaesthetised cat at doses of 1 and 3 mg/kg but not at 0.1 or 0.3 mg/kg. Yoshimura et al[12] observed a transient inhibition of the respiratory movement during the slow wave sleep stages in 3 of 4 dogs at 10 mg/kg and in 6 dogs at 30 mg/kg of oxycodone hydrochloride, similar responses were also observed at 10 to 30 mg/kg of morphine. Acute and subchronic oral toxicity studies (through 3-months in rats and dogs) indicate that respiratory depression following high doses of oxycodone hydrochloride is an extension of its pharmacological activity. [1]Biberfeld J., Zur Kenntnis der Gewöhnung. IV. Über gewöhnung an kodeinderivate (Eukodal u. Parakodin). Biochem. Ztschr. 1920; 111: 91-104. [2]Small L.F., Eddy N.B., Mosettig E., and Himmelsbach C.K. Studies on drug addiction with special reference to chemical structure of opium derivatives and allied synthetic substances and their physiological action. Pub. Health Rep. 1938; Supplement 138: 22-31. [3]Oelkers H.A. Vergleichende untersuchungen über die Wirkungsstärke des morphins seiner derivate. I Mitteilung Naunyn-Schmiedebergs Archiv. fur experiment Path. u Pharmakol. 1940; 194: 296-307. [4]Kreuger H., Eddy N.B., and Sunwalt M. Pharmacology of opium alkaloids. Federal Security Agency, Public Health Reports, USPHS Supplement 165, US Government Printing Office, 1943:969-975. [5]Roesch E. Über den antagonismus von n-allynormorphin zu morphin und eukodal am Kreislauf von wachen Hunden. Arch. Exper. Path. Pharmakol., 1955; 226: 518-526. [6]Meert T.F., Vermeirsch H.A. A preclinical comparison between different opioids: antinociceptive versus adverse effects. Pharmacol Biochem Behav. 2005; 80(2): 309-26. [7]Olsen G.D., Wilson, J.E., Robertson, G.E., 1981. Respiratory and ventilatory effects of methadone in healthy women. Clin. Pharmacol. Ther. 29, 373–380. [8]Silverman, D.A., Nettleton, R.T., Spencer, K.B., Wallisch, M., Olsen, G.D. S methadone augments R-methadone induced respiratory depression in the neonatal guinea pig. Respir. Physiol. Neurobiol. 2009, 169, 252–261. [10]Myers, G.N. An investigation on the pharmacological action of some new substitutes for morphine and heroin. Brit. Med. J. 1933; 2: 282-287.	Respiratory depression is a known adverse effect of full mu-agonist opioids, including oxycodone hydrochloride and may be additive with other medications that have a depressant effect on the respiratory centre[1,2]. [1] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies. [2]Wilson W and Benumof J Miller's Anesthesia Chapter 17, 679-722 Sixth Edition 2005 Elsevier Churchill Livingstone.
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Key Safety findings (from non-clinical studies)	Relevance to human usage
Respiratory Depression Continued: [11]Doteuchi, M., Sato, H., Otani, K. Koshida, H., Hirono, S., Hirose, F., Koyabu, K., Ryu, T., Takemoto, Y., and Yoshimura, K., Pharmacological Studies of Oxycodone Hydrochloride 1. Antinociceptive Effect and General Pharmacology Pharmacometrics.1995; 49: 257 - 273 [12]Yoshimura, K., Horiuchi, M., Inoue, Y., and Doteuchi, M. Pharmacological Studies of Oxycodone Hydrochloride 2. Polygraphic Analysis in Conscious Dogs. Pharmacometrics. 1995; 49: 275-286.	

Key Safety findings (from non-clinical studies)	Relevance to human usage
General CNS Depression/Gross Behaviour: Oxycodone hydrochloride has narcotic/motor depressive effects in frogs, dogs, rabbits, mice, and rats[1, 2, 3, 4, 5]. Poyhia and Kalso[6] found CNS depression was apparent after subcutaneous and intraperitoneal dosing in Wistar rats and depression was more profound with oxycodone hydrochloride than with morphine. The CNS depressive effects caused by intraperitoneal dosing were reversed by naloxone. Meert and Vermeirsch[7] assessed the ataxic effects of intraperitoneal opioids, determining that all opioids produced ataxia, with oxycodone hydrochloride being more potent than morphine (ED_{50} values: 5.04 and 11.51 mg/kg, respectively). Doteuchi et al[8] compared gross behaviour and spontaneous motor activity of mice administered oral doses of morphine and oxycodone hydrochloride. Oxycodone hydrochloride at a dose range of 3–30 mg/kg resulted in behaviour associated with opioid analgesic activity (e.g., increased muscle tone, mydriasis, general hypersensitivity, hyperactivity and/or decreased food consumption). Spontaneous motor activity was increased in mice administered oral doses of 10–30 mg/kg oxycodone hydrochloride while similar increases in activity were observed with morphine after doses of 100 mg/kg. Yoshimura et al[9] observed that oral administration of 10 mg/kg of oxycodone hydrochloride (but not 1 or 3 mg/kg) resulted in slight sedation in dogs and moderate sedation was observed after a dose of 30 mg/kg. Morphine at 10 and 30 mg/kg caused similar degrees of sedation in dogs to those found with oxycodone hydrochloride. Ishida et al[10] found that 3 mg/kg of oral oxycodone hydrochloride led to decreased latency to fall asleep, but did not affect total REM sleep time. Acute and subchronic oral toxicity studies (through 3-months in rats and dogs) indicate that CNS depression following high doses of oxycodone hydrochloride is an extension of its pharmacological activity. [1]Biberfeld J. Zur Kenntnis der Gewöhnung. IV. Über gewöhnung an kodeinderivate (Eukodal u. Parakodin). Biochem. Ztschr. 1920; 111: 91-104. [2]Small L.F., Eddy N.B., Mosettig E., and Himmelsbach C.K. Studies on drug addiction with special reference to chemical structure of opium derivatives and allied synthetic substances and their physiological action. Pub. Health Rep. 1938; Supplement 138: 22-31. [3]Oelkers H.A. Vergleichende untersuchungen über die Wirkungsstärke des morphins seiner derivate. I Mitteilung Naunyn-Schmiedebergs Archiv. fur experiment Path. u Pharmakol. 1940; 194: 296-307. [4]Kreuger H., Eddy N.B., and Sunwalt M. Pharmacology of opium alkaloids. Federal Security Agency, Public Health Reports, USPHS Supplement 165, US Government Printing Office. 1943:969-975. [5]Roesch E. Über den antagonismus von n-allynormorphin zu morphin und eukodal am Kreislauf von wachen Hunden. Arch. exper. Path. u Pharmakol. 1955; 226: 518-526. [6]Poyhia R. and Kalso E. Antinociceptive effects and central nervous system depression caused by oxycodone and morphine in rats. Pharmacol. & Toxicol. 1992a; 70: 125-130. [7]Meert T.F. and Vermeirsch H.A. A preclinical comparison between different opioids: antinociceptive versus adverse effects. Pharmacol Biochem Behav. 2005; 80(2): 309-26 [8]Doteuchi M., Sato H., Otani K., Koshida H., Hirono S, Hirose F., Koyabu K., Ryu T., Takemoto Y., and Yoshimura K. Pharmacological Studies of Oxycodone Hydrochloride 1. Antinociceptive Effect and General Pharmacology Pharmacometrics. 1995; 49: 257-273	Opiates including oxycodone hydrochloride may cause sedation and other signs of CNS depression which may be additive to other medications that have CNS depressant activity[1]. [1] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies.

Key Safety findings (from non-clinical studies)	Relevance to human usage
General CNS Depression/Gross Behaviour Continued: [9]Yoshimura K., Horiuchi M., Inoue Y., and Doteuchi M. Pharmacological Studies of Oxycodone Hydrochloride 2. Polygraphic Analysis in Conscious Dogs. Pharmacometrics. 1995; 49: 275-286. [10]Ishida, T., Suga, A., Tsutsui, R., Obara, Y., and Kamei, C. Effects of opioid analgesics on the sleep-wake rhythm in rats. Jpn Pharmacol. Ther, 2009; 8: 643-647.	
Effects on Rectal Temperature: Doteuchi et al[1] identified that an oral dose of 3 mg/kg oxycodone hydrochloride (but not 1 mg/kg) in mice resulted in an elevation of the rectal temperature one hour after dosing. The duration of the elevation in rectal temperature was proportional to the dose. Observations with morphine were similar to those with oxycodone hydrochloride. Yoshimura et al[2] reported that in dogs, oxycodone hydrochloride at 3 and 10 mg/kg resulted in a slight decrease in body temperature and 30 mg/kg resulted in a significant ($P < 0.01$) decrease in body temperature. Likewise, in dogs, oral administration of morphine at 10 and 30 mg/kg also resulted in a significant decrease in body temperature. [1]Doteuchi M/, Sato H., Otani K., Koshida ., Hirono S., Hirose F., Koyabu K, Ryu T., Takemoto Y., and Yoshimura K. Pharmacological Studies of Oxycodone Hydrochloride 1. Antinociceptive Effect and General Pharmacology Pharmacometrics. 1995; 49: 257-273 [2]Yoshimura K., Horiuchi M., Inoue Y., and Doteuchi M. Pharmacological Studies of Oxycodone Hydrochloride 2. Polygraphic Analysis in Conscious Dogs. Pharmacometrics. 1995; 49: 275-286.	In humans, opioids alter the equilibrium point of the hypothalamic heat-regulatory mechanism, such that body temperature usually falls slightly. However, chronic high dosage may increase body temperature[1,1a]. [1]Reisine T and Pasternak G. Opioid Analgesics and Antagonists. In Hardman, J.G. et al., Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th Edition. NY: McGraw Hill. 1996; 521-555. [1a] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Excitatory Effects: High doses of opioids in animals produce convulsions. Several mechanisms appear to be involved, and different types of opioids produce seizures with different characteristics. Morphine-like drugs excite certain groups of neurons, especially hippocampal pyramidal cells; these excitatory effects probably result from inhibition of the release of GABA by interneurons[1]. Convulsions in rats, dogs, cats, guinea pigs, and rabbits in response to treatment by oxycodone hydrochloride and other opioids, have been reported[2,3,4]. Doteuchi et al[5] reported that oral doses of oxycodone hydrochloride enhanced pentylenetetrazol-induced convulsions and had an inhibitory effect on electroshock convulsions. Although orally administered morphine had no effect, the authors concluded that these results confirmed earlier experiments by Poyhia and Kalso[6] and others in which intraperitoneal morphine enhanced pentylenetetrazol-induced convulsions and elevated the threshold in electroshock-induced convulsions. [1]Reisine T. and Pasternak G. Opioid Analgesics and Antagonists. In Hardman, J.G. et al., Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th Edition. NY: McGraw Hill. 1996; 521 555. [2]Kreuger H., Eddy N.B., and Sunwalt M. Pharmacology of opium alkaloids. Federal Security Agency, Public Health Reports, USPHS Supplement 165, US Government Printing Office. 1943;969-975. [3]Oelkers H.A. Vergleichende untersuchungen über die Wirkungsstärke des morphins seiner derivate. I Mitteilung Naunyn-Schmiedebergs Archiv. fur experiment Path. u Pharmakol. 1940; 194: 296-307. [4]Small L.F., Eddy N.B., Mosettig E., and Himmelsbach C.K. Studies on drug addiction with special reference to chemical structure of opium derivatives and allied synthetic substances and their physiological action. Pub. Health Rep. 1938; Supplement 138: 22-31. [5]Doteuchi, M., Sato, H., Otani, K. Koshida, H., Hirono, S., Hirose, F., Koyabu, K., Ryu, T., Takemoto, Y., and Yoshimura, K., Pharmacological studies of oxycodone hydrochloride 1. Antinociceptive effect and general pharmacology. Pharmacometrics.1995; 49: 257-273 [6]Poyhia R. and Kalso E. Antinociceptive effects and central nervous system depression caused by oxycodone and morphine in rats. Pharmacol. & Toxicol. 1992a; 70: 125-130.	High doses of opiates may cause convulsions in older children and adult humans[1]. Myoclonus and seizures have been reported in opioid tolerant patients on high doses of opiates, such as may be encountered in hospice and terminal stages of pain therapy[2]. [1] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies. [2]Vella-Brincat J and Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. J Pain Palliat Care Pharmacother, 2007; 21:15–25.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Cardiovascular Effects: Kreuger et al[1] reported the effects of a variety of opioids, including oxycodone hydrochloride, on the cardiovascular system. Generally, no changes in blood pressure and heart rate in human, rabbit and frog were observed. Doteuchi et al[2] found that intraduodenal doses of 1 mg/kg of oxycodone hydrochloride had no effect on the cardiovascular system of anaesthetized rats. A slight increase in the blood pressure and heart rate ($P < 0.01$) was observed at a dose of 3 mg/kg. The heart rate was decreased at a dose of 10 mg/kg. Morphine decreased the blood pressure and heart rate at 3 mg/kg. Despite these observations, blood flow rate through the abdominal artery and electrocardiogram were not affected by either oxycodone hydrochloride or morphine. Yoshimura et al[43] reported that the heart rate in conscious dogs, surgically fitted with radiotelemetric devices, was significantly reduced by an oral dose of 30 mg/kg of oxycodone hydrochloride. A dose of 10 mg/kg resulted in a moderate effect. A dose of 30 mg/kg of morphine resulted in a similar reduction in heart rate. Oral administration of oxycodone hydrochloride at doses of 3 to 30 mg/kg resulted in a progressive increase in systolic blood pressure accompanied by an increased pulse pressure. Diastolic and mean blood pressures were not significantly changed at any dose. Morphine, administered at oral doses of 10 and 30 mg/kg in dogs, resulted in an increase in mean, systolic and diastolic blood pressure. The potential of oxycodone hydrochloride to inhibit cardiac delayed rectifier potassium currents has been studied using the hERG assay with isolated human embryonic kidney cells transfected with the hERG gene. In one study[4], exposures to 250 ng/mL (≈1 µM) of oxycodone, noroxycodone, or oxymorphone (metabolites of oxycodone) as well as other opioids (such as morphine and codeine) and non-opioid pharmaceuticals were used. Oxycodone hydrochloride produced negligible inhibition of the hERG current at this concentration. Noroxycodone and oxymorphone had minor and moderate inhibitory effects, respectively, on hERG currents in this model. Oxycodone hydrochloride inhibited hERG to a similar extent as morphine and the inhibition associated with oxymorphone was slightly less than that found with codeine. Fanoe, et. al[5] tested oxycodone hydrochloride at concentrations from 0.4 µM to 100 µM. The IC_{50} value was determined to be 171 µM. In contrast, the IC_{50} values for methadone which has been associated with QTc prolongation in humans, ranged from 2 µM to 9.8 µM. In an *in vitro* study, Ennis et al[6] compared the ability of several opioids, including morphine hydrochloride and oxycodone hydrochloride to cause histamine release from mast cell suspensions from porcine heart, kidneys, liver and lungs. It was found that high concentrations of morphine (10mM) caused little release of histamine, whereas the same concentration of oxycodone hydrochloride caused histamine release, especially in the heart-derived mast cells. Interpretation of these data is difficult since no inferential statistics were presented and because the concentrations of drugs used were so high. [1]Kreuger H., Eddy N.B., and Sunwalt M. Pharmacology of opium alkaloids. Federal Security Agency, Public Health Reports, USPHS Supplement 165, US Government Printing Office. 1943:969-975. [2]Doteuchi M., Sato H., Otani K., Koshida H., Hirono S., Hirose F., Koyabu K., Ryu T., Takemoto Y., and Yoshimura K. Pharmacological studies of oxycodone hydrochloride 1. Antinociceptive effect and general pharmacology. Pharmacometrics. 1995; 49:257-273	Although the effects of opioid drugs on the cardiovascular system are complex, therapeutic doses generally have no major effect on blood pressure, cardiac rate and cardiac rhythm. However, peripheral vasodilatation, reduced peripheral resistance, and an inhibition of baroreceptor reflexes have been observed. Opioids provoke the release of histamine, which results at times in hypotension[1]. Oxycodone hydrochloride caused histamine release in heart-derived mast cells. Clinical implications for these findings are unlikely since Pöyhiä et al[2] found no histamine liberation after oral administration of oxycodone hydrochloride in healthy human volunteers. Fanoe et. al. suggested that hERG IC_{50} values should be compared to the maximal plasma concentrations (IC_{50}/C_{max}) to estimate therapeutic index, with concern raised if the ratio is < 30. Kaiko et al[3], reported a 20 mg dose of sustained-release oxycodone hydrochloride yielded a mean C_{max} oxycodone concentration of approximately 23 ng/mL (0.073 nM). The IC_{50}/C_{max} ratio for oxycodone is therefore >2000. (In comparison, the IC_{50}/C_{max} ratio for methadone was 2.7 and for morphine >400). Accordingly, oxycodone is not expected to result in significant QTc prolongation at therapeutic doses. [1]Reisine T and Pasternak G. Opioid Analgesics and Antagonists. In Hardman, J.G. et al., Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th Edition. NY: McGraw Hill. 1996; 521-555. [2]Pöyhiä, R., Kalso, E., and Seppälä, T. Pharmacodynamic inter-actions of oxycodone hydrochloride and amitriptyline in healthy volunteers. Curr. Ther. Res., 1992b; 51:739-749. [3]Kaiko, R. F., Benziger, D.P., Fitzmartin, R.D., Burke, B.E., Reder, R.F., and Goldenheim, P.D. Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. Clin. Pharm. Ther. 59: 52-61 (1996).
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Key Safety findings (from non-clinical studies)	Relevance to human usage
Cardiovascular Effects continued: [3]Yoshimura K., Horiuchi, M., Inoue, Y,. and Doteuchi, M. Pharmacological studies of oxycodone hydrochloride 2. Polygraphic analysis in conscious dogs. Pharmacometrics, 1995, 49:275-286. [redacted] [5] Fanoe S., Jensen G.B., Sjøgren P., Korsgaard M.P., and Grunnet M. Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity in vitro. Br J Clin Pharmacol. 2009, 67(2):172-9. [6]Ennis M., Schneider C., Nehring E., and Lorenz W. Histamine release induced by opioid analgesics: A comparative study using porcine mast cells. Agents and Actions, 1991; 33:20-22.	
Renal Function: Doteuchi et al[1] reported that oral doses of oxycodone hydrochloride and morphine (10 and 30 mg/kg respectively) resulted in an inhibition of the excretion rate of electrolytes, sodium and chloride ions. Urine volume and the excretion rate of potassium ion and creatinine were unaffected by their experimental conditions. [1]Doteuchi M., Sato, H., Otani, K. Koshida, H., Hirono, S., Hirose, F., Koyabu, K., Ryu, T., Takemoto, Y., and Yoshimura, K., Pharmacological studies of oxycodone hydrochloride 1. Antinociceptive effect and general pharmacology. Pharmacometrics, 1995; 49:257 – 273.	The relevance of urinary electrolyte findings to human use of oxycodone hydrochloride is unclear. Opiates are known to inhibit the micturition reflex clinically[1]. [1]Rosow CE, Gomery P, Chen TY, et al. Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. Clin Pharmacol Ther, 2007, 82:48–53.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Immune System Effects: Little information was found on the specific effects of oxycodone hydrochloride on the immune system. However, opioid agonists and antagonists are well known to affect measures of immune system function and performance *in vitro* and in animals dependent on route of administration, dose, duration of treatment, pain state, and specific opioid assessed[1,2,3,4,5,6,7,8,9]. Depending on these factors, effects may be reflected by immunosuppression or stimulation. Alterations in immune system function induced by opioid agonists and antagonists (e.g., morphine) may be directly and/or indirectly, centrally and/or peripherally mediated via interaction with opioid receptors and can be mitigated by administration of opioid antagonists[3,7,8,9,10]. In contrast to the highly immunosuppressive effects of morphine, oxycodone hydrochloride was reported to be devoid of immunosuppressive activity in mice as measured by its effects on splenocyte proliferation, Natural Killer (NK) cell activity and interleukin-2 (IL-2) production [1]. [1]Sacerdote P., Manfredi, B., Mantegassa P., and Panerai A.E. Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study. British Journal of Pharmacology, 1997; 121:834-840. [2]Sacerdote P. Opioids and the immune system. Palliative Medicine, 2006; 20:s9-s15. [3]Odunayo A., Dodam J.R., Kerl M.E., and DeClue, A.E. Immunomodulatory effects of opioids. Journal of Veterinary Emergency and Critical Care, 2010; 20:376-385. [4]Page G.G, Immunological effects of opioids in the presence or absence of pain. Journal of Pain and Symptom Management, 2005; 29:S25-S31. [5]Franchi S., Panerai A.E., and Sacerdote P. Buprenorphine ameliorates the effect of surgery on hypothalamus-pituitary-adrenal axis, natural killer cell activity and metastatic colonization in rats in comparison with morphine or fenatanyl treatment. Brain Behavior, and Immunity, 2007; 21:767-774. [6]Dinda A., Gitman M., and Singhal P.C. Immunomodulatory effect of morphine therapeutic implications. Expert Opinion on Drug Safety, 2005; 4:669-675. [7]Chang MC., Fan SZ., Hsiao PN., Cheng WF., and Sun WZ. Influence of morphine on host immunity. Acta Anaesthesiologica Taiwanica 2011; 49:105-108. [8]Zhang EY., Xiong J., Parker B.L., Chen AY., Fields P.E., Ma X., Qiu J., and Yankee TM. Depletion and recovery of lymphoid subsets following morphine administration. British Journal of Pharmacology 2011; 164:1829-1844. [9]Mellon R.D. and Bayer B.M. Evidence for central opioid receptors in the immunomodulatory effects of morphine: review of potential mechanism(s) of action. Journal of Neuroimmunology 1998; 83:19-28. [10]Gaverieaux-Ruff C., Matthes H.W.D., Peluso J., and Kieffer B.L. Abolision of morphine-immunosuppression in mice lacing the μ-opioid receptor gene. Proceedings of the National Academy of Sciences, USA 1998; 95:6326-6330.	It is generally accepted that opioids can inhibit or enhance immune system function in humans dependent, as in animals, on the context of their use and the health status of the individual[1,2]. However, it is not entirely clear from animal studies to what extent opioid-induced immunomodulation is clinically relevant. Similarly, the extent to which oxycodone hydrochloride may differ from other opioid agonists such as morphine in immunomodulatory properties in humans is also not clear. [1] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies. [2]Sacerdote P. Opioid-induced immunosuppression. Current Opinion in Supportive and Palliative Care, 2008; 214-218.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Neuroendocrine System Effects: Studies to evaluate the effect of oxycodone hydrochloride on the neuroendocrine system have not been conducted and reports of effects associated with oxycodone hydrochloride administration in animals were not found in the literature. Most animal studies reported in the literature have involved the use of the agonist, morphine and antagonists, naloxone. Opioid agonists and antagonists are well known to affect the function of the hypothalamic-pituitary-adrenal/gonadal axes in animals with associated physiological sequelae on the relevant organ systems (e.g., gonads and accessory organs, adrenal cortex)[1-5]. The effects on the organ systems are the result of the influence of opioids on stimulation or inhibition of hypothalamic gonadotropic releasing factor, antidiuretic hormone, growth hormone releasing hormone/somatostatin, adrenal corticotrophin-releasing hormone and/or pituitary growth hormone, luteinizing hormone, follicle stimulating hormone, corticosterone, testosterone, and/or oestrogen and do not reflect a direct toxic effect of opioids on the organs. Additionally, opioids have also been associated with stimulation and inhibition of the central release of prolactin, oxytocin, and vasopressin[1,14-16,17]. Elicitation of specific neuroendocrine and associated physiological effects in animals appears to be complex and depends on the specific opioid, dose and duration of treatment, species evaluated, sex, and age/sexual maturity[5,6-15,17,18]. [1]Morley JE. The endocrinology of the opiates and opioid peptides. Metabolism 1981; 30:195-209. [2]Pechnick RN. Effects of opioids on the hypothalamo-pituitary-adrenal axis. Annual Review of Pharmacology and Toxicology 1993; 32:353-358. [3]Cicero TJ. Effects of exogenous and endogenous opiates on the hypothalamic-pituitary-gonadal axis in the male. Federation Proceedings 1980; 39: 2551-2554. [4]Sharma P., Bhardwaj S.K., Sandhu S.K., and Kaur G. Opioid regulation of gonadotropin release: role of signal transduction cascade. Brain Research 2000; 52:135-142. [5]Aloisi A.M., Aurilio C., Bachiocco V., Biasi G., Fiorenzani P., Pace M.C., Paci V., Pari G., Passavanti G., Rvaioli L., Sindaco G., Vellucci R., and Ceccarelli I. Endocrine consequences of opioid therapy. Psychoneuroendocrinology 2009; 345:5162-5168. [6]Cicero T.J., O'Connor L., Nock B., Adams M.L., Bell R.D., and Meyer E.R. Age-related differences in the sensitivity to opiate-induced perturbations in the reproductive endocrinology in the developing and adult male rat. Journal of Pharmacology and Experimental Therapeutics 1989; 248:256-261. [7]Cicero T.J., Nock B., and O'Connor L. Naloxone does not reverse the inhibitory effect of morphine on luteinizing hormone secretion in the prepubescent male rats. Journal of Pharmacology and Experimental Therapeutics 1993; 264: 47-53. [8]Simpkins J.W., Millard W.J., and Berglund L.E. Effects of chronic stimulation or antagonism of opiate receptors on GH secretion in male and female rats. Life Sciences 1993; 52: 1443-1450. [9]Kowalski W.B., Parsons M.T., Pak S.K,, and Wilson L. Morphine inhibits nocturnal oxytocin secretion and uterine contractions in the pregnant baboon. Biology of Reproduction 1998; 58:971-976. [9]Yilmaz B., Konar V., Kutlu S., Sandal S., Canpolat S., Gezen M.R., and Kelestimur H. Influence of chronic morphine exposure on serum LH, FSH, testosterone levels, and body and testicular weights in the developing male rat. Archives of Andrology 1999; 43:189-196.	Opioid agonists including oxycodone hydrochloride and antagonists are also well known to reversibly affect the function of the hypothalamic-pituitary-adrenal/gonadal axes in humans with associated physiological sequelae on the relevant organ systems[1-4]. In males, acute opiate agonist treatment may reduce plasma cortisol, testosterone, and gonadotrophins. Inhibition of adrenal function is reflected by reduced cortisol production and reduced adrenal androgens. In females, morphine may additionally result in lower LH and FSH release. In males and females, chronic administration has been associated with hypogonadotrophic hypogonadism. (decreased libido, reduced secondary sex characteristics in males;. menstrual cycle irregularities in women). Additionally, opiate agonists may increase plasma prolactin and growth hormone and affect release of vasopressin and oxytocin. As in animals, response to opiate agonist administration may vary somewhat depending on specific opioid. [1]Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies. [2]Aloisi A.M., Aurilio C., Bachiocco V., Biasi G., Fiorenzani P., Pace M.C., Paci V., Pari G., Passavanti G., Rvaioli L., Sindaco G., Vellucci R., and Ceccarelli I. Endocrine consequences of opioid therapy. Psychoneuroendocrinology 2009; 345:5162-5168. [3]Rajagopal A. and Bruera E.D. Improvement in sexual fuction after reduction of chronic high-dose opioid medication in a cancer survivor. Pain Medicine 2003; 4:379-383. [4]SmPC UK Oxycontin tablets Combined (5-80 mg), 2011.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Neuroendocrine System Effects (continued): [10]Pechnik R., George R., and Poland R.E. Identification of multiple opiate receptors through neuroendocrine responses. I. Effects of Agonists. Journal of Pharmacology and Experimental Therapeutics 1985; 232:163-169 [11] Pechnik R., George R., and Poland R.E. Identification of multiple opiate receptors through neuroendocrine responses. II Antagonism of Mu, Kappa and Sigma Aagonists by naloxone and WIN44,441-3. Journal of Pharmacology and Experimental Therapeutics 1985; 232:170-177. [12]Amoroso S., DiRenzo G., Cuocolo R., Amantea B., Leo A., Taglialatela M., and Annunziato L. Evidence for differential interaction of buprenorphine with opiate receptor subtypes controlling prolactin secretion. European Journal of Pharmacology 1988; 145:257-260. [13]Ceccarelli I., DePadova A.M., Fiorenzani P., Massafra C., and Aloisis A.M. Single opioid administration modifies gonadal steroids in both the CNS and plasma of male rats. Neuroscience 2006; 140:929-937. [14]Byrnes E.M. Chronic morphine exposure during puberty decreases postpartum prolactin secretion in adult female rats. Pharmacology, Biochemistry, and Behaviour 2005; 80:445-451. [15]Li J., You Z., Chen Z., Song C., and Lu C. Chronic morphine treatment inhibits oxytocin release from the supraoptic nucleus slices of rats. Neuroscience Letters 2001; 300:54-58. [16]Dobson R.M. and Brown B.L. Involvement of the hypothalamus in opiate-stimulated prolactin secretion. Regulatory Peptides 1988; 20:305-310. [17]Callahan P., Janik J., Grandison L., and Rabii J. Morphine does not	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mechanisms for drug interactions: Enzyme inhibition studies indicate that oxycodone hydrochloride does not inhibit the major P450 metabolizing enzymes and therefore, few if any drug interactions would be expected with other co-administered drugs metabolised by most CYP isoforms, with the exception of ketoconazole, a known potent CYP3A4 inhibitor. [1]Hassan, H.E., Myers, A. L., Lee, I. J., Coop, A., and Eddington, N. D., Oxycodone induces overexpression of P-glycoprotein (ABCB1) and affects Paclitaxel's tissue distribution in Sprague Dawley rats. Journal of Pharmaceutical Sciences, 2007: 96:2494-2506.	Oxycodone hydrochloride is reported to be a P-gp substrate, however clinical significance of this observation related to drug-drug interaction is not known[1,1a]. Clinically, concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6, resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t½ elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%, AUC by 85%, and t½ elim. by 42%). The pharmacodynamic effects of oxycodone hydrochloride were not altered. This interaction may be observed for other potent inhibitors of cytochrome P450-2D6 enzyme. Cimetidine and inhibitors of cytochrome P450-3A such as ketoconazole and erythromycin may inhibit the metabolism of oxycodone (OxyNorm and OxyContin SmPCs). [1]Reisine T and Pasternak G. Opioid Analgesics and Antagonists. In Hardman, J.G. et al., Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th Edition. NY: McGraw Hill. 1996; 521-555. [1a] Tony L. Yaksh, Mark S. Wallace. II. Neuropharmacology > Chapter 18. Opioids, Analgesia, and Pain Management. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. The McGraw-Hill Companies.

SII Conclusions on non-clinical data

Part II. SII. Table 2 - Conclusions on non-clinical data

Safety concerns
Important identified risks (confirmed by clinical data) • Drug abuse • Psychological dependence • Respiratory depression

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

1. The first oxycodone hydrochloride products to be developed were the 10, 20, 40 & 80 mg prolonged release tablets. These dosage forms were developed for the treatment of pain as [redacted] prolonged release tablets and the safety and efficacy of oxycodone hydrochloride was supported by 59 clinical studies (Table 1).

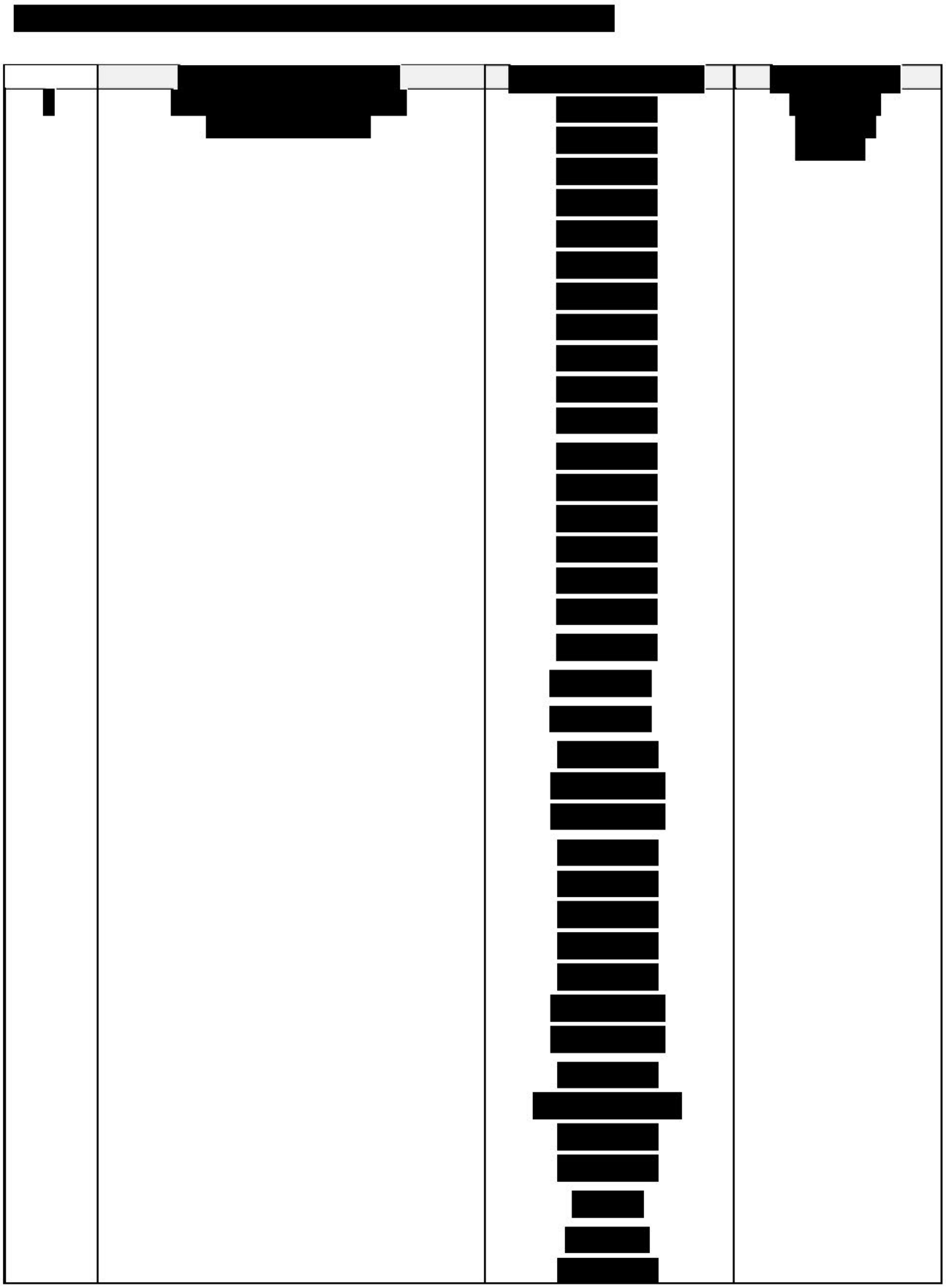
2. Additional dosage form.
   The scientific community and clinicians indicated a need for immediate release dosage forms to complement the prolonged release dosage forms and as a result the immediate release oxycodone hydrochloride oral liquids [redacted] and oral capsules [redacted] were developed. The clinical program consisted of 3 pharmacokinetic studies (Table 1) that showed that the immediate release oral dosage forms had equivalent bioavailability of oxycodone to each other and to the prolonged release tablets.

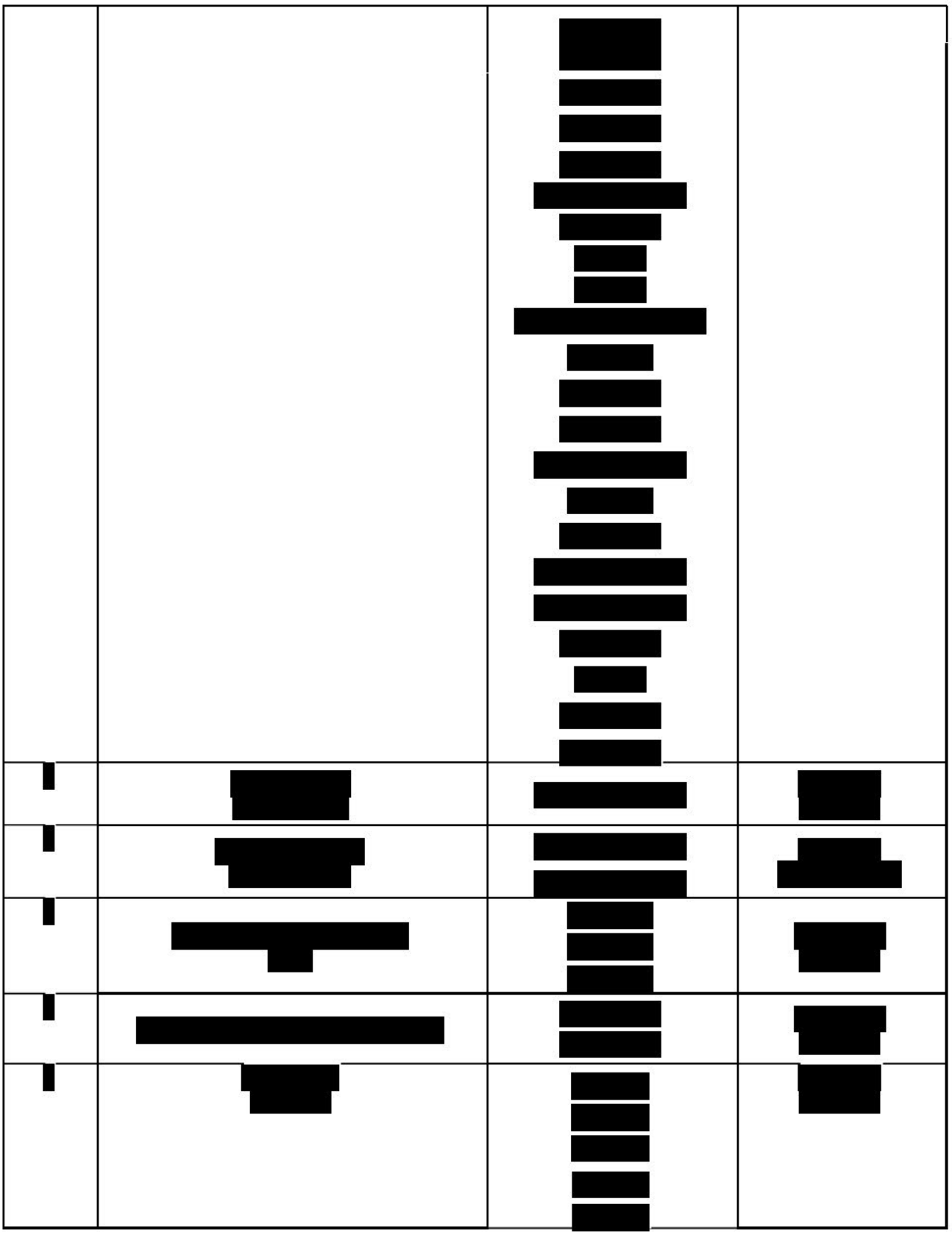
[redacted]

[redacted]

9. Extension of indication.
   Since the prolonged release tablets were first approved in Europe, the clinical indications have differed between some countries (where the products were approved via national procedures) and based on their local medical custom/practice. During this time activities have been performed to try and obtain a more consistent clinical indication, resulting in changes to the initially approved indication, e.g. [redacted] United Kingdom [redacted]

[redacted]

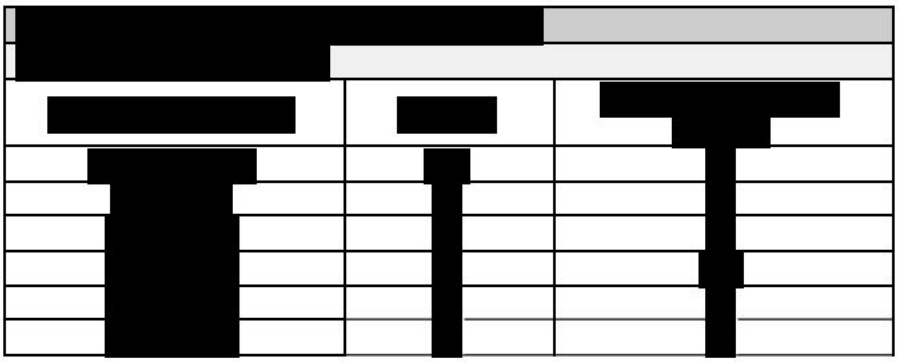


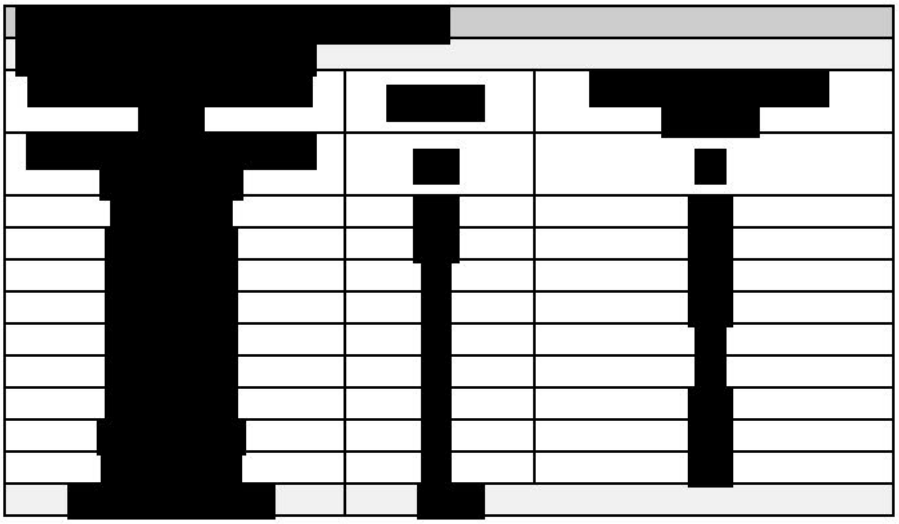


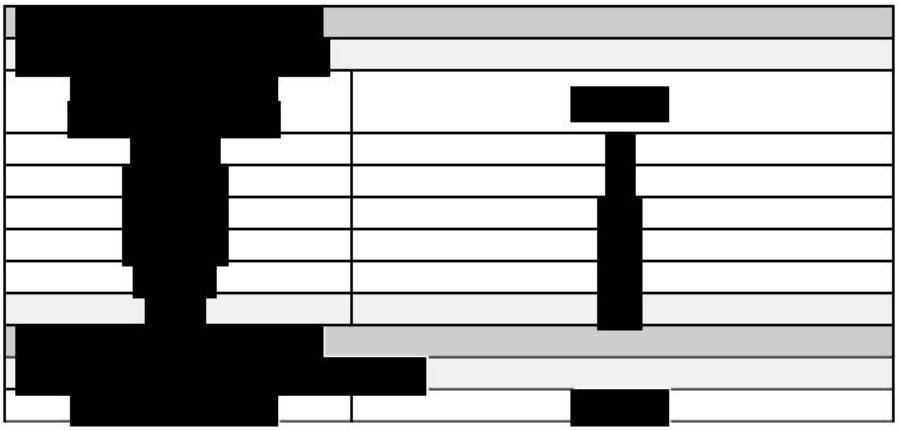
SIII.2 Clinical Trial exposure

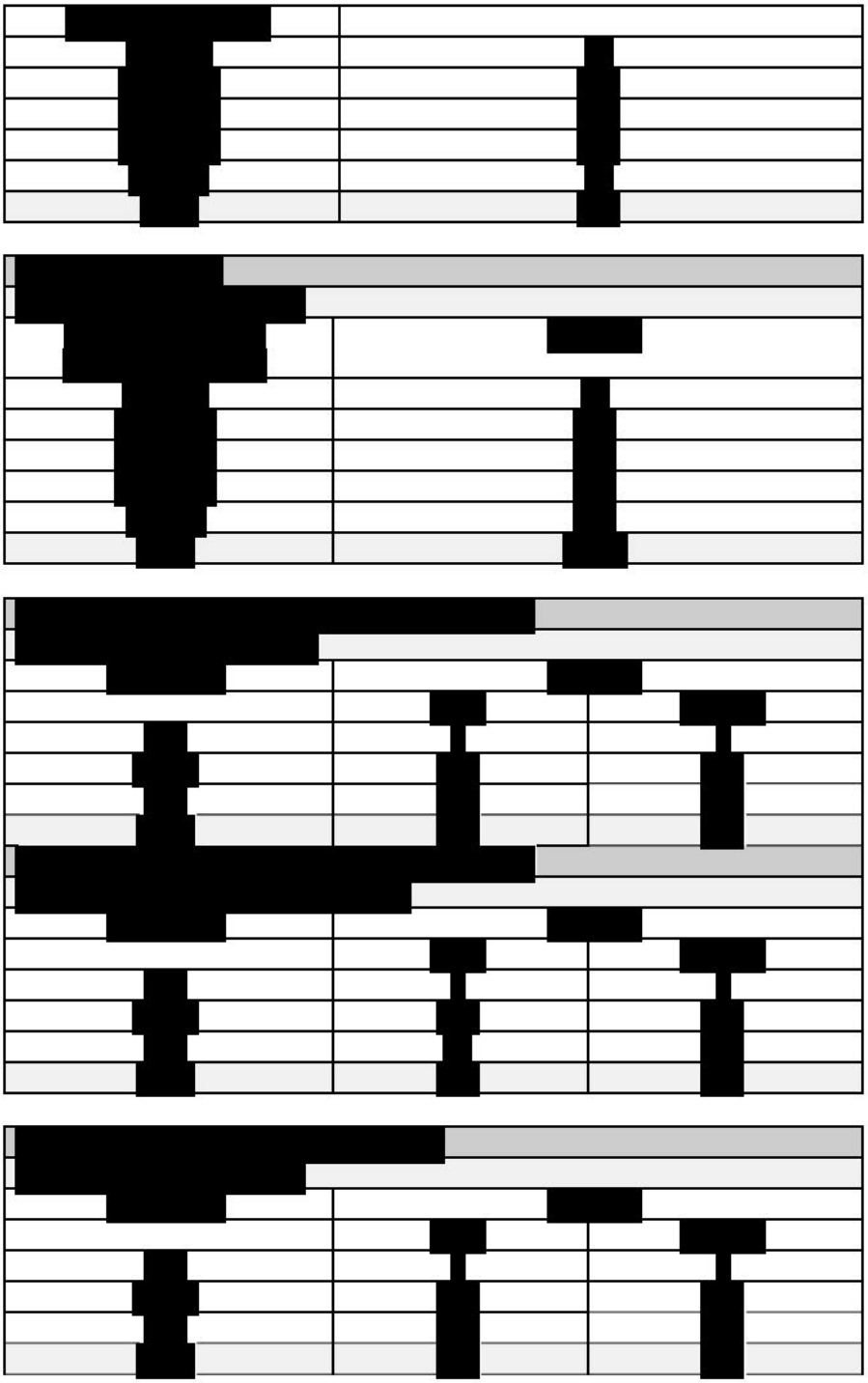
The clinical trial exposure calculations below have been retrieved from the Integrated Summary of Safety (ISS) for oxycodone hydrochloride prolonged release tablets (2001) when the last aggregate analysis was performed for the oxycodone hydrochloride development programme. It is not possible to distinguish the patient exposure from randomised, blinded trial population compared to the patient exposure from the total clinical trials population in this ISS. The figures in the exposure tables outlined below reflect the minimum exposure throughout the clinical development. For the calculation of 'Persons time', a conservative approach has been taken by using the lower boundary for each exposure duration. For example for the '2 to 3 month' exposure, two months of exposure is the most conservative duration and therefore for each patient exposure in this duration two person months of exposure was counted.

Part II. SIII. Tables 2 – Clinical trial exposure for development programme









Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Limitations of ADR detection common to clinical trial development programmes

Oxycodone hydrochloride formulations:

Part II. SIV. Table 1 – Limitations of ADR detection common to clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	More than 1,500 patients exposed to oxycodone in clinical trials allows identification of AEs up to a frequency of uncommon.	Based on the extensive market experience of the established product the implication should be minimal, if at all.
Due to prolonged exposure	More than 50 % of subjects received oxycodone for up to 4 weeks and long-term exposure (1 year) data is available for a small patient group [redacted]	Based on the extensive market experience of the established product the implication should be minimal, if at all.
Due to cumulative effects	The potential for cumulative effects, resulting in increased plasma levels, has been investigated in the respective populations (elderly, hepatic/renal impairment)	Appropriate dosing instructions for those patients are provided in the respective SmPC.
Which have a long latency	Clinical studies were designed to identify long-latency adverse reactions up to 56 weeks [redacted]	Opioids are not known to cause long latency side effects. Postmarketing safety monitoring includes identification and assessment of long-latency adverse reactions.

SIV.2 Effect of exclusion criteria in the clinical trial development plan

Part II. SIV. Table 2 – Effect of exclusion criteria in the clinical trial development programme – Contraindications

Exclusion criteria which will remain as contraindications	
Criteria	**Implications for target population**
Patients who are allergic to oxycodone hydrochloride or who have a history of allergies to oxycodone.	No implication, as alternative strong opioids are available.
Patients with paralytic ileus, or other conditions (e.g. cor pulmonale, severe respiratory depression, severe COPD) which in the judgment of the investigator, adversely affects safety or obscures efficacy.	Minimal implication, as alternative non-opioid pain treatment medications are available.
Patients, who are breastfeeding.	Minimal implication, as alternative non-opioid pain treatment medications are available.

Part II. SIV. Table 3 – Effect of exclusion criteria in the clinical trial development programme – Not contraindications

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
Patients who are pregnant. Patients of childbearing potential must obtain a negative urine pregnancy test within 10 days prior to study entry.	Ethical reason as no experience in pregnant women exists and efficacy can be established by studying in non-pregnant women.	Pre-clinical testing does not indicate toxicology findings in therapeutic doses. Clinical experience of this drug class does not indicate any specific risk to pregnant women or foetus (except neonatal withdrawal of newborn).
Patients with severe organ dysfunction: renal failure and severe hepatic impairment.	To not compromise the dose range subject to investigation.	No significant risk, as doses can be adjusted to renal or hepatic function.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

SIV.3.1 *Children*

[redacted]

SIV.3.2 *Elderly*

Oxycodone hydrochloride differs from morphine in its pharmacokinetics in the elderly. These individuals have a substantially reduced clearance of morphine resulting in clinically significant increases in drug effect, compared with younger age groups[1,2]. In contrast, the plasma concentrations (AUC) of oxycodone hydrochloride have been shown to be only nominally (15%) greater in the elderly than in young healthy subjects study ([redacted]).

[1]*Baillie SP, Bateman DN, Coates PE, Woodhouse KW: Age and the Pharmacokinetics of Morphine, Age and Ageing 1989: 18, 258–262.*
[2]*Loick G, Radbruch L, Sabatowski R, Sießegger M, Grond St, Lehmann KA: Morphindosis und Nebenwirkungen – Ein Vergleich älterer mit jüngeren Tumorschmerzpatienten. Dtsch. Med. Wschr. 2000; 125: 1215–1221.*

SIV.3.3 Pregnant or breast feeding women

There are limited data from clinical trials with respect to exposure to oxycodone hydrochloride during pregnancy, however the Applicant has extensive post marketed experience and pregnancies and their outcomes are analysed from the post marketed data.

SIV.3.4 Patients with hepatic impairment

A study in patients with mild to moderate hepatic dysfunction ([redacted]) showed peak (Cmax) plasma oxycodone hydrochloride and noroxycodone concentrations approximately 50% and 20% higher, respectively, than those in normal subjects. Total (AUC) plasma concentrations were approximately 90% higher for oxycodone hydrochloride and 75% higher for noroxycodone. In contrast, peak and total plasma oxymorphone Cmax and AUC were approximately 15% to 50% lower in subjects with hepatic dysfunction. The elimination half-life for oxycodone hydrochloride was prolonged by 2.3 hours. These differences were accompanied by an increase in some opioid effects. Overall, maximal and total drug effects were greater in the hepatically impaired patients. Concordance between increasing plasma oxycodone hydrochloride concentration and increasing drug effect suggests, as previously demonstrated by Lalovic et al, that oxycodone hydrochloride is primarily responsible for mediating its own pharmacodynamics. This is especially notable in light of the decreasing plasma oxymorphone concentration in subjects with hepatic dysfunction. The degree of oxycodone hydrochloride accumulation in hepatic impairment is lower than that which has been reported for opioid analgesics that undergo a greater first-pass metabolism and which have a lower oral bioavailability than oxycodone hydrochloride. This may provide advantages for oral oxycodone hydrochloride over agents with higher first-pass metabolism in patients with unstable hepatic function. Therapy with IR oxycodone hydrochloride in subjects with hepatic impairment, as with all opioid analgesics, should be initiated at 1/2 the usual doses and titrated carefully. Based on this information, the oxycodone hydrochloride Core safety profile (CSP) contains a warning that caution must be exercised when administering oxycodone hydrochloride to patients with impaired hepatic function.

Lalovic B, Kharasch E, Hoffer C et al- Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites. Clinical Pharmacology & Therapeutics, May 2006.

SIV.3.5 Patients with hepatic impairment

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]				[redacted]
	[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

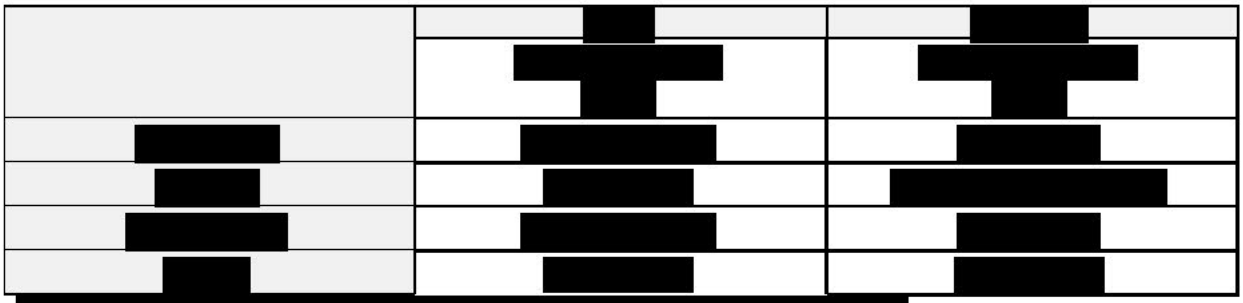
[redacted]

[redacted]

SIV.4 Patients with a disease severity different from the inclusion criteria in the clinical trial population

SIV.4.1 Patients of different racial and/or ethnic origin

[redacted]



[redacted]

[redacted]

SIV.5 Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Important missing information

Part II. SIV. Table 6 – Important missing information from clinical trial development programme

Safety concerns due to limitations of the clinical trial programme		Outstanding concern?
Safety concern	**Comment**	**Yes/No**
Use in Pregnant or breast feeding women	There are no controlled studies on the effect of oxycodone hydrochloride on pregnancy and lactation. Therefore, the potential risk for humans is unknown and the use of oxycodone hydrochloride in this patient population is considered important missing information	Yes

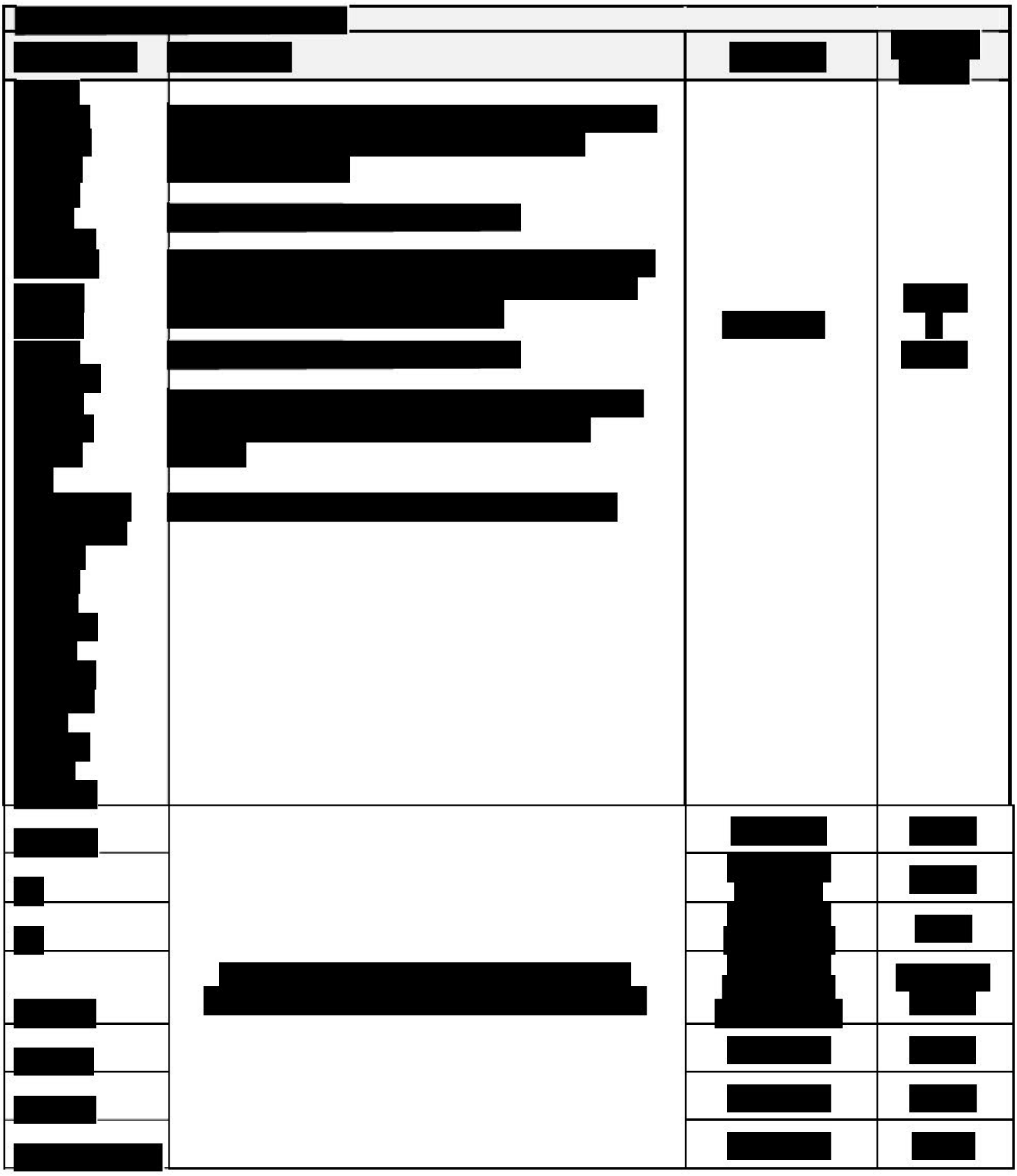
Part II: Module SV - Post-authorisation experience

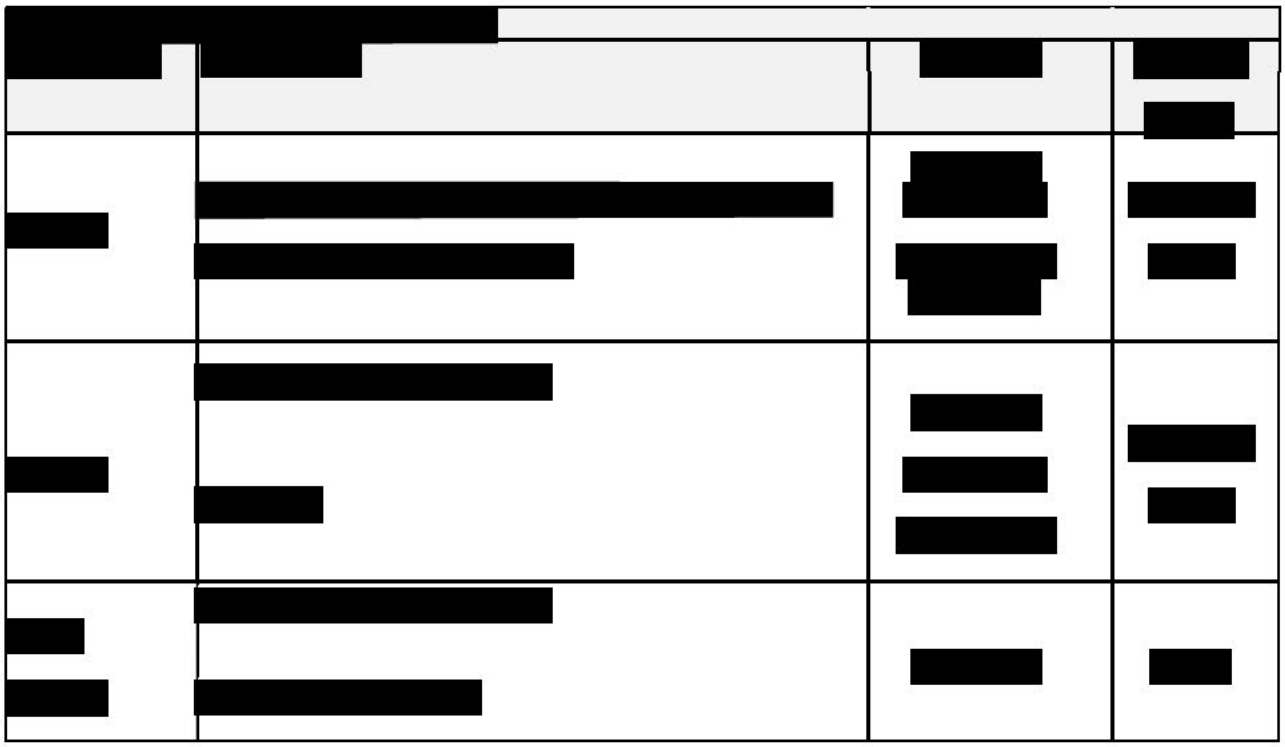
SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

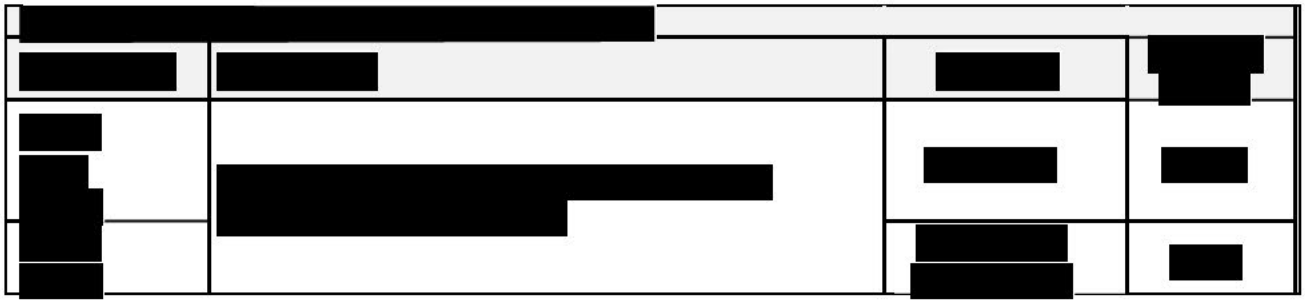
Part II. SV. Table 1 – Actions taken by regulatory authorities and/or MAH for safety reasons – Interval

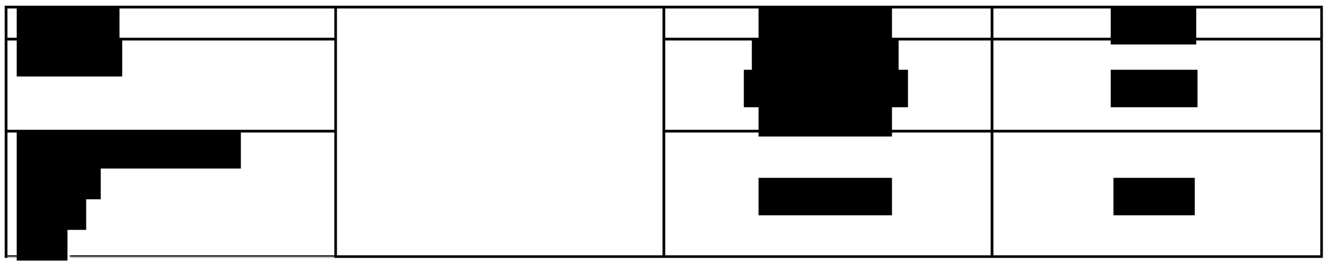
Safety Issue	**Rewording of warnings, precautions and interactions**
Background to issue	The FDA required class-wide safety labelling changes for opiates, including oxycodone immediate-release and controlled release products, to including a black box warning and updates to the Warnings and Precautions, Drug Interactions, and Patient Counselling Information sections to warn against the serious risks associated with the combined use of opioids and benzodiazepines, or opiates and other central nervous system depressants.
Evidence source	MAH conducted a benefit risk analysis into the issue and recommended that Warnings and Precautions, Drug Interactions, and Patient Counselling Information sections need re-wording for added clarity
Action taken	MAH made an update to the oxycodone company core safety information to clarify warnings.
Countries affected	USA
Date(s) of action	August 2016

[redacted]









SV.2 Non-study post-authorisation exposure

SV.2.1 Method used to calculate exposure

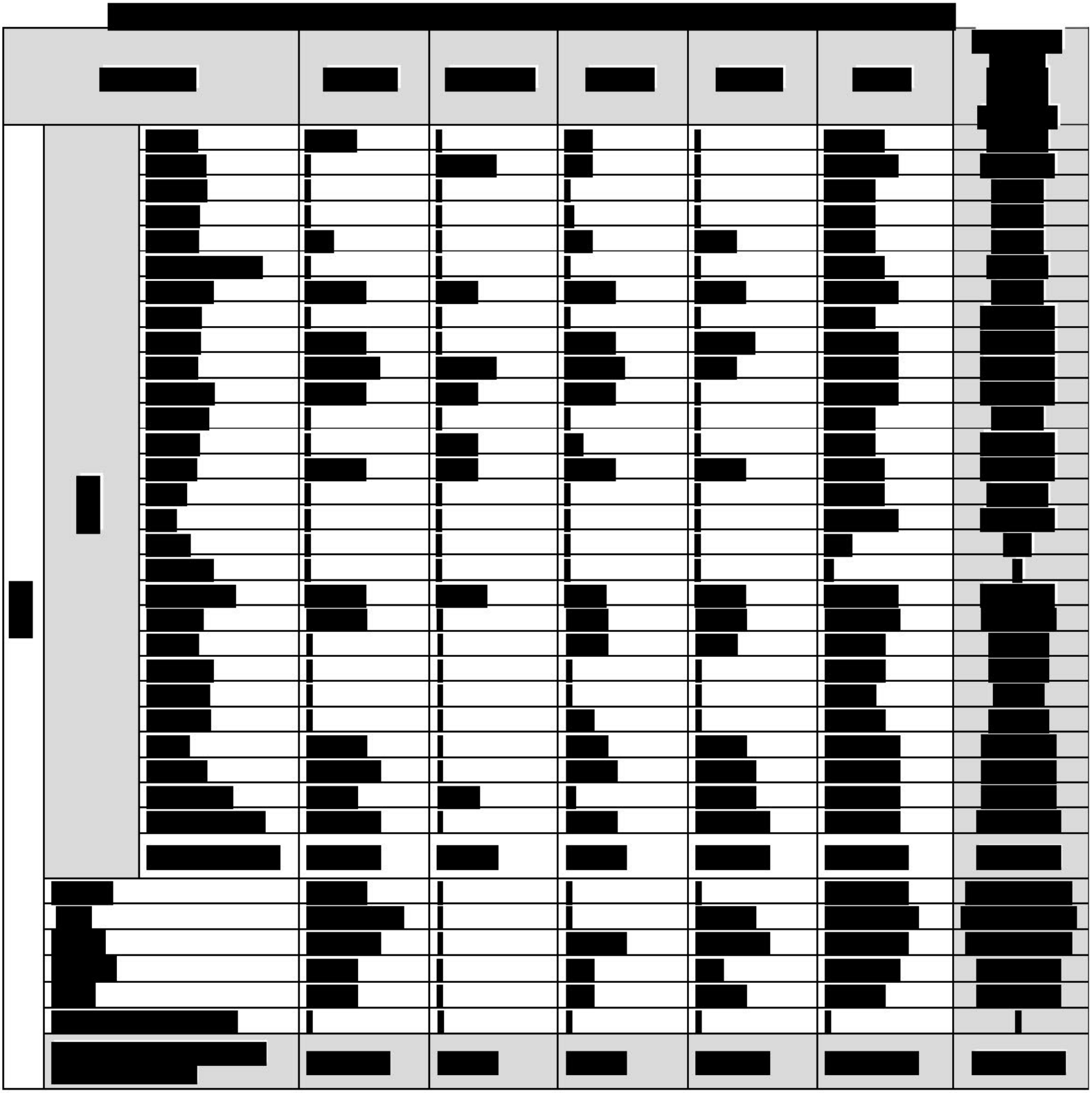
The worldwide cumulative estimates of patient exposure (January 1996- March 2017) are derived according to a standard approach from sales data obtained from all countries in which the active ingredient is sold. The variance between different countries reflects not only the population of the country but also the medical pattern of use and the time since launch of the preparation.

The exposure figures were estimated on the basis of [redacted] The number of patient days treatment for each strength, for each pack size, and for each country was then calculated. Taking a conservative approach, the summation provides an estimate of the number of "patient months" exposure.

[redacted]

SV.2.2 Exposure

The sales data obtained from all countries in which the active ingredient is sold was broken down by formulation (tablets, injections, capsules, dispersible tablets, solution) and region. The data is summarised below:



SV.3 Post-authorisation use in populations not studied in clinical trials

The calculation of the estimated use of oxycodone hydrochloride all formulations broken down by special population groups was performed using data from the international database and the sales data for the total patient exposure. For an accurate representation of the special population exposure, cases from the IBD (12 December 1995) were used. The method of calculation is depicted in the tables below;

Part II. SV. Table 4 – Post-authorisation use in populations not studies in clinical trials – Paediatric use

Paediatric use		
Estimated use	**Number of patient months**	**Comment on any variation in benefit or risk from overall target population**
Neonates (birth up to 27 days) (n=[redacted])	[redacted]	The review of the available paediatric data did not indicate any unexpected new risk regarding therapeutic administration of oxycodone hydrochloride in children, and does not suggest that oxycodone hydrochloride administration has a different safety profile in children compared to the well defined profile in the adult population. Under the EU worksharing in the assessment of paediatric data, as agreed as by the Heads of Medicines Agencies (HMA), a paediatric clinical expert statement has been prepared and submitted. The MAH proposed dosing recommendations for the paediatric population in the EU, based upon the available clinical and safety data.
Infants and toddlers (1 month to 23 months) (n=[redacted])		
Children (2 years to 11 years) (n=[redacted])		
Adolescents (12 years to 18 years) (n=[redacted])		
Data source: International drug safety database and patient exposure (patient months)		
Method of calculation: The number of worldwide neonate cases divided by the total number of worldwide cases for oxycodone hydrochloride all formulations from the international database multiplied by total patient exposure for oxycodone all formulations (cumulative) e.g: Number of neonates cases x Total patient exposure Total number of cases		

Part II. SV. Table 5 – Post-authorisation use in populations not studies in clinical trials – Elderly use

Elderly use		
Estimated use	**Number of patient months**	**Comment on any variation in benefit or risk from overall target population**
65-74 years (n=[redacted])	[redacted]	No new relevant safety concerns have been identified in the elderly data.
75-84 years (n=[redacted])		
85+ years (n=[redacted])		
Data source: International drug safety database and patient exposure (patient months)		
Method of calculation: The number of worldwide elderly cases divided by the total number of worldwide cases for all oxycodone hydrochloride formulations from the international database multiplied by total patient exposure for all oxycodone hydrochloride formulations (cumulative). Number of elderly cases x Total patient exposure Total number of cases		

Part II. SV. Table 6 – Post-authorisation use in populations not studies in clinical trials – Pregnant or breastfeeding women

Pregnant or breast feeding woman		
Estimated use	**Number of patient months**	**Comment on any variation in benefit or risk from overall target population**
• Pregnant (n=[redacted])	[redacted]	Use of oxycodone hydrochloride in pregnant and breast feeding patients has been classified as important missing information. The oxycodone hydrochloride CSP states that the drug should be avoided in patients who are pregnant and that the drug penetrates the placenta and can be found in breast milk.
• Breast feeding (n=[redacted])		
Data source: International drug safety database Patient exposure (patient months)		
Method of calculation: The number of pregnancy cases divided by the total number of cases for oxycodone hydrochloride all formulations from the international database multiplied by total patient exposure (cumulative) Number of pregnancy cases x Total patient exposure Total number of cases Number of breastfeeding cases x Total patient exposure Total number of cases		

Part II. SV. Table 7 – Post-authorisation use in populations not studies in clinical trials – Hepatic impairment

Hepatic impairment		
Estimated use	**Number of patient months**	**Comment on any variation in benefit or risk from overall target population**
• Hepatic impairment (n=[redacted])	[redacted]	The oxycodone hydrochloride CSP contains a warning that caution must be exercised when administering oxycodone hydrochloride to patients with impaired hepatic function.
Data source: International drug safety database Patient exposure (patient months)		
Method of calculation: The number of cases of use in patients with hepatic impairment divided by the total number of cases for oxycodone hydrochloride all formulations from the international database multiplied by total patient exposure (cumulative). Number of hepatic impairment x Total patient exposure Total number of cases		

Part II. SV. Table 8 – Post-authorisation use in populations not studies in clinical trials – Renal impairment

Renal impairment		
Estimated use	**Number of patient months**	**Comment on any variation in benefit or risk from overall target population**
• Renal impairment (n=[redacted])	[redacted]	The oxycodone hydrochloride CSP contains a warning that caution must be exercised when administering to patients with impaired renal function.
Data source: International drug safety database Patient exposure (patient months)		
Method of calculation: The number of cases of use in patients with renal impairment divided by the total number of cases for oxycodone hydrochloride all formulations from the international database multiplied by total patient exposure (cumulative). Number of renal impairment x Total patient exposure Total number of cases		

SV.4 Post-authorisation off-label use

In Europe, a total number of [redacted] cases describing off label use as a PT were identified. A review of cumulative off label cases originating from Europe found [redacted] cases where oxycodone was prescribed for Restless Leg Syndrome and one case for Parkinson's disease with tremor. In France, [redacted] cases showed patients being prescribed oxycodone as a substitution therapy.

The events reported are not indicative of any additional safety concern information with respect to the use of oxycodone hydrochloride in therapeutic use. Therefore there is no change in the benefit risk balance relating to the off label administration of oxycodone hydrochloride.

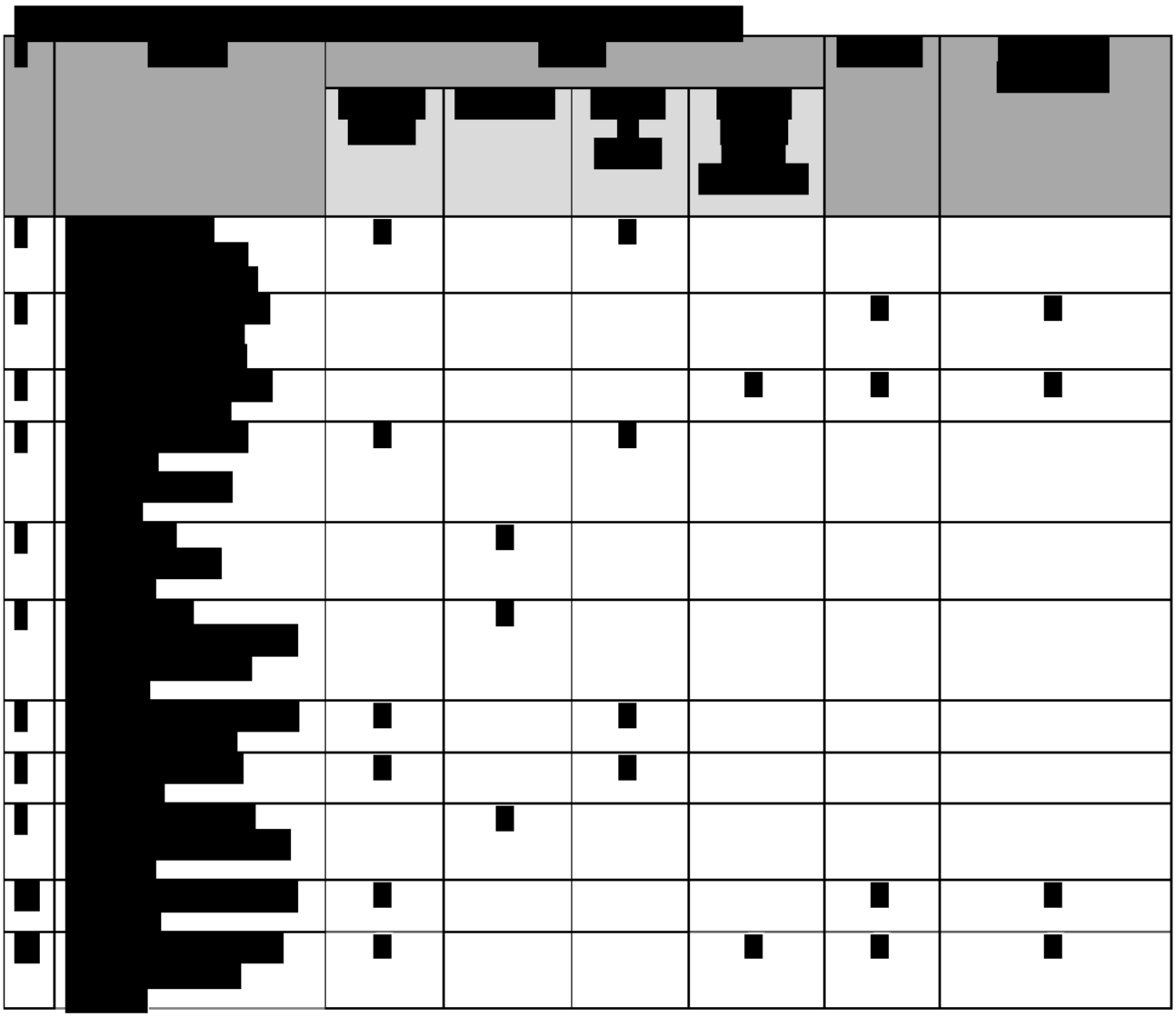
SV.5 Epidemiological study exposure

Europe:
The MAH has completed one epidemiological study to elucidate safety issues.

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person time (if appropriate)	Comment
Prevalence and Incidence of Problematic Prescription Opioid Use and Abuse in the United Kingdom and Germany	To investigate the 5-year prevalence, incidence rate and cumulative incidence of problematic prescription opioid use and abuse in the UK between 01 January 2008 and 31 December 2012	CPRD (UK) and German IMS Disease Analyzer (Germany)	5 years (2008-2012)	37 incident opioid use disorder cases diagnosed after 39,295 patient-years of oxycodone exposure (UK). 24 incident opioid use disorder cases diagnosed after 12,941 patient-years of oxycodone exposure (Germany)	Oxycodone in this study relates to all oxycodone products and not specifically to oxycodone sold and distributed by the MAH

[redacted]

[redacted]



Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for harm from overdose

A worldwide cumulative search of the international safety database was performed in April 2017 to identify all cases reporting potential harm from an oxycodone hydrochloride overdose (intentional and accidental).

There were [redacted] cases identified reporting [redacted] events with the following MedDRA Preferred Terms (MedDRA PTs):

- Accidental overdose (n=[redacted])
- Intentional overdose (n=[redacted])
- Prescribed overdose (n=[redacted])
- Overdose (n=[redacted])
- Toxicity to various agents (n=[redacted])

Of these [redacted] cases, [redacted] cases (4.0 %) occurred within Europe, and [redacted] cases (96.0 %) outside Europe. During the oxycodone hydrochloride development programme there were no incidences of overdose.

Of the [redacted] cases, [redacted] cases had a fatal outcome, of which [redacted] cases (2.3 %) originated from Europe and [redacted] cases (97.7 %) originated from outside Europe.

Of the [redacted] reported events of overdose, [redacted] events (90.1 %) were categorised as serious and [redacted] events (9.9 %) as non-serious.

The most commonly reported events were respiratory depression, somnolence and coma which are known symptoms of oxycodone hydrochloride overdose and are listed in the CSP.

SVI.2 Potential for transmission of infectious agents

No components of animal or human origin are used in the manufacture of oxycodone hydrochloride formulations. Therefore, there is no risk for transmission of infectious agents.

SVI.3 Potential for misuse for illegal purposes

SVI.3.1 Abuse potential for Oxycodone hydrochloride formulations

A cumulative search of the international safety database was performed in April 2017 to identify all worldwide cases country of incidence Europe including MedDRA PTs related to misuse for illegal purposes.

There were [redacted] events reported with the following MedDRA PTs:

- Drug use disorder (n=[redacted])
- Drug abuser (n=[redacted])
- Intentional product misuse (n=[redacted])
- Substance use disorder (n=[redacted])
- Substance abuser (n=[redacted])

In addition there were a further [redacted] of drug diversion in Europe. Whilst these cases of drug diversion

do not describe actual abuse or misuse, they indicate the potential for abuse of diverted drug product.

Of the total [redacted] events reported, [redacted] (68.6 %) events were serious and [redacted] (31.4 %) events were non-serious.

Outcome

Of the [redacted] events, [redacted] (5.9 %) events described fatal outcomes and [redacted] (6.7 %) events had an outcome of recovered.

Trends of misuse

The table below provides the trends identified in the cases reporting misuse of oxycodone hydrochloride for illegal purposes;

Part II. SVI. Table 1 – Trends of misuse for illegal purposes with oxycodone hydrochloride

Method of misuse for illegal purposes	Incidence count
Obtainment of oxycodone hydrochloride	
Illegal purchase of OxyContin tablets	[redacted]
Fraudulent purchase of OxyContin tablets from different pharmacies	
Purchase of OxyContin from the street market	
Illegal possession of non-prescription drugs including theft and trafficking	
Prescription tampering	
Nurse emptying OxyNorm capsules prescribed for the patients with the purpose of using the oxycodone hydrochloride for her own personal use	[redacted]
Patients trying to obtain oxycodone hydrochloride prescription from different physicians	[redacted]
Taking oxycodone hydrochloride that was prescribed for their relatives (husbands, friends, father, brother-in-law and brother)	[redacted]
Inappropriate administration	
Crushing and intravenously injecting OxyContin	[redacted]
Crushing and snorting OxyContin	
Crushing and drinking OxyContin	

SVI.3.2 Abuse potential for Oxycontin New Formulation (ONF)

SVI.3.2 .1 Clinical trial data

[redacted]

[redacted]

SVI.3.2 .2 Epidemiological data

[redacted]

[redacted]

[redacted]

SVI.3.2 .3 Postmarketing data

[redacted]

[redacted]

[redacted]

[redacted]

SVI.4 Potential for medication errors

SVI.4.1 Description of medication errors during the clinical trial programme

Not applicable due to time elapsed since clinical development programme and extensive post-market data which provides a more relevant analysis of risk of medication error and actions taken.

SVI.4.2 Preventive measures for the final product(s) being marketed

As a controlled substance, legislation states that a prescription is required before oxycodone hydrochloride can be obtained. This is to ensure that appropriate healthcare professionals oversee the utilisation of the product by appropriate patients and within appropriate dosage, route and frequency. Dispensation of limited quantities of the drug will also limit the potential for medication errors.

[redacted]

The packaging of all formulations of oxycodone hydrochloride is carefully designed to allow clear differentiation between different formulations, routes of administration and doses. The SmPCs and PILs provide clear guidance on posology, including special warnings on avoidance of inappropriate administration that may be associated with risk of harm.

SVI.4.3 Effect of device failure

This section is not applicable for the oxycodone hydrochloride formulations.

SVI.4.4 Reports of medication errors with the marketed product(s)

A search of the international safety database was performed in April 2017 to identify all cases with EU country of incidence since the IBD (12 December 1995) involving terms related to medications errors.

There were [redacted] cases identified reporting [redacted] adverse events with the following MedDRA PTs:

- Accidental overdose (n=[redacted])
- Drug administration error (n=[redacted])
- Drug dispensing error (n=[redacted])
- Drug prescribing error (n=[redacted])
- Inappropriate schedule of drug administration (n=[redacted])
- Incorrect dose administered (n[redacted])
- Incorrect route of drug administration (n[redacted])
- Prescribed overdose (n[redacted])
- Intentional overdose (n=[redacted])
- Overdose (n[redacted])
- Toxicity to various agents (n[redacted])
- Wrong drug administered (n[redacted])
- Wrong technique in product usage process (n[redacted])

A description of the trends of medication errors is depicted in the table below

Part II. SVI. Table 3 – Trends of medication error with oxycodone hydrochloride

Product name: oxycodone hydrochloride (oral and injectable formulations)				
Description of error	**Number of occurrences**	**Analysis of cause**	**Steps taken to prevent**	**Comment**
Dispensing error	[redacted] identified in the international safety database that document dispensing errors	Confusion over product packaging between prolonged-release formulation and immediate release formulation, due to similarity of the boxes	Redesign the cartons, labels and foils (where applicable) so there is a clear difference between the immediate release and prolonged release ranges With respect to the oral dosage forms the wording immediate release and prolonged release have been used to further differentiate between the ranges Added the dosing schedule wording to each pack for further clarification	Variations have been submitted to various regulatory agencies
Incorrect route of drug administration	[redacted] identified in the international safety database that document incorrect route of drug administration	Oral oxycodone hydrochloride liquid administered intravenously ([redacted] and subcutaneously [redacted]	In France the design and arrangement of information on cartons and blisters for oxycodone hydrochloride injection were changed in 2010 following notifications of medication errors from French HA	
	[redacted] of instances in which oxycodone hydrochloride was crushed due to swallowing difficulties in patients with cancer	Administration of crushed oxycodone hydrochloride tablets	The CSP for oxycodone hydrochloride states in section 4.4 Special warnings and precautions for use that '*The prolonged release tablets must be swallowed whole, and not broken, chewed or crushed*'.	

SVI.5 Potential for off-label use

The Applicant has extensive post marketing experience with oxycodone hydrochloride and therefore can analyse actual off label. The data describing actual off-label use documented in section SV.4 demonstrate that off-label use in the post-marketing setting is limited to few cases of use for the indication of restless legs syndrome. The adverse events reported in these cases do not demonstrate any additional safety concerns.

SVI.6 Specific Paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

There are no Paediatric Investigational Plans for oxycodone hydrochloride products in Europe as their national registrations pre-date the paediatric legislation.

SVI.6.2 Potential for paediatric off-label use

It cannot be excluded that in particular situations, physicians in specialised pain centres might decide to prescribe oxycodone hydrochloride to children suffering from chronic severe pain due to lack of alternative therapeutic options. [redacted]

SVI.7 Conclusions

Part II. SVI. Table 4 – Safety concerns from this module to be carried through to Part II SVIII.

Safety concerns from this module (to be carried through to Part II Module SVIII)	
Safety concern	**Comment**
Overdose intentional	Important identified risk
Overdose accidental	Important identified risk
Drug abuse	Important identified risk
Medication error	Important potential risk

Part II: Module SVII - Identified and potential risks

Non-ATMP version

SVII.1 Newly identified safety concerns (since this module was last submitted)

This is the seventh RMP that amalgamates all oxycodone hydrochloride formulations (parenteral, orodispersible tables prolonged release tables and oral capsules). No new risks have been identified and added to this RMP since the last oxycodone hydrochloride RMP.

SVII.2 Recent study reports with implications for safety concerns

No new safety findings have been identified from Clinical Study Reports since the last RMP.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

Part II. SVII. Table 1 – Detail of Important identified risk – Respiratory depression

Identified risk	Respiratory depression
Frequency	*Clinical data* The frequency of respiratory depression based on the clinical data is uncommon (1/1,000 to < 1/100) *Post-marketing data* Cumulatively to date [redacted] worldwide cases, reporting [redacted] adverse events indicative of respiratory depression were identified. The most frequently reported respiratory depression adverse events included the following PTs: Dyspnoea (n= [redacted], 31.9%), Respiratory depression (n= [redacted], 14.3%), Respiratory arrest (n= [redacted], 6.3%), Respiratory rate decreased (n= [redacted], 4.9%), Oxygen saturation decreased (n= [redacted], 4.5%), Cardiac arrest (n= [redacted], 4.3%), Respiratory failure (n= [redacted], 4.0%), Cyanosis (n= [redacted], 3.3%), Bradypnoea (n= [redacted], 2.8%), Apnoea (n= [redacted] 2.6%), Hypoxia (n= [redacted], 2.6%). The previous list of events make up 81.5% of the total reported. The remaining 18.5% of PTs consist of Respiratory distress, Asphyxia, Cardio-respiratory arrest, Hypopnoea, Respiratory disorder, Sleep apnoea syndrome, Respiration abnormal, Blood pH decreased, PCO2 abnormal, Hypoventilation, Acute respiratory failure, Respiratory acidosis, PO_2 abnormal, Breath sounds abnormal, PO_2 decreased, PCO_2 increased, Anoxia, Blood pH abnormal, Oxygen saturation abnormal. [redacted] Of the [redacted] worldwide cases, [redacted] (88.7%) cases of respiratory depression originated outside Europe and [redacted] (11.3%) cases originated from within Europe. [redacted] Breakdown by formulation (where data available): • Prolonged release oral tablets: [redacted] (77.2%) adverse events • Immediate release oral capsules: [redacted] (3.0%) adverse events • Immediate release oral liquid: [redacted] (<1%) adverse events • Orodispersible tablets: [redacted] (<1%) adverse events • Injectable formulation: [redacted] (1.0%) adverse events

Seriousness / outcomes	**Seriousness**: Of the [redacted] worldwide adverse events, [redacted] (60.9%) adverse events were serious **Outcome**: Of the [redacted] worldwide adverse events: • [redacted] (15.2%) were associated with a fatal outcome. • [redacted] (19.3%) were associated with a recovered outcome • [redacted] (<1%) were associated with a recovered with sequelae outcome • [redacted] (2.2%) was associated with a recovering outcome • [redacted] (3.6 %) were not recovered • [redacted] (59.4%) did not report an outcome
Severity and nature of risk	Respiratory depression is potentially life-threatening and may result in hypoventilation or neurologic injury. In terms of associated risk factors, out of the [redacted] worldwide cases: • [redacted] (15.1%) of the cases also report an adverse event of drug abuse • [redacted] (30.3%) of the cases also report an adverse event of intentional overdose, accidental overdose
Background incidence / prevalence	As respiratory depression is a broad term with varying severity and multifactorial causes, an incidence rate in the general population is not available.

Risk groups or risk factors	Risk groups: • Opioid naive patients • Patients abusing oxycodone hydrochloride • Overdose • Neonates (risks of respiratory depression in neonates) Risk factors for respiratory depression include: • Chronic obstructive airways disease • Cor pulmonale • Severe bronchial asthma • Pre-existing respiratory depression • Patients with substantially decreased respiratory reserve • Hypercarbia • Hypoxia when oxycodone is given together with other agents that depress respiratory drive or consciousness such as sedatives or hypnotics • Delayed gastric emptying • Pre and post-operative oxycodone hydrochloride administration
Potential mechanisms	The primary mechanism of respiratory depression by opioids involves a reduction in the responsiveness of the brainstem respiratory centres to carbon dioxide[1].
Preventability	Preventable by proper patient selection especially with cautious use in the pre and post-operative period, in opioid naive patient and patients with a history of drug or alcohol abuse. Respiratory depression may be reversed by the use of intravenous naloxone.
Impact on individual patient	Respiratory depression represents an acute risk to health rather than a long-term effect with associated impact on quality of life.

Potential public health impact of safety concern	The worldwide reporting rate of respiratory depression was one event per [redacted] patient months and its frequency based upon clinical trials is uncommon. Respiratory depression arising from opioids has a risk of significant harm to patients. Public health impact can be minimised by focussing on the risk factors for respiratory depression, especially abuse and overdose.
Evidence source	International drug safety database search (worldwide data reported since DIBD)
MedDRA terms (version 19.1)	Acute central respiratory depression (narrow SMQ), Postoperative respiratory distress (PT)

[1]Goodman and Gilman. The Pharmacological basis of therapeutics eleventh edition. McGraw-Hill.

Part II. SVII. Table 2 – Detail of Important identified risk – Ileus

Identified risk	Ileus
Frequency	*Clinical data* The frequency of ileus based on the clinical data is uncommon (1/1,000 to < 1/100) *Post-marketing data* [redacted] cases reporting [redacted] adverse events falling into the ileus search strategy were identified. The reported adverse events included the following PTs: Gastrointestinal hypomotility ([redacted]), Gastrointestinal motility disorder ([redacted]), Ileus ([redacted]), Ileus paralytic ([redacted]), Subileus ([redacted]). [redacted] Breakdown by formulation (where data available): • Prolonged release oral tablets: [redacted] (71.3%) adverse events • Immediate release capsule: [redacted] (7.4%) adverse events • Powder for oral solution: [redacted] (4.1%%) adverse events • Solution for injection: [redacted] (<1%)

Seriousness / outcomes	**Seriousness**: Of the [redacted] worldwide adverse events identified in the international drug safety database, [redacted] (77.0%) adverse events were serious and [redacted] (23%) adverse events were non-serious. **Outcome**: of the [redacted] worldwide adverse events: • [redacted] (3.8%) adverse events had a fatal outcome • [redacted] (10.1%) were recovering • [redacted] (12.4%) were not recovered • [redacted] (36.4%) were recovered • [redacted] (1.4%)were recovering with sequelae • [redacted] (35.9%) did not report an outcome
Severity and nature of risk	Postoperative ileus persists longer than three days, however the time depends on the nature of surgery (i.e. colonic surgery has the longest duration). The clinical consequences may be substantial as patients are at risk of developing pulmonary complications.
Background incidence / prevalence	In the United States, postoperative ileus occurs in approximately 50% of patients that undergo major surgeries[1].
Risk groups or risk factors	The most common cause of developing ileus is following abdominal surgery. A potential association between immediate post-operative administration of oxycodone hydrochloride and ileus is likely to be more severe, less predictable, and more difficult to reverse with controlled release formulations Risk factors for paralytic ileus include: • Gastrointestinal surgery, infection or injury[4] • Acute abdomen • Abdominal cancers • Electrolyte imbalance • Spinal surgery • Conditions that affect muscle and nerve function such as Parkinson's disease • Paralytic ileus • Chronic constipation • Severe constipation • Obesity[5] • Pre and post-operative oxycodone hydrochloride administration

Potential mechanisms	Pain, emotional stress, pre-medication, anaesthesia (including associated cold, hypoxia and electrolyte disorders) and surgery itself (especially abdominal surgery) all can delay gastric emptying in the pre and post-operative periods[2]. Thus administration of oral medications during this period of gastric stasis can result in unpredictable pharmacokinetics. This is particularly relevant for controlled release formulations, where a greater degree of dissolution may occur during gastric stasis, leading to increased drug absorption ('dose dumping') when normal gastric activity resumes and drug passes into the small intestine. The surgical stress response contributes to the systemic generation of endocrine and inflammatory mediators that causes the development of ileus[3].
Preventability	Controlled release products, normal/immediate release products (oral and parenteral), are not recommended for pre-operative use or within the first 12-24 hours post-operatively.
Impact on individual patient	Ileus itself is subjectively unpleasant (anorexia, nausea, vomiting, colicky abdominal pain, distension). However the most significant potential impact on the patient for this risk relates to the potential for unpredictable pharmacokinetics.
Potential public health impact of safety concern	The worldwide reporting rate of ileus was one event per [redacted] patient months and its frequency based upon clinical trials is uncommon. A potential association between immediate post-operative administration of oxycodone hydrochloride and ileus is likely to be more severe, less predictable, and more difficult to reverse with controlled release formulations.
Evidence source	International drug safety database search (worldwide data reported since DIBD)
MedDRA terms	Gastrointestinal hypomotility (PT), Gastrointestinal motility disorder (PT), Ileus (PT), Ileus paralytic (PT), Postoperative ileus (PT), Subileus (PT)

[1].Livingston EH, Passaro EP Jr. Postoperative ileus. *Dig Dis Sci.* Jan 1990;35(1):121-32

[2]. Petring OU and Blake DW. Gastric emptying in adults: an overview related to anaesthesia. Anaesth Intensive Care. 1993; 21(6): 774-78

[3]. Mukherjee S. Ileus. Medscape : http://emedicine.medscape.com/article/178948-overview#a0101, last accessed on December 2012

[4] Kronberg U, Kiran RP, Soliman MS, et al. A characterization of factors determining postoperative ileus after laparoscopic colectomy enables the generation of a novel predictive score. Ann Surg. 2011;253:78-8

[5] Reference:A.J. P karsky, Y. Saida, T. Yamaguchi et al.Is obesity a high-risk factor for laparoscopic colorectal surgery?Surg Endosc., 16 (2002), pp. 855–858

Part II. SVII. Table 3 – Detail of Important identified risk – Accidental overdose

Identified risk	Accidental overdose
Frequency	*Post-marketing data* [redacted] cases reporting [redacted] adverse events indicative of accidental overdose were identified, including the following PTs: Overdose (n=[redacted] 65.7%), Accidental overdose (n=[redacted], 30.9%) and Toxicity to various agents (n=[redacted], 3.4%). [redacted] Of the [redacted] worldwide cases, [redacted] (4.2%) originated from Europe and [redacted] (95.8%) from outside Europe. [redacted] Breakdown by formulation (where data available) • Prolonged release oral tablets : [redacted] (60.9%) adverse events • Immediate release capsules : [redacted] (1.2%) adverse events • Orodispersible tabets: [redacted] (<1%) adverse events • Immediate release oral solution: [redacted] (<1%) adverse events • Injectable formulation: [redacted] (<1%) adverse events

Seriousness / outcomes	**Seriousness**: Of the [redacted] worldwide adverse events, [redacted] (89.8%) adverse events were serious and [redacted] (10.2%) adverse events were non-serious. **Outcome**: Of the [redacted] worldwide adverse events: • [redacted] (63.6%) had a fatal outcome • [redacted] (<1%) had not recovered • [redacted] (5.5%) recovered • [redacted] (<1%) recovered with sequelae • [redacted] (<1%) were recovering • [redacted] (30.1%) did not report an outcome
Severity and nature of risk	Accidental overdoses can manifest as extensions of the pharmacological action of oxycodone hydrochloride including respiratory depression, somnolence, progressing to stupor or coma, skeletal muscle flaccidity, miotic pupils, bradycardia, hypotension and death. In terms of associated risk factors, out of the [redacted] worldwide cases: • [redacted] (21.0%) of the cases also report drug abuse • [redacted] (7.0%) of the cases also report drug dependence
Background incidence / prevalence	Not applicable.
Risk groups or risk factors	• Patients with hepatic and renal impairment. • Co-administration of oxycodone hydrochloride with drugs that reduce the clearance of the drug, which leads to an increase in plasma concentration • Patients who are abusing opioids are at risk of accidental overdose. • Delayed gastric emptying • Pre and post-operative oxycodone hydrochloride administration

Potential mechanisms	The accumulation of oxycodone hydrochloride in the body due to reduced clearance, increased dosages or inappropriate drug administration may lead to accidental overdose.
Preventability	Correctly adjust the dose in patients that have hepatic or renal impairment or whom are taking concomitant medication that may potentially lead to an increase in plasma concentration. Symptoms of accidental overdose are predictable: upon recognition, overdose can be successfully reversed by administration of naloxone.
Impact on individual patient	Accidental overdose requires immediate medical intervention.
Potential public health impact of safety concern	The worldwide frequency of accidental overdose in the post-marketing setting is approximately one in [redacted] patient months exposure.Approximately 21% of the events occurred in cases also describing drug abuse, and 92 % of the events occurred in the USA. Whilst it is not possible to put this frequency into the context of background incidence, the symptoms of overdose are predictable and reversible. Accidental overdose of oxycodone hydrochloride is usually serious and can result in fatal outcomes. Symptoms of overdose are reversible by administration of naloxone.
Evidence source	International drug safety database search (worldwide data reported since DIBD)
MedDRA terms	Overdose (PT), Accidental overdose (PT), Toxicity to various agents (PT)

Part II. SVII. Table 4 – Detail of Important identified risk – Intentional overdose

Identified risk	Intentional overdose
Frequency	Post-marketing data [redacted] worldwide cases reporting [redacted] adverse events indicative of intentional overdose were identified. The reported intentional overdose adverse events included: Intentional overdose (n=[redacted]) and Prescribed overdose (n=[redacted]) [redacted] Of the [redacted] worldwide cases, [redacted] (97.0%) cases of intentional overdose originated outside Europe and [redacted] cases (3.0%) cases originated from Europe. Cumulative sales data originating from Europe for all oxycodone hydrochloride formulations was approximately [redacted] patient months or one case per [redacted] patient months and outside of Europe was [redacted] patient months or one case per [redacted] patient months exposure. Breakdown by formulation (where data available): • Prolonged release oral tablets: [redacted] (59.2%) adverse events • Immediate release capsules: [redacted] (<1%) adverse events
Seriousness / outcomes	**Seriousness**: Of the [redacted] worldwide adverse events identified [redacted] (92.5%) adverse events were serious and [redacted] (7.5%) adverse events were non-serious. **Outcome**: Of the [redacted] worldwide adverse events: • [redacted] (46.4%) adverse events had a fatal outcome

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	• [redacted] (5.6%) adverse events recovered • [redacted] (<1%) adverse events were recovering • [redacted] (<1%) adverse event was recovered with sequelae • [redacted] (47.5%) adverse events did not report an outcome
Severity and nature of risk	Of the [redacted] worldwide adverse events [redacted] (96.8%) adverse events originated from the USA and [redacted] (3.2 %) adverse events from Europe. Intentional overdoses can manifest as extensions of oxycodone hydrochlorides pharmacological action including respiratory depression, somnolence, progressing to stupor or coma, skeletal muscle flaccidity, miotic pupils, bradycardia, hypotension and death.
Background incidence / prevalence	Not applicable.
Risk groups or risk factors	Patients likely to abuse oxycodone hydrochloride: Of the [redacted] worldwide events of intentional overdose, [redacted] adverse events were reported in cases also describing drug abuse (55 %) of which [redacted] adverse events had a fatal outcome.Patients with a medical history of, or concurrent, depression or suicidal ideation.
Potential mechanisms	The wish of the patient to reduce his pain burden, to abuse oxycodone hydrochloride or to utilise oxycodone hydrochloride to self harm, may lead to an intentional overdose of oxycodone hydrochloride.
Preventability	Identifying patients with chronic pain whose drug use patterns have changed, patients at risk of abusing oxycodone hydrochloride including those with previous drug and alcohol problems and patients at risk of self-harming.
Impact on individual patient	Intentional overdose requires immediate medical intervention.
Potential public health impact of safety concern	The worldwide frequency of intentional overdose in the post-marketing setting is approximately one in [redacted] patient months exposure. 95 % occurred in the USA. Whilst it is not possible to put this frequency into the context of background incidence, the symptoms of overdose are predictable and reversible. Intentional overdose of oxycodone hydrochloride is usually serious and can result in fatal outcomes. Symptoms of overdose are reversible by administration of naloxone.
Evidence source	International drug safety database search (worldwide data reported since DIBD)
MedDRA terms	Intentional overdose (PT), Prescribed overdose (PT)

Part II. SVII. Table 5 – Detail of Important identified risk – Drug withdrawal syndrome and physical dependence

Identified risk	Drug withdrawal syndrome and physical dependence
Frequency	Post-marketing data [redacted] worldwide cases reporting [redacted] adverse events indicative of were identified. The reported PTs included: Drug withdrawal syndrome (n=[redacted], 82.7%), Withdrawal syndrome (n=[redacted] 13.3%), Drug withdrawal syndrome neonatal [redacted], <1%), Rebound effect (n[redacted], <1%), Drug detoxification (n[redacted], 1.6%), Drug withdrawal convulsion (n[redacted], <1%), Drug withdrawal headache (n[redacted], <1%), Drug rehabilitation (n[redacted], <1%). The worldwide exposure data for all oxycodone formulations was [redacted] patient months. The number of worldwide cases falling into the search criteria received was [redacted]. This equates to one case of drug withdrawal syndrome and physical dependence per [redacted] patient months of exposure. Breakdown by formulation (where data available): • Prolonged release oral tablets: [redacted] (94.2%) adverse events • Immediate release capsules: [redacted] (1.5%) adverse events • Orodispersible tablets: [redacted] (<1%) adverse events • Immediate release oral solution: [redacted] (<1%) adverse
Seriousness / outcomes	**Seriousness:** Of the [redacted] worldwide adverse events [redacted] adverse events (12.9 %) were serious and [redacted] (87.1%) were non- serious. **Outcome**: Of the [redacted] worldwide adverse events: • [redacted] (<1%) adverse events were associated with a fatal outcome • [redacted] (6%) adverse events were not recovered • [redacted] (9.4%) adverse events recovered • [redacted] (<1%) adverse events recovered with sequelae • [redacted] (1.1%) adverse events were recovering • [redacted] (83.3%) adverse events did not report an outcome

Severity and nature of risk	Withdrawal (abstinence syndrome), when it occurs, may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.
Background incidence / prevalence	Not applicable.
Risk groups or risk factors	• Patients on prolonged opioid use or those whom abruptly cease therapy. • Neonates (withdrawal effects in newborns following maternal exposure)
Potential mechanisms	In response to long-term exposure to relatively high doses of exogenous opioids, cells internalize their mu and delta opioid receptors. Therefore, increased opioid levels and/or increased opioid potency are necessary to generate the same effect on fewer receptors. Similarly, once the exogenous opioids are removed from the system, the remaining endogenous opioids are unable to sufficiently activate the small number of remaining receptors (withdrawal).
Preventability	Patients on long term use of opioids should gradually reduce the dose of opioids before discontinuation.
Impact on individual patient	The symptoms of drug withdrawal may require treatment.
Potential public health impact of safety concern	The worldwide frequency of physical dependence and drug withdrawal syndrome in the post-marketing setting is approximately one in [redacted] patient months exposure. Approximately 87% of the adverse events reported were non-serious. Drug withdrawal syndrome is a well known and described pharmacological effect, and is preventable with sensible dose reduction in properly managed pain patients.
Evidence source	International drug safety database search (worldwide data reported since DIBD).
MedDRA terms	Drug withdrawal convulsions (PT), Drug rehabilitation (PT), Drug withdrawal headache (PT), Drug withdrawal maintenance therapy (PT), Drug withdrawal syndrome (PT), Drug withdrawal syndrome neonatal (PT), Rebound effect (PT), Steroid withdrawal syndrome (PT), Withdrawal arrhythmia (PT), Withdrawal syndrome (PT), Drug detoxification (PT), Detoxification (PT).

Part II. SVII. Table 6 – Detail of Important identified risk – Drug abuse

Identified risk	Drug abuse
Frequency	**Oxycodone hydrochloride formulations excluding ONF (*data from March 2015)** *Post-marketing data* Cumulatively to date [redacted] worldwide cases, reporting [redacted] adverse events indicative of abuse were retrieved from international safety database. Of the [redacted] worldwide cases, [redacted] (1%) cases originated from Europe and [redacted] (99%) from outside of Europe. The reported PTs included: Drug abuse (n=[redacted], 51%), Drug abuser (n=[redacted] 16%), Drug diversion (n=[redacted], <1 %), Intentional drug misuse (n=[redacted], 5%), Needle track marks (n[redacted], <1%), Neonatal complication of substance abuse (n[redacted], <1%), Substance abuse (n=[redacted], 28%), Substance use (n[redacted], <1%). The worldwide exposure data for all oxycodone hydrochloride formulations (excluding ONF) was [redacted] patient months. The number of worldwide cases falling into the search criteria received was [redacted]. This equates to one case of drug abuse per [redacted] patient months of exposure. Of the [redacted] worldwide cases, [redacted] (99%) cases of drug abuse originated outside Europe and [redacted] (1%) cases originated from Europe. Cummulative sales data originating from Europe for all oxycodone hydrochloride formulation was approximately [redacted] patient months or one case per [redacted] patient months and outside of Europe was [redacted] patient months or one case per [redacted] patient months exposure. [redacted]

	• [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]
Seriousness / outcomes	**Oxycodone hydrochloride formulations excluding ONF (*data from March 2015)** **Seriousness**: Of the [redacted] worldwide adverse events, [redacted] (96%) were serious and [redacted] (4%) were non-serious. **Outcome:** Of the [redacted] worldwide adverse events: • [redacted] adverse event (6%) were fatal • [redacted] adverse events (<1%) were not recovered • [redacted] adverse events (2%) were recovered • [redacted] adverse events (<1%) recovered with sequelae • [redacted] (1%) adverse events were recovering • [redacted] (90%) did not report an outcome [redacted]

Severity and nature of risk	**Oxycodone hydrochloride formulations excluding ONF (*data from March 2015)** • [redacted] (7%) cases also report an adverse event of overdose • [redacted] (4%) cases also report an adverse event of drug dependence, polysubstance dependence • [redacted] (5%) cases report alcohol use, alcohol abuse, alcoholism as medical history [redacted]
Background incidence / prevalence	A true prevalence is difficult to establish as it depends on the substance abused and on the geographical region. The 2012 EMCDDA report states that recent national estimates of problem opioid use (including heroin) vary between < one and seven cases per 1 000 population aged 15–64[1]. The report does not provide any estimates of the prevalence of problem prescription opioid use in Europe however.
Risk groups or risk factors	Risk factors include socio-demographic factors, pain and drug-related factors, genetics, environment, psychosocial and family history and alcohol and substance use disorders[2].
Potential mechanisms	Mu receptor agonists have also effect on mood and often they can cause euphoria. Abuse refers to the use of the product for non-medical purpose, recreational.
Preventability	Identifying, manage and tailor pain treatment for patients at risk.
Impact on individual patient	Abuse of drugs often leads to serious medical problems and the individual's social and economic status may be affected with an inability to retain a job and changes in relationships with family and friends.
Potential public health impact of safety concern	Abuse of drugs often leads to serious medical problems and the individuals social and economic status may be affected with an inability to retain a job and changes in relationships with family and friends; however vulnerable patients can be identified and monitored accordingly. The potential impact on public health may be substantial, although the post-market data in Europe indicates that the issues with prescription opiate abuse are significantly different to the risks seen with the USA healthcare system.
Evidence source	• International drug safety database search • Published literature

MedDRA terms	Drug abuse (PT), Drug abuser (PT), Intentional drug misuse (PT Maternal use of illicit drugs (PTNeedle track marks (PT), Neonatal complications of substance abuse (PT), Substance abuse (PT), Substance abuser (PT), Substance use (PT), Drug diversion (PT)

[1].European Monitoring Centre for Drugs and Drug Addiction. Annual Report 2012. The State of the Drugs Problem in Europe.
[2].Liebschutz JM, Saitz R, Weiss RD, Averbuch T, Schwartz S, Meltzer EC, Claggett-Borne E, Cabral H, Samet JH. Clinical factors associated with prescription drug use disorder in urban primary care patients with chronic pain. J Pain 2010; 11:1047-1055.

Part II. SVII. Table 7 – Detail of Important identified risk – Psychological dependence

Identified risk	Psychological dependence
Frequency	*Post-marketing data* **For Europe:** Cumulatively to date [redacted] cases reporting [redacted] adverse events indicative of psychological dependence were retrieved from international safety database. For psychological dependence patterns only European data was selected as patterns of psychological dependence in the context of the USA healthcare system is of little relevance for Europe. [redacted] From a **total worldwide** perspective, cumulatively to date there has been [redacted] cases reporting [redacted] The most frequently reported PTs included: Drug dependence (n=[redacted], 97.6%), Substance dependence (n=[redacted], 1.8%) and Dependence (n[redacted], <1%) Breakdown by formulation (where data available): [redacted]
Seriousness / outcomes	**Seriousness**: Of the 18,696 adverse events, [redacted] adverse events (99.7%) were serious and [redacted] (0.3%) adverse events were non-serious. **Outcome**: Of the 18,696 adverse events: • [redacted] (0.5%) adverse events were fatal • [redacted] (1.7%)adverse events not recovered • [redacted] (2.35%) adverse events were recovered • [redacted] (<1%)adverse events recovered with sequelae • [redacted] (6%) adverse events were recovering • [redacted] (93.3%) adverse events did not report an outcome

Severity and nature of risk	Patients who experience psychological dependence may have impaired control over drug use, compulsive use, and continued use despite harm or craving, the severity of which varies from patient to patient varying impacts on their social functioning.
Background incidence / prevalence	A true prevalence is difficult to establish as it depends on the substance the patient is dependent on and on the geographical region.
Risk groups or risk factors	Risk factors include socio-demographic factors, pain and drug-related factors, genetics, environment, psychosocial and family history and alcohol and substance use disorders[1].
Potential mechanisms	Mu receptor agonists have also effect on mood and often they can cause euphoria. Abuse refers to the use of the product for non-medical purpose, recreational. Psychological dependence is thought to result from neurological changes, with genetic, psychosocial, and environmental factors influencing its development and manifestations.
Preventability	Identifying, manage and tailor pain treatments for patients at risk.
Impact on individual patient	The patient's psychological dependence may manifest in drug seeking behaviours which may impact their ability to function normally socially. The patient may also continue to seek medications even after the resolution of their pain.
Potential public health impact of safety concern	Reporting rate of European psychological dependence from the post-market data is one event per [redacted] patient months exposure in the EU.
Evidence source	• International drug safety database search (data reported since DIBD). • Published literature
MedDRA terms	Dependence (PT), Drug dependence (PT), Substance dependence (PT), Drug dependence antepartum (PT), Drug dependence postpartum (PT).

Part II. SVII. Table 8 – Detail of Important identified risk – Use in patients with hepatic impairment

Identified risk	Use in patients with hepatic impairment
Frequency	*Clinical trial data* Please see Part II SIV.3. *Post-marketing data* Cumulatively to 01 April 2013, [redacted] worldwide cases with medical history MedDRA PTs falling into the hepatic disorders SMQs have been received. These [redacted] cases contained [redacted] adverse events [redacted]
Seriousness / outcomes	**Seriousness**: Of the [redacted] worldwide adverse events reported in patients with medical history of hepatic impairment [redacted] (40 %) were serious and [redacted] (60%) were non-serious. **Outcome**: Of the [redacted] worldwide adverse events reported in patients with medical history of hepatic impairment • [redacted] (10.1%) were fatal • [redacted] (6.6%) were not recovered • [redacted] (3.5%) were recovering • [redacted] (13.4%) were recovered • [redacted] (<1%) was worsening • [redacted] (<1%) recovered with sequelae • [redacted] (66.0%) did not report an outcome
Severity and nature of risk	The table below depicts the most commonly reported PTs in cases documenting the use of oxycodone hydrochloride in patients with hepatic impairment. Proportional reporting rate was calculated to compare patients with hepatic impairment with patients without hepatic impairment. The formula below was used: PRR= a/(a+b) c/(c+d) where: a= Number of AE of interest in patients with hepatic impairment, b= Number of AE of interest in patients without hepatic impairment, c= Total number of AEs in patients with hepatic impairment, d= Total number of AEs in patients without hepatic impairment

PTs	Number of AEs in patients with hepatic impairment	Number of AEs patients without hepatic impairment	Proportional reporting ratio
Anxiety	[redacted]	[redacted]	0.75
Constipation			0.97
Drug abuse			0.51
Drug dependence			0.41
Drug ineffective			0.49
Drug withdrawal syndrome			0.60
Insomnia			1.06
Accidental overdose			2.08
Nausea			0.68
Pain			0.87
Somnolence			0.79
Substance abuse			0.72
Vomiting			0.85

* Cases included in the proportional reporting rate calculation covers data from IBD - April 2012

The list of most frequently reported PTs for cases of use of oxycodone in patients with hepatic impairment do not show any unexpected risks. *Multiple drug overdose* (PPR=2.08) occurs more than twice as frequently in patients with hepatic impairment compared with patients with normal hepatic function.

This can be explained by the fact that the metabolism of oxycodone is altered in patients with hepatic impairment and may lead to an increase in plasma level of oxycodone hydrochloride.

Background incidence / prevalence

The true incidence and prevalence of liver disease is difficult to ascertain because there are few population based registers of liver disease available to ensure proper case and comparator selection. The epidemiology of liver disease in Tayside (ELDIT) is a specially built register of liver disease for a well-defined geographical area of Scotland. All subjects resident in Tayside, and registered with a general practitioner (approximately 400,000 people), took part in a study between 1980 and 1999. In 2003, the database had records of 10,000 subjects who had been identified with liver disease or abnormal liver function[1].

In a retrospective study, it was found that 200 patients (1 in 1,000 of the West Suffolk population) with a mean age of 52 years were referred to a hepatology service per year. One-third of patients had cirrhosis (almost half due to alcohol). Annual incidence (per 100,000 population) were as follows: non-alcoholic fatty liver disease (29: of which 23.5 non-cirrhotic and 5.5 cirrhotic), hepatitis C (25), hepatitis B (3), alcohol-related cirrhosis (12.5), primary biliary cirrhosis (3.5), autoimmune hepatitis

	(3), primary sclerosing cholangitis (2), haemochromatosis (2), hepatocellular carcinoma (1.5) and oesophageal variceal haemorrhage (6.5).[2]
Risk groups or risk factors	Risk factors for hepatic disorders may include pre-existing liver disease, drug and substance use, obesity, alcohol consumption, exposure to liver toxins.
Potential mechanisms	Oxycodone hydrochloride is metabolised in the liver to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. CYP3A4 and CYP2D6 are the primary enzymes responsible for the formation of noroxycodone, oxymorphone and noroxymorphone.[3] When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, hence this may be accompanied by an increase in drug effects[4]
Preventability	Dosage adjustment for drugs used in patients with hepatic impairment. Caution must be exercised when administering oxycodone hydrochloride to patients with impaired hepatic function.
Impact on individual patient	In patients with moderate to severe liver disease the failure to biotransform oxycodone to oxymorphone may lead to an accumulation of oxycodone and noroxycodone in liver which subsequently leads to an increase in adverse events[5].
Potential public health impact of safety concern	The worldwide frequency of use in patients with hepatic impairment is approximately one case in [redacted] patient months of exposure. Approximately 60% of the reported adverse events were non-serious. The occurrence of adverse events in patient with hepatic impairment can be mitigated by careful dose titration and appropriate patient selection .The pattern of adverse events reported in patients with hepatic impairment was similar compared to the adverse events reported in patients with normal hepatic function.
Evidence source	• International drug safety database search (worldwide data reported since DIBD). • Published literature
MedDRA terms	Hepatic disorders (SMQ)

[1]Steinke−Douglas−T, Weston−Tanya−L, Morris−Andrew−D, MacDonald T. Dillon−John M. The epidemiology of liver disease in Tayside database: A population− based record−linkage study. Journal of Biomedical Informatics. 2002 June;35(3):186−193

[2] Whalley S, Puvanachandra P, Desai A, Kennedy H. Hepatology outpatient service provision in secondary care: a study of liver disease incidence and resource costs. Clinical Medicine, Journal of the Royal College of Physicians of London. 2007 April;7(2):119−124

[3] Kirvela M, Lindgren L, Seppala T *et al.* The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. J Clin Anesth. 1996; 8: 13-8

[4] [redacted]

[5]Foster A, Mobey E, Wang Z. Complicated pain management in a CYP450 2D6 poor metabolizer. Pain pract. 2007 Dec;(4):352-356. Epub 2007 Nov 6.

Part II. SVII. Table 9 – Detail of Important identified risk – Use in patients with renal impairment

Identified risk	Use in patients with renal impairment
Frequency	*Clinical trial data* Please see Part II SIV.3. *Post-marketing data* Cumulatively to 12 April 2017, [redacted] worldwide cases with medical history falling into the MedDRA search criteria have been received. These [redacted] worldwide cases contained [redacted] adverse events. [redacted]
Seriousness / outcomes	**Seriousness:** Of the [redacted] worldwide adverse events reported in patients with medical history of renal impairment [redacted] (49%) were serious and [redacted] (51%) were non-serious. **Outcome:** Of the [redacted] worldwide adverse events reported in patients with medical history of renal impairment • [redacted] (8.3%) were fatal • [redacted] (5.9%) were not recovered • [redacted] (5.1%) were recovering • [redacted] (24.0%) were recovered • [redacted] (<1%) were recovered with sequelae • [redacted] (56.4%) did not report an outcome
Severity and nature of risk	The study [redacted], aimed to investigate the effects of oxycodone hydrochloride prolonged release tablets in patients with moderate or severe renal impairment, has suggested that although renal impaired patients experienced an increase in sedation, no differences in other parameters such as respiratory rate, papillary constriction or overall 'drug effect' rating were observed. The table below depicts the most commonly reported PTs in cases documenting the use of oxycodone hydrochloride in patients with renal impairment. Proportional reporting rate was calculated to compare patients with renal impairment with patients without renal impairment. The formula below was used: $PRR = \frac{a/(a+b)}{c/(c+d)}$

	where: a= Number of AE of interest in patients with renal impairment, b= Number of most reported AE of interest in patients without renal impairment, c= Total number of AEs in patients with renal impairment, d= Total number of AEs in patients without renal impairment. [redacted] * Cases included in the proportional reporting rate calculation covers data over a period of 10 years (July 2002- June 2012) The list of most frequently reported PTs for cases of use of oxycodone in patients with renal impairment do not show any unexpected risks. The PRR of 10.27 for renal failure reflects the pre-existing renal disease.
Background incidence / prevalence	The incidence of renal failure in a population over 75 years of age is 10 times higher at 400 per million population (pmp) than it is in those under 40 years of age. The incidence is higher in males (1.3:1), in areas of social deprivation and in particular ethnic groups. In the United Kingdom it is 3.5 times higher in citizens of Asian or Afro-Caribbean backgrounds. In 1997 in Australia the incidence in Aboriginals was 435 pmp. In New Zealand the incidence in Maoris is three to four times higher than in Caucasoids. These ethnic variations may be related to the higher prevalence of diabetes and hypertension[2].
Risk groups or risk factors	Key risk factors for renal impairment may include diabetes and hypertension.
Potential mechanisms	Approximately 45% of oxycodone hydrochloride is bound to plasma proteins[3]. The drug and its metabolites are excreted in urine[4]. When compared to normal subjects, patients with mild to severe renal dysfunction (creatinine clearance <60 ml/min) may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-

	life of oxycodone and this may be accompanied by an increase in drug effects[5]. Renal impairment increases the concentration of oxycodone and noroxycodone in by approximately 50% and 20%[6].
Preventability	Risk reduced by using with caution in patients with renal failure. In addition, adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.
Impact on individual patient	Depending on the severity of the renal dysfunction. An increase in drug effects occurs in patients with renal dysfunction as a result of higher plasma concentration of the drug or its metabolites.
Potential public health impact of safety concern	The study [redacted] that aimed to investigate the effects of oxycodone prolonged release tablets in patients with moderate or severe renal impairment, has suggested that although renal impaired patients experienced an increase in sedation, no differences in other parameters such as respiratory rate, papillary constriction or overall 'drug effect' rating were observed. The frequency of use in patients with renal impairment is approximately one case in [redacted] patient months of exposure. The occurrence of adverse events in patient with renal impairment can be mitigated by careful dose titration.
Evidence source	• International drug safety database search (worldwide data reported since DIBD). • Published literature • Clinical trial data
MedDRA terms	Renal disorders (excl. Nephropathies HLGT) plus Nephropathies HLGT and selected preferred terms from renal function analyses HLT such as: Blood creatinine abnormal, Blood creatinine increased, Creatinine renal clearance decreased, Glomerular filtration rate abnormal, Glomerular filtration rate decreased, Inulin renal clearance abnormal, Inulin renal clearance decreased, Renal function test abnormal and Creatinine renal clearance abnormal.

[redacted]

[2] D.A. Warrell, T.M. Cox, J.D. Firth and E.J. Benz Jr (editors). Oxford Textbook of Medicine, 4th Edn. Oxford: Oxford University Press; 2003. p 3.26
[3] Leow K.P, *et al.* /determination of the serum protein binding of oxycodone and morphine using ultrafiltration. There Drug Monit 1993; 15:440-47
[4] Original NDA Section VI.C; Vol. 16:64. Human Pharmacokinetics and Bioavailability Integrated Summary
[5] Kirvela M, Lindgren L, Seppala T *et al.* The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. J Clin Anesth. 1996; 8: 13-8
[6] Oxycontin (oxycodone HCL controlled-release tablets) [package insert]. Stamford CT: Purdue Pharma LP,2007

Part II. SVII. Table 10 – Detail of Important identified risk – Hypersensitivity

Identified risk	Hypersensitivity
Frequency	*Clinical trial data* The frequency of anaphylactic/anaphylactoid reaction based on the clinical data is not known. *Post-marketing data* Cumulatively to 12 April 2017, [redacted] worldwide cases reporting [redacted] adverse events falling into the hypersensitivity search strategy have been received involving the following PTs: rash (n=[redacted] 31.8%), urticaria (n=[redacted] 14.7%), drug hypersensitivity (n=[redacted] 14.5%), hypersensitivity (n=[redacted], 8.3%). [redacted]
Seriousness / outcomes	**Seriousness**: Of the [redacted] worldwide adverse events falling into the hypersensitivity search strategy [redacted] (14%) were serious. **Outcome**: Of the [redacted] worldwide adverse events indicative of hypersensitivity • [redacted] (<1%) were fatal • [redacted] (4.3%) were recovering • [redacted] (22.7%) were recovered • [redacted] (<1%) recovered with sequelae • [redacted] (6.7%) not recovered • [redacted] (65.6%) did not report an outcome
Severity and nature of risk	Symptoms of hypersensitivity may range from mild contact dermatitis to anaphylactoid reaction such as angioedema which varies in severity. In rare cases symptoms can be life-threatening due to involvement of the airways, and circulatory system. Often the symptoms develop within a few minutes of contact with the allergen, so immediate treatment is essential.
Background incidence / prevalence	The incidence of anaphylactic reaction is approximately 4–5 per 100,000 persons per year [1], with an estimated life-time prevalence of 0.5–2%[2]. True allergic reactions appear to be very rare.
Risk groups or risk factors	Patients with a history of anaphylaxis, other allergies or auto-immune disorders such as asthma, or patients with a family history of anaphylactic responses [3].
Potential mechanisms	Opioids are capable of inducing Type I hypersensitivity reactions with repeat exposures, predominantly through mast cell degranulation resulting in histamine release[4].

Preventability	True allergic reactions appear to be rare; any immune-mediated reaction should be investigated. The use of oxycodone is contraindicated in patients with known hypersensitivity to oxycodone or to any of the excipients.
Impact on individual patient	Anaphylaxis, a severe form of hypersensitivity, is a rare response that can be life-threatening. Once the offending antigen is identified, anaphylaxis is preventable by avoiding future exposure. Any patient experiencing anaphylaxis should seek medical assistance. Anaphylaxis has a well established and successful treatment algorithm; the key is emergency access to treatment.
Potential public health impact of safety concern	Anaphylaxis, the severe form of hypersensitivity, is a rare response that can be life-threatening. Once the offending antigen is identified anaphylaxis is preventable by avoiding future exposure. Any patient experiencing anaphylaxis should seek medical assistance. Anaphylaxis has a well established and successful treatment algorithm; the key is emergency access to treatment.
Evidence source	• International drug safety database search (worldwide data reported since DIBD). • Published literature
MedDRA terms	Hypersensivity SMQ- narrow search

[1] Lee, JK; Vadas, P. Anaphylaxis: mechanisms and management. Clinical and experimental allergy. 2011. Journal of the British Society for Allergy and Clinical Immunology. Vol 41 (7). p923–938.
[2]Simons, FE; World Allergy, Organization. World Allergy Organization survey on global availability of essentials for the assessment and management of anaphylaxis by allergy-immunology specialists in health care settings. 2010. Annals of Allergy, Asthma & Immunology: Official publication of the American College of Allergy, Asthma, & Immunology. Vol 104(5). p405–412
[3] Li, F. Pharmacologically Induced Histamine Release: sorting out Hypersensitivity reaction to Opioids. 2006. Drug Therapy Topics. Vol 35 (4) p 13-16.
[4] Woodall HE Opioid allergic reactions available at: http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_175.htm

Part II. SVII. Table 10 – Detail of Important identified risk – Use in patients with head injury (due to risk of increased intracranial pressure)

Identified risk	Use in patients with head injury (due to risk of increased intracranial pressure)
Frequency	Cumulatively to 12 April 2017, there were no cases identified within the [redacted] database (using the new methodology described below) involving the use of oxycodone in patients with head injury.
Severity and nature of risk	The use of oxycodone hydrochloride in patients with head injury poses the risk of: • Masking the symptoms that healthcare professionals should monitor following a head injury (i.e. eye-opening, consciousness level). The risk of using oxycodone hydrochloride in patients with head injury also poses the risk of: drowsiness, altering the level of consciousness. • Opioid-induced respiratory depression and CO2 retention can result in cerebral vasodilation and thus an increase in cerebrospinal fluid pressure[2]. Raised intracranial pressure may worsen the severity of the head injury.
Background incidence / prevalence	The National Health Interview Survey in the United Sates estimated that annually, 1.9 million persons sustain a skull fracture or intracranial injury, thus accounting for approximately 1% of all injuries. The incidence of mild traumatic brain injury is about 131 cases per 100,000 people, of moderate traumatic brain injury is about 15 cases per 100,000 people, and the incidence of severe traumatic brain injury is approximately 14 cases per 100,000 people. The prevalence of brain injury is difficult to establish given the fact that most cases such as mild traumatic brain injury are not fatal, and patients may not have been hospitalised.[1]
Risk groups or risk factors	• Patients with head injury

Potential mechanisms	Therapeutic doses of opioids do not affect cerebral circulation. However, opioid-induced respiratory depression and CO_2 retention can result in cerebral vasodilation and thus an increase in cerebrospinal fluid pressure[2]. In addition, the use of oxycodone hydrochloride in patients with head injury poses the risk of masking the symptoms that healthcare professionals should monitor following a head injury.
Preventability	Caution must be exercised when administering oxycodone hydrochloride to patients with head injury due to risk of increased intracranial pressure and also due to masking of the symptoms of head injury.
Impact on individual patient	Dependent on the severity of the head trauma, and the requirement for ventilation.
Potential public health impact of safety concern	The worldwide frequency of the use of oxycodone hydrochloride in patients with head injury in the post-marketing setting is approximately one in [redacted] months exposure. Increased intracranial pressure does not occurr when PCO_2 is maintained within normal levels by artificial ventilation[2].
Evidence source	• International drug safety database search (worldwide data reported since DIBD). • Literature
MedDRA terms	MedDRA PTs of interest from High Level Term (HLT) Cerebral injuries NEC (Brain herniation, Cerebrospinal fluid leakage, Concussion, Extradural haematoma, Optic pathway injury, Subarachnoid haemorrhage, Subdural haematoma, Subdural haemorrhage, Brain oedema, Decerebration, Brain contusion, Meningorrhagia, Traumatic intracranial haemorrhage, Traumatic coma, Diffuse axonal injury, Craniocerebral injury, Epidural haemorrhage); or MedDRA PTs from HLT Skull fractures, facial bone fractures and dislocations; or at least one of the selected MedDRA PTs of interest from HLT Site specific injuries NEC (Cephalohaematoma, Face crushing, Head injury, Neck crushing, Traumatic torticollis, Face injury, Neck injury, Traumatic tooth displacement, Post-traumatic neck syndrome). The search output was further narrowed down by searching for cases containing adverse events with at least one MedDRA PT from HLGT Increased intracranial pressure and hydrocephalus or PTs CSF pressure increased, CSF pressure abnormal.

[1] Dawodu ST. Traumatic Brain Injury (TBI) - Definition, Epidemiology, Pathophysiology. Updated 06 March 2013. http://emedicine.medscape.com/article/326510-overview. Accessed on 09 April 2013.
[2]Goodman and Gilman. The Pharmacological basis of therapeutics eleventh edition. McGraw-Hill.

Part II. SVII. Table 11 – Detail of Important potential risk – Prolongation of QTc

Potential risk	Prolongation of QTc
Frequency	*Clinical trial data* Three adverse events of ventricular tachycardia were reported during clinical trials. *Post-marketing data* Cumulatively to 12 April 2017, [redacted] worldwide cases reporting [redacted] adverse events falling into the prolongation QTc search strategy have been received involving the following PTs: Electrocardiogram QT prolonged (n=54, 83.1%), Long QT syndrome ([redacted] 1.5%), Torsade de pointes [redacted] 3.1%) and Ventricular tachycardia [redacted] 12.3%). [redacted]
Seriousness / outcomes	**Seriousness**: Of the [redacted] worldwide adverse events (total including clinical trial and post-marketing data) reported [redacted] 47.1%) were serious. **Outcome**: Of the [redacted] worldwide adverse events indicative of QTc prolongation: • [redacted] (4.4%) were fatal • [redacted] (4.4%) were recovering • [redacted] (14.7%) were recovered • [redacted] (76.5%) did not report an outcome
Severity and nature of risk	Of the [redacted] reported cases, [redacted] were associated with drug abuse and/or overdose. Of the remaining six cases; three cases were reported for clinical trial subjects enrolled in oxycodone hydrochloride abuse potential studies in the USA for an oxycodone hydrochloride formulation not marketed in Europe. Each patient underwent routine telemetry observations which noted that the patients all experienced ventricular tachycardia which recovered. Of the remaining three cases, one case reported adverse events of Torsades de pointes and Electrocardiogram QT prolonged, possibly associated with opioid withdrawal, although the patient's medical history was significant for previous prolonged QTc and the adverse events occurred during an exacerbation of pre-existing COPD. At the time of reporting the patient was recovering. One case reported an event of Long QT syndrome. Long QT syndrome is a genetically inherited syndrome and is not drug related. The third case, reporting an adverse event of Electrocardiogram QT prolonged, was assessed as related to sotalol therapy. The patient's medical history was significant for atrial flutter, angina pectoris and hypertension.

Background incidence / prevalence	QT prolongation in the general population can be due to common genetic variants or the acquired long QT syndrome (LQTS). The incidence of acquired long QT syndrome is much higher than the incidence of congenital LQTS [1]. The prevalence of LQTS is estimated to be approximately 1 in 2000-2500 live births [2,3.] In a survey from the UK and Italy, non-cardiac drugs that have pro-arrhythmic potential account for 3% and 2% of total prescriptions in both countries[4].
Risk groups or risk factors	Acute hypoxia has been shown to prolong repolarisation time, measured by QT interval duration, in humans: the degree of arterial oxyhaemoglobin desaturation also correlated with lengthening of QTc intervals.Hypothermia has also been associated with prolongation of the QTc interval. Opioid toxicity following overdose or abuse is associated with a number of physiological changes including acidosis and hypoxia, some of which have been associated with prolonged QTc.
Potential mechanisms	QT prolongation occurs through drug induced blockade of cardiac hERG potassium channels.
Preventability	Avoid the use of drugs known to prolong QTc in patients at risk (e.g. patients with LQTS) or the co-administration of multiple QTc prolongers. Adverse effects of QT prolonging drugs can be prevented by not exceeding the recommended dose; avoiding their use in patients with preexisting heart disease, LQTS or previous ventricular arrhythmias; avoiding their use in patients with or at risk for hypokalaemia; and, by avoiding co-administration with drugs that inhibit cytochrome P450 or other QTc prolonging drugs.
Impact on individual patient	The occurrence of a rare but potentially life-threatening pro-arrhythmic risk could be significant
Potential public health impact of safety concern	There is currently little evidence for QTc prolongation associated with oxycodone hydrochloride administration. The potential public health impact of QTc prolongation is dependent on the clinical impact – i.e. if shown to result in Torsades de Pointes, public health impact could be significant.
Evidence source	• International drug safety database search (worldwide data reported since DIBD). • Published literature
MedDRA terms	Torsades de pointes/QTc prolongation SMQ (narrow scope)

[1]Noord C, Eijgelshein M, Stricker B. Drug- and non-drug-associated QT interval prolongation. BJCP. 2010, Feb; 70(1):16-23.
[2]Stramba-Badiale M, Crotti L, Goulene K, Pedrazzini M, Mannarino S, Salice P, *et al*. Electrocardiographic and genetic screening for long QT syndrome: results from a prospective study on 44,596 neonates. Circulation 2007; 116:II_377.
[3] Schwartz PJ, Priori SG, Napolitano C. How really rare are rare diseases?: the intriguing case of independent compound mutations in the long QT syndrome. J Cardiovasc Electrophysiol 2003; 14: 1120–1.
[4] De Ponti F, Poluzzi E, Montanaro N, et al. QTc and psychotropic drugs. Lancet 2000;356:75–6

Part II. SVII. Table 12 – Detail of Important potential risk – Medication error

Potential risk	Medication error
Frequency	*Post-marketing data* Cumulatively to date [redacted] cases reporting [redacted] adverse events falling into the medication errors search strategy were retrieved from international safety database. The most frequently reported PTs included: Wrong technique in product usage process (n=[redacted], Drug administration error (n=[redacted]), Medication error (n=[redacted] and Accidental exposure to product (n=[redacted]). The worldwide exposure data from for all oxycodone formulations was [redacted] 4 patient months. This equates to one case of medication error per [redacted] patient months of exposure. [redacted]
Seriousness / outcomes	**Seriousness**: Of the [redacted] European adverse events, [redacted] (15%) adverse events were serious and [redacted] (46.4 %). **Outcome**: Of the [redacted] adverse events, [redacted] (2.4%) adverse events were associated with a fatal outcome.

Severity and nature of risk	Medication errors can result in severe, including fatal, outcomes.
Background incidence / prevalence	Not applicable.
Risk groups or risk factors	Patients with cognitive impairment Patients undergoing opioid rotation
Potential mechanisms	Not applicable
Preventability	Clear labelling, utilising best practice in prescribing and dispensing medication errors.
Impact on individual patient	Medication errors require immediate medical intervention as they can be potentially fatal.
Potential public health impact of safety concern	Medication errors occurring with opioid medications pose an important risk for patients. However the potential impact can be minimized by clear labelling and utilising best practice and vigilance when prescribing and dispensing opioid medications, as well as educating the patients and caregivers of the potential harm to the patient if a medication error were to occur
Evidence source	International drug safety database search (worldwide data reported since DIBD).
MedDRA terms	Medication Errors SMQ (Excluding PTs Accidental overdose and Overdose).

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

As with all opioids, there can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as alcohol, other opioids, sedatives, hypnotics, antidepressants, sleeping aids, phenothiazines and neuroleptic drugs[1].

Oxycodone hydrochloride should be used with caution and the dosage may need to be reduced in patients using these medications. Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hyper- or hypotensive crisis.

Similarly, agents with anticholinergic actions can potentiate the anticholinergic side effects (constipation, paralytic ileus, urinary hesitancy and retention and dry mouth) of oxycodone hydrochloride.

Oxycodone hydrochloride is metabolised by the cytochrome P450 enzyme system (CYP2D6 and CYP3A4) but a full evaluation of interactions with other drugs metabolised by this route has not been undertaken. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs which may alter plasma oxycodone hydrochloride concentrations. Therefore, oxycodone hydrochloride doses may need to be adjusted accordingly.

Oxycodone hydrochloride is O-demethylated at carbon-3 by cytochrome P450-2D6 to form oxymorphone. Oxymorphone has approximately 60-fold greater affinity for opioid receptors than oxycodone hydrochloride (Chen *et al*[2]). Following oral administration of oxycodone hydrochloride, plasma concentrations of oxymorphone are typically 2-3% those of the parent compound. A study by Otton *et al*[3] would suggest that drugs that are potent inhibitors of the cytochrome P450-2D6 enzyme (including several serotonin uptake inhibitors and quinidine) may interfere with the metabolism of oxycodone hydrochloride. Fluoxetine, for example, could potentially have a significant effect as it inhibits the cytochrome P450-2D6. However, it has been shown by Heiskanen *et al*[4] that blocking oxymorphone formation with concomitant quinidine administration had no pharmacodynamic consequences in patients who received oxycodone hydrochloride orally.

It has been suggested that amitriptyline interferes with the metabolism of morphine, but Poyhia et al[5] showed that amitriptyline had no significant effects on the pharmacokinetics of oxycodone hydrochloride. In addition, amitriptyline did not significantly affect psychomotor performance when co-administered with oxycodone hydrochloride as compared with oxycodone hydrochloride plus placebo.

The effects of cimetidine on the biotransformation of oxycodone hydrochloride (3.5, 7 and 14 µM) to noroxycodone have been investigated using both co incubation and pre-incubation of cimetidine (17.5, 35 and 70 µM) with human liver microsomes. The maximum inhibition was about 20%. At the lowest oxycodone hydrochloride concentration even in the presence of 70 µM cimetidine, the inhibition was about 13%. These results suggest that, even in the presence of cimetidine at approximately 20-fold the therapeutic concentrations, inhibition of noroxycodone formation may be minimal *in vivo*.

The oxycodone hydrochloride CSP states that there can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS and that oxycodone hydrochloride is metabolised via CYP2D6 and CYP3A4 pathways, which may be inhibited or induced by various co-administered drugs, which may alter plasma oxycodone hydrochloride concentrations[1,6,7].

Oxycodone hydrochloride is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).

- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).

- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).

- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).

- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

[1] Goodman and Gilman's. The Pharmacological Basis of Therapeutics, 10th ed. Hardman JG, Gilman AG,Limbird LE eds. New York; McGraw-Hill Companies, Inc, 2001: p569-619.
[2] Chen ZR, Irvine RJ, Somogyi AA et al. Mu receptor binding affinity of some commonly used opioids and their metabolites. Life Sci. 1991; 48:2165-2171.
[3] Otton SV, Wu D, Joffe RT, et al. Inhibition by fluoxetine of cytochrome P450 2D6 activity. Clin Pharmacol Ther. 1993; 53: 401-9.
[4] Heiskanen T, Olkkola KT, Kalso E. Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone . Clinical Pharmacol Ther. 1998; 64:603-11.
[5] Poyhia R, Kalso E, Seppala T. Pharmacodynamic interactions of oxycodone and amitriptyline in healthy volunteers. Current Therapeutic Research. 1992; 51:739-49.
[6] Hagelberg NM, Nieminen TH, Saari TI, Neuvonen M, Neuvonen PJ, Laine K, Olkkola KT. Voriconazole drastically increases exposure to oral oxycodone. Eur J Clin Pharmacol. 2009; 65 (3) :263-71.
[7] Heiskanen T, Olkkola KT, Kalso E. Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. Clin Pharmacol Ther. 1998 Dec;64(6):603-11.

SVII.4.2 Important identified and potential interactions

Part II. SVII. Table 13 – Detail of Important identified interaction – Oxycodone hydrochloride and MAO inhibitors

Interacting substance(s): Oxycodone hydrochloride and MAO inhibitors
Effect of interaction : CNS excitation or depression associated with hypertensive or hypotensive crisis
Evidence source: • Literature • International drug safety database search (worldwide data reported since DIBD).
Possible mechanisms: MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis. The interaction between MAOIs and opioids may occur when the opioid has serotonergic effects. Oxycodone hydrochloride however, does not possess serotonin reuptake inhibitor activity and therefore not be expected to cause serotonin syndrome when given with MAOIs[1]
Potential health risk: Both opioids and the MAO inhibitors have a hypotensive effect. Concurrent administration of opioids and MAO inhibitors may potentiate hypotensive or hypertensive crisis.
Discussion: The literature on this interaction, proposed mechanism that does not relate to oxycodone hydrochloride pharmacology and very limited post-market data leads to a conclusion that there is not strong evidence for this interaction.

[1]Codd EE, Shank RP, Schupsky JJ, Raffa RB. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. *J Pharmacol Exp Ther* (1995) 274, 1263–70

Part II. SVII. Table 14 – Detail of Important identified interaction – Oxycodone hydrochloride and CNS depressants including alchohol

Interacting substance(s): Oxycodone hydrochloride and CNS depressants including alcohol
Effect of interaction: The concurrent use of oxycodone hydrochloride and CNS depressants such as alcohol benzodiazepines can result in an enhanced depressant effect which can be life threatening. It can affect motor skills and result in cognitive impairment.
Evidence source: • Literature • International drug safety database search (worldwide data reported since DIBD).
Possible mechanisms: Additive pharmacodynamic interaction. The mechanism of action of the supra-additive depressant effects following co-administration of opioids and CNS depressants is not fully understood, but may involve alteration in the rate of metabolic transformation of the opioid or alterations in neurotransmitters involved in the actions of opioids[1].
Potential health risk: There is an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS. Alcohol may enhance the pharmacodynamic effects of oxycone hydrochloride; concomitant use should be avoided.
Discussion: There is an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS including benzodiazepines and alcohol.

[1]Goodman and Gilman. The Pharmacological basis of therapeutics eleventh edition. McGraw-Hill

SVII.5 Pharmacological class effects

The pharmacological actions of oxycodone hydrochloride are common to all opioid analgesics, which produce their major effects on the CNS and smooth muscle. The effects include analgesia, sedation, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea and vomiting, pruritus and alterations in the endocrine and autonomic nervous system. As with other opioids, oxycodone hydrochloride was shown to increase prolactin secretion and decrease cortisol levels.

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

Part II. SVII. Table 15 – Pharmacological class risks included as risks

Risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (source of data/journal reference)*	Comment
Respiratory depression	Not reported	Uncommon (Hydromorphone hydrochloride) Uncommon (Morphine sulphate) Rare (Buprenorphine hydrochloride) Uncommon (Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate)	-
Ileus	Uncommon	Uncommon (Hydromorphone hydrochloride) Uncommon (Morphine sulphate) Not listed as an adverse event for Buprenorphine hydrochloride *Paralytic ileus* - Uncommon (Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate)	-
Drug abuse	Not reported	Not applicable: not listed as ADRs in section 4.8; labelled in section 4.4 of CCDSs for (Hydromorphone hydrochloride, Morphine sulphate, Buprenorphine hydrochloride, Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate)	
Psychological dependence	Not reported	Uncommon (Hydromorphone hydrochloride Not known (Morphine sulphate) Not listed as an adverse event for Buprenorphine hydrochloride	-

		Uncommon (Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate)	
Overdose accidental	Not reported	Not applicable: not listed as ADRs in section 4.8	-
Overdose intentional	Not reported	Not applicable: not listed as ADRs in section 4.8	-
Drug withdrawal syndrome and physical dependence	Not reported	Uncommon (Hydromorphone hydrochloride Not known (Morphine sulphate) Uncommon (Buprenorphine hydrochloride) Uncommon (Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate)	-
Use in patients with hepatic impairment	Not reported	Not applicable: not listed as ADRs in section 4.8; labelled in section 4.4 of CCDSs for (Hydromorphone hydrochloride, Buprenorphine hydrochloride, Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate	-
Use in patients with renal impairment	Not reported	Not applicable: not listed as ADRs in section 4.8; labelled in section 4.4 of CCDSs for (Hydromorphone hydrochloride, Morphine sulphate, Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate	
Hypersensitivity	Uncomon	Uncomon (Hydromorphone hydrochloride) Not known (Morphine sulphate) Rare (Buprenorphine hydrochloride	-
Head injury (due to increase intracranial pressure)	Not reported	Not applicable: not listed as ADRs in section 4.8; labelled in section 4.4 of CCDSs for (Hydromorphone hydrochloride, Morphine sulphate, Buprenorphine hydrochloride Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate)	-
Use of oxycodone in patients taking MAO	Not reported	Not applicable: not listed as ADRs in section 4.8; labelled in section 4.4 of CCDSs for	-

inhibitors		(Hydromorphone hydrochloride, Morphine sulphate, Buprenorphine hydrochloride Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate ;labelled in section 4.5 of CCDSs for (Hydromorphone hydrochloride, Morphine sulphate, Buprenorphine hydrochloride, Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate)	
Interactions with CNS depressants	Not reported	Not applicable: not listed as ADRs in section 4.8; labelled in section 4.5 of CCDSs for (Hydromorphone hydrochloride, Morphine sulphate, Buprenorphine hydrochloride Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate	-

* The source data utilised for the frequencies: Company Core Data Sheet Hydromorphone hydrochloride dated 01 April 2010, Company Core Data Sheet Morphine dated 08 April 2011, Company Core Data Sheet Buprenorphine base transdermal system dated 30 August 2012 and Company Core Data Sheet Dihydrocodeine tartrate and paracetamol/ Dihydrocodeine tartrate dated 08 February 2012.

SVII.5.2 Important pharmacological class effects not discussed above

All pharmacological class effects have been discussed in section SVII.3.

Part II: Module SVIII - Summary of the safety concerns

Summary of safety concerns

Part II. SVIII. Table 1 – Summary of safety concerns for oxycodone hydrochloride RMP

Summary of safety concerns	
Important identified risks	Respiratory depression Ileus Drug abuse Psychological dependence Overdose accidental Overdose intentional Drug withdrawal syndrome and physical dependence Use in patients with hepatic impairment Use in patients with renal impairment Hypersensitivity Use in patients with head injury (due to increased intracranial pressure) Use of oxycodone hydrochloride in patients taking MAO inhibitors Interactions with CNS depressants including alcohol
Important potential risks	Medication error Prolongation of QTc
Important missing information	Use in pregnant and lactating women

Part III: Pharmacovigilance Plan

III.1 Safety concerns and overview of planned pharmacovigilance actions

Important identified risks

Part III. Table 1 – Safety concerns and overview of planned pharmacovigilance actions – Respiratory depression

Safety concern 1: Respiratory depression		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Part III. Table 2 – Safety concerns and overview of planned pharmacovigilance actions – Ileus

Safety concern 2: Ileus		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Part III. Table 3 – Safety concerns and overview of planned pharmacovigilance actions – Drug abuse

Safety concern 3: Drug abuse		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities - Targeted follow-up questionnaire	To ensure the applicant receives all available data on patient demographics, risk factors and nature and trends of the reported adverse events in ICSRs.
Nature of drug abuse / misuse in Europe	Routine pharmacovigilance – periodic characterisation of nature (e.g. source of product; route and method of abuse, etc)	1. Utilise targeted follow-up questionnaire to obtain more detailed data 2. Periodically characterise

	of abuse / misuse data	nature of abuse / misuse data via a document twice a year. This gathers all published studies and information from public health bodies, addiction centres and drug abuse organisations.
Prevalence and patterns of abuse / misuse in Europe	Additional pharmacovigilance activities - Monitoring centre reports	1. Obtain information and reports from European monitoring centres for drug misuse 2. Periodically characterise the patterns of abuse / misuse provided in available reports
Incidence and patient demographics of abuse / misuse	Additional pharmacovigilance activities – non-interventional observational study	Characterise the demographics and incidence of oxycodone hydrochloride abuse in Europe

Part III. Table 4 – Safety concerns and overview of planned pharmacovigilance actions – Psychological dependence

Safety concern 4: Psychological dependence		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities - Targeted follow-up questionnaire	To ensure the applicant receives all available data on patient demographics, risk factors and nature and trends of the reported adverse events in ICSRs.

Part III. Table 5 – Safety concerns and overview of planned pharmacovigilance actions – Overdose accidental

Safety concern 5: Overdose accidental		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Nature of accidental overdose (e.g. accidental exposure, incorrect dose administered)	Routine pharmacovigilance – periodic analysis of the published literature and International safety database case data	Periodically analyse and characterise data received from single cases and literature to confirm that the nature, trends and risk factors of the risk have not changed

Part III. Table 6 – Safety concerns and overview of planned pharmacovigilance actions – Ovedose intentional

Safety concern 6: Overdose intentional		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Nature of intentional overdose	Routine pharmacovigilance – periodic analysis of the published literature and International safety database case data	Periodically analyse and characterise data received from single cases and literature to confirm that the nature, trends and risk factors of the risk have not changed

Part III. Table 7 – Safety concerns and overview of planned pharmacovigilance actions – Drug withdrawal syndrome and physical dependence

Safety concern 7: Drug withdrawal syndrome and physical dependence		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Part III. Table 8 – Safety concerns and overview of planned pharmacovigilance actions – Use in patients with hepatic impairment

Safety concern 8: Use in patients with hepatic impairment		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Part III. Table 9 – Safety concerns and overview of planned pharmacovigilance actions – Use in patients with renal impairment

Safety concern 9: Use in patients with renal impairment		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Part III. Table 10 – Safety concerns and overview of planned pharmacovigilance actions – Hypersensitivity

Safety concern 10: Hypersensitivity		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Part III. Table 11 – Safety concerns and overview of planned pharmacovigilance actions – Use in patients with head injury (due to increased intracranial pressure)

Safety concern 11: Use in patients with head injury (due to increased intracranial pressure)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor the severity of the adverse events in patients with head injury	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data to analyse the impact of use of oxycodone hydrochloride in patients with head injury

Part III. Table 12 – Safety concerns and overview of planned pharmacovigilance actions – Use of oxycodone hydrochloride in patients taking MAO inhibitors

Safety concern 12: Use of oxycodone hydrochloride in patients taking MAO inhibitors		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor severity of resulting adverse events in patients taking MAO inhibitors	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data to analyse evidence supporting an interaction and the clinical result of an interaction

Part III. Table 13 – Safety concerns and overview of planned pharmacovigilance actions – Interactions with CNS depressants including alcohol

Safety concern 13: Interactions with CNS depressants including alcohol		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor severity of resulting adverse events	Routine pharmacovigilance activities – Important identified risk is on list of close monitoring topics subject to highest level of follow up attempts	To ensure the applicant receives all available data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Important potential risks

Part III. Table 14 – Safety concerns and overview of planned pharmacovigilance actions – Medication error

Safety concern 14: Medication error		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate trends and patterns of medication error	Routine pharmacovigilance activities including analysis of the published literature and single case reports	Periodically analyse and characterise data received from single cases and literature to confirm that the nature, trends and risk factors of the risk have not changed

Part III. Table 15 – Safety concerns and overview of planned pharmacovigilance actions – Prolongation of QTc

Safety concern 15: Prolongation of QTc		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Continue to monitor and evaluate risk factors and trends	Routine pharmacovigilance activities including analysis of the published literature and single case reports	To ensure the applicant receives all available data to analyse evidence supporting an association between oxycodone hydrochloride administration and QTc prolongation

Missing information

Part III. Table 16 – Safety concerns and overview of planned pharmacovigilance actions – Use in pregnant or lactating patients

Safety concern 16: Use in pregnant or lactating patients		
Areas requiring confirmation or further investigation	**Propose routine and additional PhV activities**	**Objectives**
Gestational period exposure outcomes	Routine pharmacovigilance activities- analyse the literature and single case data on gestational period exposure	To increase the applicant's current knowledge of this missing information by identifying and analysing data on outcomes based on gestational period exposure.
Outcomes associated with exposure during breast feeding	Routine pharmacovigilance activities analyse the literature and single case data available on the outcome following exposure during breast feeding	To increase the applicant's current knowledge of this missing information by identifying and analysing data on outcomes following exposure during breast feeding

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

No additional pharmacovigilance activities will be employed in the measurement of the effectiveness of the planned risk minimisation activities.

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

There have been no clinical studies or other activities completed since the last update of the oxycodone hydrochloride RMP.

III.4 Details of outstanding additional pharmacovigilance activities

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

No additional pharmacovigilance activities have been imposed on the applicant.

III.4.2 Mandatory additional PhV Activity (being a Specific Obligation)

No additional pharmacovigilance activities are classified as mandatory to the applicant.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

No required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures.

III.4.4 Stated additional pharmacovigilance activities

There are no stated additional pharmacovigilance activities for oxycodone hydrochloride.

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Part III. Table 18 – Ongoing and planned additional pharmacovigilance activities

III.5.2 Table of completed studies/activities from the Pharmacovigilance Plan

Study / activity	Objectives	Safety concerns address	Status	Date for submission of interim or final reports
Non-interventional observational study Category 3	Prevalence of problematic prescription use and abuse of opioids in the United Kingdom and Germany	Oxycodone hydrochloride abuse in Europe	Completed	The final study report was submitted to BfArM on 19 December 2016

This study investigated the 5-year prevalence and incidence of problematic prescription opioid use and abuse in the UK between 01 January 2008 and 31 December 2012 by using from the electronic medical records of patients from the UK Clinical Practice Research Datalink (CPRD) database and the German IMS Disease Analyzer. Patients in the UK CPRD and German IMS Disease Analyzer with an inclusion opioid prescription during the study period were analysed (N=1,613,465 and 508,212 respectively). Patients solely prescribed opioids generally used for substitution therapy were excluded from the main analysis but were included in the sensitivity analysis.
In the UK, the 5-year period prevalence of problematic opioid use and abuse was 46.1 per 100,000 opioid prescription patients; while in Germany this was 166.3 per 100,000 opioid prescription patients.
Results from both countries showed that the overall risk of abuse was very low, although it was more likely in younger males with a previous record of problematic prescription opioid use and abuse.

Part IV: Plans for post-authorisation efficacystudies

IV.1 Applicability of efficacy to all patients in the target population

OxyContin is a prolonged-release formulation of oxycodone hydrochloride. A range of tablet strengths are available (5, 10, 15, 20, 30, 40, 60, 80, 120 and 160mg) to facilitate titration to an individualised dose. Furthermore immediate release oral formulations have also been approved immediate release capsules, liquids and orodispersible tablets). In addition there are situations in which oral administration is not possible, e.g. patients with dysphagia, nausea, vomiting, gastrointestinal obstruction, or in post-operative patients. For these patients, a parenteral formulation of oxycodone hydrochloride (OxyNorm Injection) has been developed.

The clinical efficacy and safety development programme of the original formulation involved more than 1500 subjects treated with oxycodone hydrochloride. The studies have been performed in both cancer (n = 723 patients based on studies being part of ISS 2001) and non-cancer pain (n = 884 patients based on studies being part of ISS 2001), with the latter including osteoarthritis and back pain (n = 455 patients based on studies being part of ISS 2001), post-operative pain (n = 356 patients based on studies being part of ISS 2001) and neuropathic pain conditions of polyneuropathy, PHN and reflex sympathetic dystrophy (n = 51 patients based on studies being part of ISS 2001). Overall 1048 patients (n = 640 nonmalignant, n = 408 malignant) in the age of 18 – 65 years and 552 patients (n = 240 nonmalignant, n = 312 malignant) above 65 years have been enrolled in the studies being part of the ISS 2001. 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 hydrochloride, 61.6 % of patients received a daily dose of 10 up to 80 mg oxycodone hydrochloride 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 hydrochloride, 91.2% of patients received a daily dose of 10 up to 80 mg oxycodone hydrochloride and 3.7 % of patients received more than 80 mg per day.

Osteoarthritis and back pain were selected as the efficacy model in several of the non cancer pain studies since they are common chronic conditions, internationally accepted as well-validated pain models in which to conduct analgesic clinical trials, the results from which may be extrapolated to the management of many other painful conditions.

The majority of studies were controlled by an active drug (morphine, immediate release oxycodone hydrochloride, a combination of acetaminophen and oxycodone hydrochloride, or hydromorphone) and 3 studies were placebo-controlled. The pain assessment tools used in the clinical development programme of oxycodone hydrochloride were those commonly used to evaluate pain and are consistent with the recommendations provided in the “Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain” (CPMP/EWP/612/00).

The clinical studies conducted in cancer pain patients showed that oxycodone hydrochloride PR tablets provided safe and effective pain control, clinically relevant differences to that provided by MR morphine, CR hydromorphone or IR oxycodone hydrochloride were not shown providing further evidence for similar efficacy of oxycodone hydrochloride PR and oxycodone

hydrochloride IR. Stable dosing was achieved as fast for oxycodone hydrochloride PR tablets as for MR morphine or CR hydromorphone, suggesting that patients could safely be transferred to oxycodone hydrochloride prolonged release tablets. The studies highlighted the need for dose titration and rescue medication to optimise pain relief. The ability of patients to perform tasks usually adversely affected by pain improved, as did their quality of life. While oxycodone hydrochloride prolonged release tablets and MR morphine or CR hydromorphone were comparable in terms of efficacy and safety, there were some differences favouring oxycodone hydrochloride, e.g. the pharmacokinetic data suggested that oxycodone hydrochloride prolonged release tablets provide a more consistent and predictable therapeutic profile than MR morphine.

Oxycodone hydrochloride was significantly better than placebo in relieving non-malignant pain and improving functional measures like WOMAC OA index ([redacted]) or pain-related interference with quality of life (BPI) or sleep quality [redacted]. CR oxycodone hydrochloride and IR oxycodone hydrochloride/APAP provided comparable pain control and sleep quality. Furthermore oxycodone hydrochloride is an effective analgesic for the management of postoperative pain. Based on the available data there is evidence that long-term treatment with CR oxycodone hydrochloride was associated with an appropriate analgesic therapy as well as an appropriate safety profile.

Overall data from clinical trials have generally shown that CR oxycodone hydrochloride was superior to placebo and equivalent to IR oxycodone hydrochloride and CR morphine in analgesic effectiveness. Patients could be converted easily from morphine (immediate or sustained release), hydromorphone with a different dosage or immediate release oxycodone hydrochloride. CR oxycodone hydrochloride was safely and effectively used in opioid-naive patients. Therefore, the results of the clinical studies demonstrated a clinically meaningful efficacy of oxycodone hydrochloride CR tablets in the relief of moderate to severe pain in patients with cancer and non-cancer pain. Oxycodone hydrochloride also represents an effective analgesic drug during the long-term treatment for pain.

The patient population included in the clinical studies are representative for the patient population in clinical practice and clearly demonstrate that oxycodone hydrochloride is efficacious and safe for the treatment of pain independent of the origin. In order to establish pharmacokinetic parameters of oxycodone hydrochloride in specific subgroups, like elderly patients, patients with renal/hepatic impairment a comprehensive Phase I programme has been performed. Based on those studies it could be demonstrated that oxycodone hydrochloride can be administered to those subpopulation, however caution should be exercised when therapy is initiated. In general the use of some concomitant medication affecting the pharmacokinetics and pharmacodynamics might have an influence on the efficacy of oxycodone hydrochloride, which is reflected in section 4.5 “drug interactions” of the SmPC. There is no evidence that the relationship to a specific ethnic group has any influence on the efficacy and safety of oxycodone hydrochloride.

[redacted]

[redacted]

IV.2 Tables of post-authorisation efficacy studies

As oxycodone hydrochloride was launched many years ago and a huge amount of postmarketing experience exists, no post-authorisation efficacy studies have been performed to address a specific efficacy concern.

Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

The effectiveness of the routine risk minimisation activities in place for the important identified risks and important potential risks associated with oxycodone hydrochloride have not been measured. This is because, as per the GVP module XVI, for the routine risk minimisation activities it is proposed the evaluation is not deemed necessary.

V.2 Risk minimisation measure failure (if applicable)

There are no risk minimisation failures.

V.3 Summary table of risk minimisation measures

Part V. Table 4 – Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measure	Additional risk minimisation measures
Respiratory depression	-Section 4.4 of the CSP include caution pre- or intra-operatively and within the first 12-24 hours post-operatively -Respiratory depression listed in section 4.8 of the CSP -Section 4.9 of the CSP includes information of acute overdose that can be manifested by respiratory depression.	None proposed
Ileus	-Section 4.4 of the CSP cautions on administration of oxycodone hydrochloride following abdominal surgery -Ileus listed in section 4.8 of the CSP	None proposed
Overdose accidental	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride -Section 4.4 of the CSP contains a warning that controlled release tablets must be swallowed whole, and not broken, chewed or crushed -Section 4.9 of the CSP includes information of acute overdose -symptoms and treatment	None proposed

Overdose intentional	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride -Section 4.4 of the CSP contains a warning that controlled release tablets must be swallowed whole, and not broken, chewed or crushed -Section 4.9 of the CSP includes information of acute overdose -symptoms and treatment	None proposed
Use in patients with hepatic impairment	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride in patients with hepatic impairment -Section 4.4 of the CSP contains a warning that caution must be exercised when administering oxycodone to impaired hepatic function	None proposed
Use in patients with renal impairment	Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride in patients with renal impairment -Section 4.4 of the CSP contains a warning that caution must be exercised when administering oxycodone to impaired renal function	None proposed
Hypersensitivity	-Section 4.3 contains a contraindication for the use in patients with hypersensitivity to oxycodone or to any of the excipients -Hypersensitivity is listed in section 4.8 of the CSP	None proposed
Use of oxycodone hydrochloride in patients with head injury (due to increased intracranial pressure)	-Section 4.4 of the CSP documents that caution must be exercised when administering oxycodone to patients with head injury (due to risk of increased intracranial pressure)	None proposed
Use of oxycodone in patients taking MAO inhibitors	- Section 4.4 of the CSP documents that caution must be exercised when administering oxycodone to patients taking	None proposed

	MAO inhibitors -Section 4.5 of the CSP documents that caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks	
Interactions with CNS depressants	-Section 4.4 of the CSP contains information regarding concomitant use of alcohol and oxycodone hydrochloride -Section 4.5 of the CSP contains information regarding that an enhanced CNS depressant effect can occur during concomitant therapy with drugs which affect the CNS like benzodiaepines	None proposed
Medication error	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride -Section 4.4 of the CSP contains a warning that controlled release tablets must be swallowed whole, and not broken, chewed or crushed	None proposed
Prolongation of QTc	Not applicable. This risk has not been confirmed and therefore not documented in the CSP	None proposed
Use in pregnant and lactating woman	-Section 4.6 of the CSP contains information regarding the use of oxycodone hydrochloride in pregnant and lactating patients.	None proposed

Part VI: Summary of activities in the risk management plan by product

VI.1.1 Summary table of safety concerns

Part VI. Table 1 – Summary table of safety concerns

Summary of safety concerns	
Important identified risks	Respiratory depression Ileus Drug abuse Psychological dependence Overdose accidental Overdose intentional Drug withdrawal syndrome and physical dependence Use in patients with hepatic impairment Use in patients with renal impairment Hypersensitivity Use in patients with head injury (due to increased intracranial pressure) Use of oxycodone hydrochloride in patients taking MAO inhibitors Interactions with CNS depressants
Important potential risks	Medication error Prolongation of QTc
Important missing information	Use in pregnant and lactating women

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

None planned

VI.1.3 Summary of post authorisation efficacy development plan

As oxycodone hydrochloride was launched many years ago and a huge amount of post marketing experience exists, no post-authorisation efficacy studies have been performed to address a specific efficacy concern

VI.1.4 Summary table of Risk Minimisation Measures

Part VI. Table 3 – Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measure	Additional risk minimisation measures
Respiratory depression	-Section 4.4 of the CSP include caution pre- or intra-operatively and within the first 12-24 hours post-operatively -Respiratory depression listed in section 4.8 of the CSP -Section 4.9 of the CSP includes information of acute overdose that can be manifested by respiratory depression.	None proposed
Ileus	-Section 4.4 of the CSP cautions on administration of oxycodone hydrochloride following abdominal surgery -Ileus listed in section 4.8 of the CSP	None proposed
Drug abuse	-Section 4.4 of the CSP include caution regarding the abuse of oxycodone hydrochloride -Controlled drug status -Restricting prescribers	None proposed
Psychological dependence	-Section 4.4 of the CSP include cautions the potential for development of psychological	None proposed

	dependence - Drug dependence listed in section 4.8 of the CSP -Controlled drug status -Restricting prescribers	
Overdose accidental	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride -Section 4.4 of the CSP contains a warning that controlled release tablets must be swallowed whole, and not broken, chewed or crushed -Section 4.9 of the CSP includes information of acute overdose -symptoms and treatment	None proposed
Overdose intentional	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride -Section 4.4 of the CSP contains a warning that controlled release tablets must be swallowed whole, and not broken, chewed or crushed -Section 4.9 of the CSP includes information of acute overdose -symptoms and treatment	None proposed
Drug withdrawal syndrome and physical dependence	-Section 4.4 of the CSP contains a warning regarding physical dependence and a withdrawal syndrome -Drug withdrawal syndrome listed in section 4.8 of the CSP.	None proposed
Use in patients with hepatic impairment	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride in patients with hepatic impairment -Section 4.4 of the CSP contains a warning that caution must be exercised when administering oxycodone to impaired hepatic function	None proposed
Use in patients with renal	Section 4.2 of the CSP includes information regarding the	None proposed

impairment	administration of oxycodone hydrochloride in patients with renal impairment -Section 4.4 of the CSP contains a warning that caution must be exercised when administering oxycodone to impaired renal function	
Hypersensitivity	-Section 4.3 contains a contraindication for the use in patients with hypersensitivity to oxycodone or to any of the excipients -Hypersensitivity is listed in section 4.8 of the CSP	None proposed
Use of oxycodone hydrochloride in patients with head injury (due to increased intracranial pressure)	- -Section 4.4 of the CSP documents that caution must be exercised when administering oxycodone to patients with head injury (due to risk of increased intracranial pressure)	None proposed
Use of oxycodone in patients taking MAO inhibitors	- - Section 4.4 of the CSP documents that caution must be exercised when administering oxycodone to patients taking MAO inhibitors -Section 4.5 of the CSP documents that caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks	None proposed
Interactions with CNS depressants	-Section 4.4 of the CSP contains information regarding concomitant use of alcohol and oxycodone hydrochloride -Section 4.5 of the CSP contains information regarding that an enhanced CNS depressant effect can occur during concomitant therapy with drugs which affect the CNS	None proposed
Medication error	-Section 4.2 of the CSP includes information regarding the administration of oxycodone hydrochloride -Section 4.4 of the CSP contains a warning that	None proposed

	controlled release tablets must be swallowed whole, and not broken, chewed or crushed	
Prolongation of QTc	-Not applicable. This risk has not been confirmed and therefore not documented in the CSP.	None proposed
Use in pregnant and lactating woman	-Section 4.6 of the CSP contains information regarding the use of oxycodone hydrochloride in pregnant and lactating patients.	None proposed

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 safety 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 effectively 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 there 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)	Drinking alcohol whilst taking oxycodone hydrochloride may 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.	It is recommended not to drink while you're taking oxycodone hydrochloride

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 to a mistake 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 [redacted] 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.	

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not applicable

Annex 2 – Core safety profile (CSP)

CORE SAFETY PROFILE

OXYCODONE HYDROCHLORIDE

05 April 2017

4.2 Posology and method of administration (safety aspects only)

Posology

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

4.3 Contraindications

Oxycodone must not be used in any situation where opioids are contraindicated: severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, severe respiratory depression with hypoxia, elevated carbon dioxide levels in the blood, or paralytic ileus.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency,
alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product [preparation] may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.

Hyperalgesia that will not respond to a further dose increase of oxycodone may very rarely occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence [addiction] to opioid analgesics, including oxycodone. {(Invented)name} should be used with particular care in patients with a history of alcohol and drug abuse.

The prolonged release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Concomitant use of alcohol and {(Invented)name} may increase the undesirable effects of {(Invented)name}; concomitant use should be avoided.

For prolonged release products:

{(Invented)name} is not recommended for pre-operative use or within the first 12-24 hours post-operatively.[1]

For normal / immediate release products (oral):

{(Invented)name} should be used with caution pre-operatively and within the first 12-24 hours post-operatively.

For normal / immediate release products (parenteral):
{(Invented)name} should be used with caution pre- or intra-operatively and within the first 12-24 hours post-operatively.

4.5 Interaction with other medicinal products and other forms of interaction

There can be an enhanced CNS depressant effect, which can result in profound sedation, respiratory depression,coma, and death, during concomitant therapy with benzodiazepines or other drugs which affect the CNS such as alcohol, other opioids, non-benzodiazepine sedatives, hyptonics, anti-depressants, phenothiazines and neuroleptic drugs,etc

Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (eg tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Alcohol may enhance the pharmacodynamic effects of {(Invented)name}, concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).

- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).

- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).

- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St Johns Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).

- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Prolonged use of oxycodone during pregnancy can result in neonatal opioid withdrawal syndrome

The drug penetrates the placenta and can be found in breast milk

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines.

4.8 Undesirable effects

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	≥ 1/10
Common	≥ 1/100 to <1/10
Uncommon	≥ 1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Frequency unknown	Cannot be estimated from the available data

Immune system disorders:
Uncommon: hypersensitivity.
Frequency unknown: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:
Common: decreased appetite.
Uncommon): dehydration.

Psychiatric disorders:
Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking
Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4).
Frequency unknown: aggression.

Nervous system disorders:
Very common: somnolence, dizziness, headache.
Common: tremor, lethargy
Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia.
Frequency unknown: hyperalgesia.

Eye disorders:
Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:
Uncommon: vertigo.

Cardiac disorders:
Uncommon): palpitations (in the context of withdrawal syndrome).

Vascular disorders:
Uncommon: vasodilatation.
Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea.
Uncommon: respiratory depression.

Gastrointestinal disorders:
Very common: constipation, nausea, vomiting.
Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.
Uncommon: dysphagia, flatulence, eructation, ileus.
Frequency unknown: dental caries.

Hepato-biliary disorders:
Uncommon: increased hepatic enzymes.
Frequency unknown: cholestasis.

Skin and subcutaneous tissue disorders:
Very common: pruritus.
Common: rash, hyperhidrosis.
Uncommon: dry skin.

Rare: urticaria.

Renal and urinary disorders:
Uncommon: urinary retention.

Reproductive system and breast disorders:
Uncommon: erectile dysfunction, hypogonadism
Frequency unknown: amenorrhoea.

General disorders and administration site conditions:
Common: asthenic conditions, fatigue
Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance. thirst.
Not known: drug withdrawal syndrome neonatal.

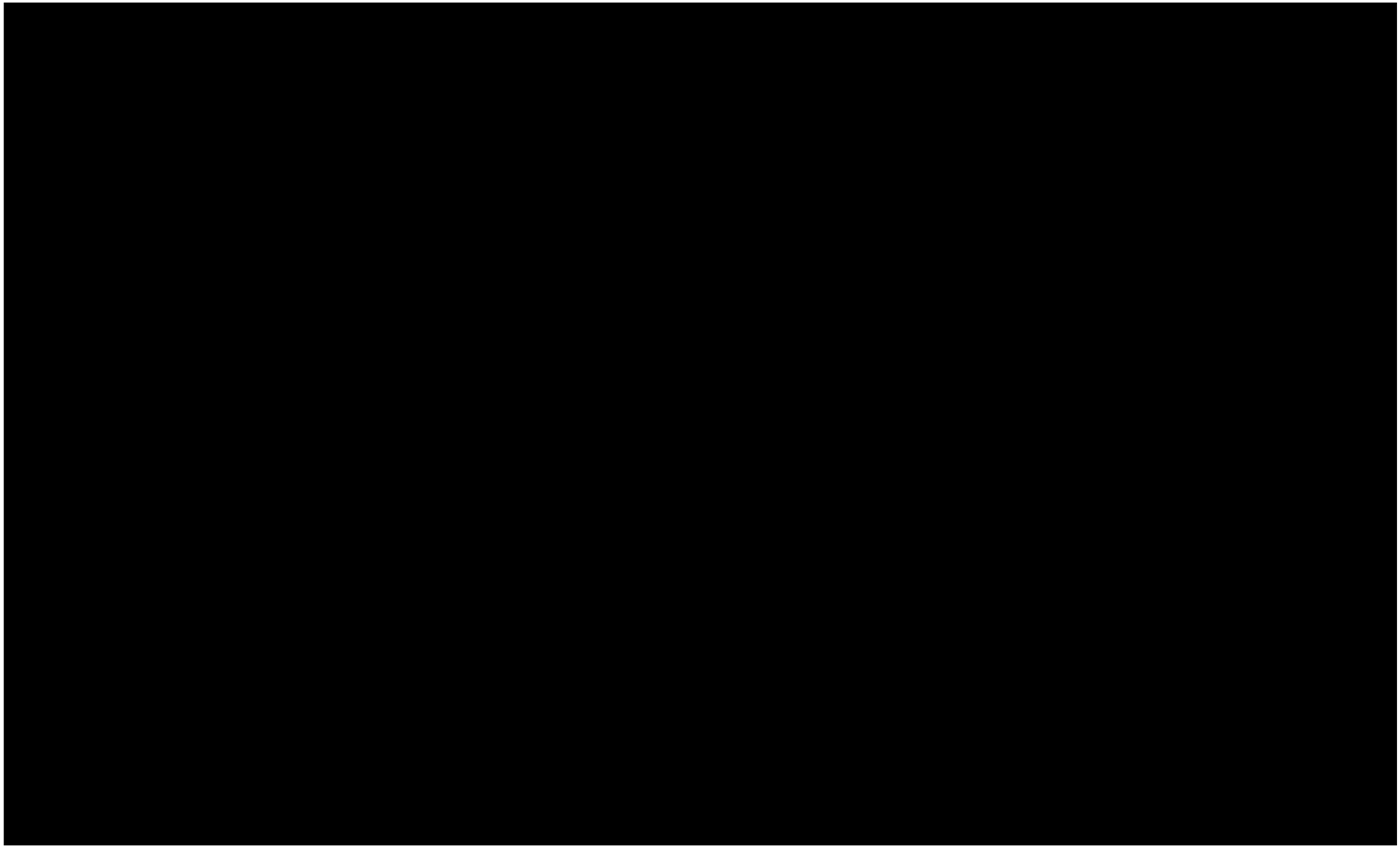
4.9 Overdose

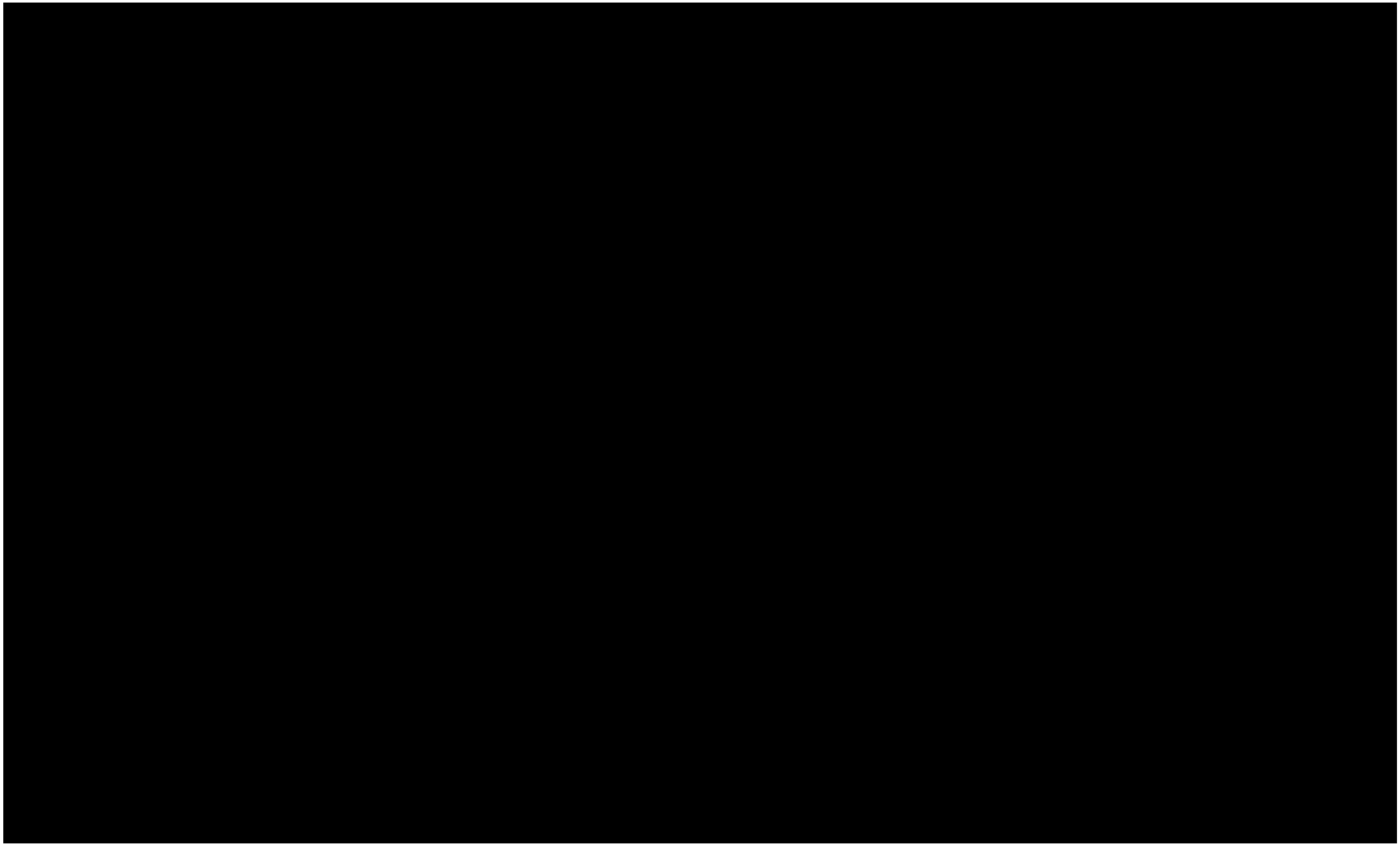
Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, hypotonia, miosis, bradycardia, hypotension, and death.

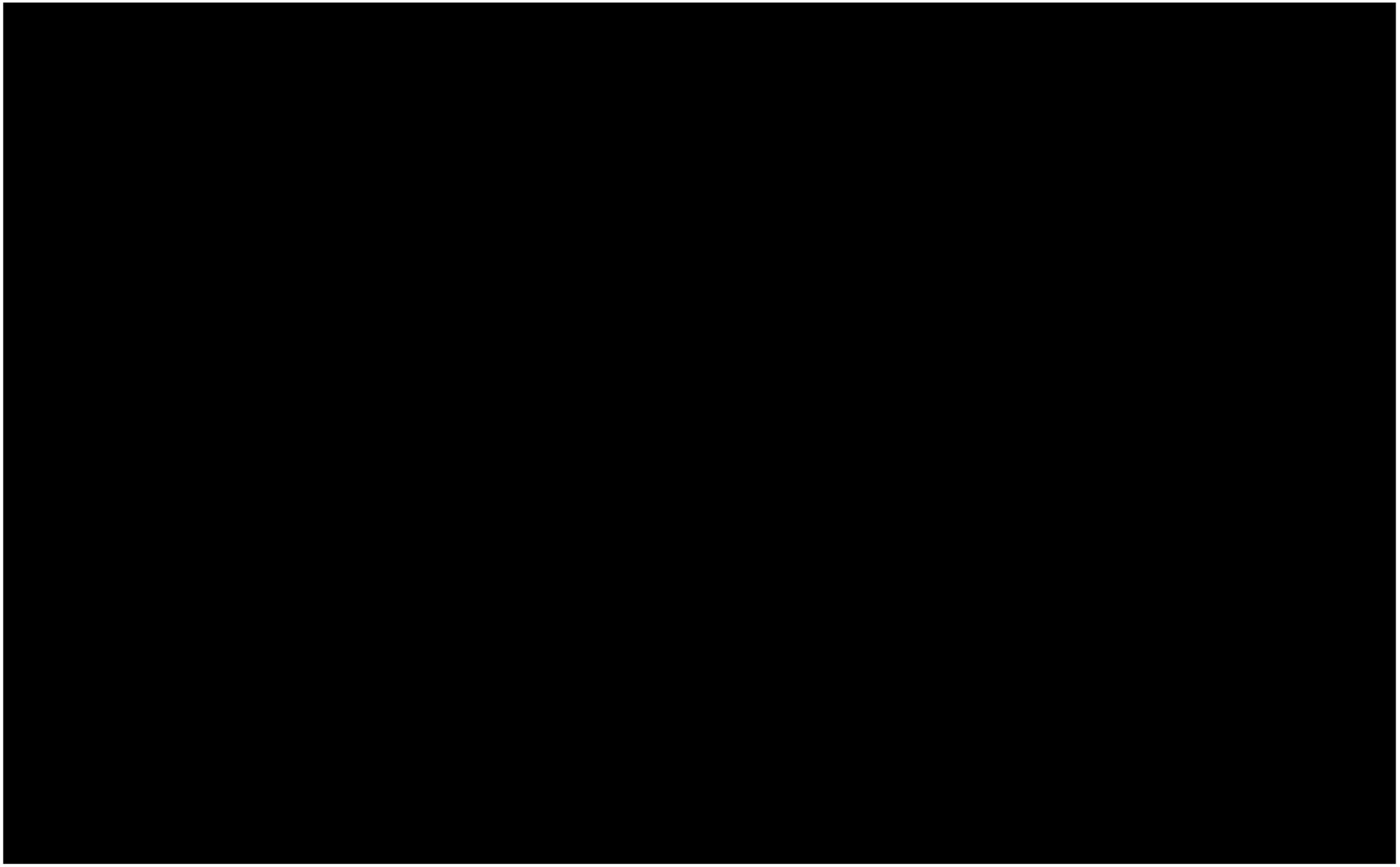
A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

Annex 3 - Worldwide marketing authorisation by country (including EEA)

[redacted]







Annex 4 - Synopsis of on-going and completed clinical trial programme

Not applicable

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Not applicable

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

Not applicable

Annex 7 - Specific adverse event follow-up forms

Indication for opioid treatment *(pain condition requiring opioid therapy):*

Current history
Summary narrative of details (dates, symptoms, signs, interventions, relapses, etc) of issue:

Diagnoses (tick all that apply):

- ☐ Addiction (psychological dependence)
- ☐ Abuse
- ☐ Physical dependence / Drug withdrawal syndrome

For addiction please indicate what is appropriate:

- ☐ *Earlier prescription seeking*
- ☐ *Claims of lost medication*
- ☐ *Intoxication*
- ☐ *Frequent missed appointments*
- ☐ *Use of other scheduled drugs*

Other details (please add if needed):

For abuse please indicate:

- *Prescription medications, illicit drugs or alcohol being abused (please specify drug names and dates):*
- *Source of drugs (e.g. prescription; family member; friend; internet; drug dealer; other):*
- *Nature or manner of abuse (e.g. route of administration, frequency, tempering):*

For physical dependence / drug withdrawal syndrome please indicate:

- *Trigger, e.g. abrupt discontinuation, abrupt dose reduction, administration of opioid antagonist, missed dose, too long a dosing interval? [Encircle or specify below]*
- *Occurrence after opioid rotation? (please specify dates, products and doses of both opioids):*
- *Primary symptoms:*

Investigations *(please provide details of any relevant investigations, specialist referrals)*:

Past history of addiction, abuse, physical dependence

Previous addiction to prescription medication, illicit drugs or alcohol (please provide details and dates)?

Previous abuse of prescription medication, illicit drugs or alcohol (please provide details and dates)?

Previous physical dependence to / drug withdrawal syndrome from prescription medication, illicit drugs or alcohol (please provide details and dates)?

Past psychiatric history

Please insert details and dates:

Family history

Family history of addiction, abuse, or physical dependence to prescription medication, illicit drugs or alcohol (please provide details):

Family history of psychiatric disease (please provide details):

Lifestyle (risk factors)

☐ Alcohol use: ☐ units / week ☐ Smoking history: ☐ cigarettes / week
☐ Other (please specify):

Treatment of the adverse event

Please insert details of previous and current treatment, including medical and behavioural therapies (e.g. addiction centre referrals, substitution therapy, etc):

Outcome

Please provide details of impact on patient's current physical and psychosocial functioning:

Name&position: signature: date:

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 9 - Newly available study reports for RMP parts III & IV

Annex 10 - Details of proposed additional risk minimisation measures

Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)

Not applicable

Annex 12 - Other supporting data (including referenced material)

Not applicable