Risk Management Plan for Dzuveo (Sufentanil (as citrate))

RMP version to be assessed as part of this application:

RMP Version number	3.1
Data lock point for this RMP	05-Apr-2024
Date of final sign off	15-Apr-2024
Rationale for submitting an updated RMP	Version 3.1: With the aim for the effectiveness survey to provide representative results, the start date of this survey was modified.
Summary of significant changes in this RMP	Version 3.1: Update of the milestones of the effectiveness of the survey and the deadline for study results
Other RMP versions under evaluation	RMP Version number: NA
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QPPV name	Ramzi SEIFEDDINE, PharmD
QPPV signature	signature is kept on file (EMA/781194/2021 Rev. 1)

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) **(INN or common name)**	Sufentanil (as citrate)
Pharmacotherapeutic group(s) (ATC Code)	Anesthetics, opioid anesthetics (N01AH03)
Marketing Authorisation Applicant	Laboratoire Aguettant
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Dzuveo 30 micrograms sublingual tablet
Marketing authorisation procedure	Centralised procedure
Legal status	Hybrid
Brief description of the product	Chemical class Sufentanil is a synthetic, potent opioid with highly selective binding to μ-opioid receptors. Sufentanil acts as a full agonist in μ-opioid receptors. Sufentanil does not induce histamine release. All effects of sufentanil can immediately and completely be blocked by administration of a specific antagonist such as naloxone.
	Summary of mode of action Sufentanil is a synthetic, potent opioid with highly selective binding to μ-opioid receptors. Sufentanil acts as a full agonist in μ-opioid receptors. Sufentanil does not induce histamine release. All effects of sufentanil can immediately and completely be blocked by administration of a specific antagonist such as naloxone. Analgesia induced by sufentanil is thought to be mediated via activation of μ-opioid receptors primarily within the CNS to alter processes affecting both the perception of and the response to pain. In humans, the potency is 7 to 10-fold higher than fentanyl and 500 to 1,000-fold higher than morphine (per oral). The high lipophilicity of sufentanil allows it to be administered sublingually and achieve a rapid onset of analgesic effect. Sufentanil may cause respiratory depression and also suppresses the cough reflex. High doses of intravenously administered sufentanil, which are typically used to induce anesthesia are known to cause muscle

	rigidity, probably as a result of an effect on the substantia nigra and the striate nucleus. Hypnotic activity can be demonstrated by EEG alterations. Analgesic plasma concentrations of sufentanil may provoke nausea and vomiting by irritation of the chemoreceptor trigger zone. Gastrointestinal effects of sufentanil comprise decreased propulsive motility, reduced secretion, and increased muscle tone (up to spasms) of the sphincters of the gastrointestinal tract. Low doses of intravenous sufentanil associated with likely vagal (cholinergic) activity cause mild bradycardia and mildly reduced systemic vascular resistance without significantly lowering blood pressure. Cardiovascular stability is also the result of minimal effects on cardiac preload, cardiac flow rate and myocardial oxygen consumption. Direct effects of sufentanil on myocardial function were not observed.
	Important information about its composition none
Hyperlink to the Product Information	See module 1.3.1
Indication(s) in the EEA	Current: Dzuveo is indicated for the management of acute moderate to severe pain in adult patients in a medically monitored setting.
	Proposed: Not applicable
Dosage in the EEA	Current: Dzuveo is to be administered by a healthcare professional in a medically monitored setting only. A medically monitored setting must have equipment and personnel trained to detect and manage hypoventilation, and availability of supplemental oxygen and opioid antagonists, such as naloxone. Dzuveo should only be prescribed by healthcare professionals who are experienced in the management of opioid therapy; particularly opioid adverse reactions such as respiratory depression. Dzuveo is provided in a disposable single-dose applicator, to be administered by a healthcare provider as needed by the individual patient to treat pain, but no more than once every hour, resulting in a maximum available dose of 720 micrograms/day. However, it is not anticipated that the maximum daily dose will be required. In the two placebo-controlled clinical trials, the mean number of doses used in the first 6 hours of dosing was 2.8 tablets, with less frequent dosing in the following 6 hours (mean of 1.7 tablets). Over 24 hours, the mean number of Dzuveo doses administered was 7.0 (210 micrograms/day). Patients with a higher pain intensity at one hour after Dzuveo treatment was initiated required more frequent

	redosing compared to patients with lower pain intensity scores at one hour. Dzuveo should not be used beyond 48 hours.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Dzuveo is a sublingual tablet that contains 30 mcg of sufentanil
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

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

Indication

Dzuveo, sufentanil 30 microgram sublingual tablet, is indicated for the management of moderate-to-severe acute pain in adult patients in medically monitored settings only.

General pain

Pain may be either acute or chronic. When pain occurs as a normal, predictable response to trauma such as chemical, thermal, or mechanical injury or an acute illness, pain is considered to be acute. When pain persists for more than three months or beyond the usual recovery period for an illness or injury, or when it continues over months or years as a result of a long-term condition the pain is considered to be chronic (Turk *et al*. 2011).

A 2008 survey in five European countries (UK, France, Spain, Germany, and Italy) revealed that nearly 50 million people in these countries reported pain in the previous month. The population prevalence of daily pain in this study was 8.85%, with 3.5% and 4.7% of respondents reporting severe and moderate daily pain, respectively (Langley 2011).

The National Epidemiologic Survey on Alcohol and Related Conditions in the US examined data from 42,750 adult respondents (48% men; 52% women), who were categorised according to three levels (no or low pain interference, moderate pain interference, and severe pain interference) of pain interference, defined as the perceived disruption in daily activities, interpersonal relationships, life roles and employment resulting from physical pain, found that female respondents were more likely than male respondents to show signs of moderate ($p < 0.001$) or severe pain interference ($p < 0.001$) (Barry *et al*. 2012). Pain is one of the most prevalent symptoms among the elderly (Davies and Higginson 2004). However, it is known that underreporting of pain is frequent in the elderly with physicians undertreating pain especially pain from non-malignant causes such as osteoarthritis (OA) and joint pain but also cancer- related pain (Davies and Higginson 2004).

Acute pain

Pain is often related to the underlying condition of the patient. Severe acute pain is followed by persistent pain in 10-40% of patients, and this can have a major effect on quality of life (Nielsen *et al*. 2007). In the US each year 15% to 20% of the population suffer acute pain, while chronic pain is estimated to affect around 68 million people, 25% of whom (17.7 million) are elderly with daily pain or occasional excruciating pain reported in 40% of nursing home residents (Code and Bonica 2001, Teno *et al*. 2001).

Post-operative pain

Acute post-operative pain is a complex physiological reaction to tissue injury, visceral distention or disease which may result in unpleasant, unwanted sensory and emotional experiences (Motiani *et al*. 2011).

In the UK, there were approximately 7 million operations per year using 4,338,709 bed days, based on data from Hospital Episode Statistics in 2007 (Duncan 2011) while in the US the number is ten-fold with 73 million patients undergoing surgical procedures each year (Apfelbaum *et al*. 2003). A meta-analysis of the incidence of moderate to severe and of severe pain after major surgery including abdominal, gynaecological, orthopaedic and thoracic surgery with IM analgesia, patient controlled analgesia (PCA)

and epidural analgesia revealed that 30% of nearly 20,000 patients from 165 studies experienced moderate to severe post- operative pain and an additional 11% of patients experienced severe pain despite opioid administration (Dolin *et al*. 2002).

In one study of 250 adults who had recently undergone surgical procedures, more than 80% of patients experienced acute post-operative pain with 20% experiencing severe pain (Apfelbaum *et al*. 2003). Another study involving 290 patients in Thailand found the prevalence of moderate to severe pain after cardiac surgery to be 61.4% (Raksamani *et al*. 2013) with the authors acknowledging that inadequate pain control can result in increased morbidity and length of hospital stay as well as leading to chronic pain. Risk factors for post-operative pain include pre-operative pain, anxiety, obesity, and certain surgical procedures (abdominal, orthopaedic and thoracic surgery), as well as prolonged duration of surgery (Wu and Raja 2011).

An increasing body of evidence exists to support the fact that if pain is not controlled in the immediate post-operative period there may be several deleterious consequences such as delayed wound healing, extended hospital stay and the development of chronic pain syndromes (Macrae 2001, Bonnet and Marret 2005). Untreated or undertreated severe post-operative pain has many deleterious effects on respiration, circulation, autonomic activity, renal function and gastrointestinal (GI) activity.

Pain in Emergency Medicine

Pain is the most common reason for seeking healthcare, and as a presenting complaint, accounts for up to 78% of visits to the emergency department (ED). Adequate analgesia in EDs is an important goal of treatment; however, the underuse of analgesics, termed "oligoanalgesia," occurs in a large portion of ED patients. A recent prospective study of moderate to severe pain across 20 North American emergency departments (PEMI; 2007) revealed pain is the primary reason people contact the Emergency Medical System and the most common reason they present to the Emergency Department (ED). Findings demonstrated that 80% of patients required treatment for their pain upon presentation to the ED, but only 60% actually received any analgesia. Furthermore, median pain score upon presenting to the ED was 8/10 and still a 6/10 at discharge, with median time from triage to analgesia >90 minutes [range 0 - 962 min] (Todd *et al*. 2007).

The main existing treatment options:

Effective pain management depends on the nature of the pain, its severity, the underlying cause of the pain, the patient's medical history, concurrent conditions and concomitant therapies, the mode of administration of analgesia and potential adverse reactions, and national guidelines and funding.

Generally, mild pain is treated with non-opioids such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol or acetylsalicylic acid whereas for moderate pain opioids may be used including hydromorphone, fentanyl or methadone or oxycodone alone or combined with acetylsalicylic acid or paracetamol. For severe pain morphine, hydromorphone, or oxycodone are possible therapies with parenteral use to control the pain and then a switch to oral or rectal medication once the pain is controlled. For acute severe pain both a quick response and high doses are necessary but once pain relief is obtained, the dose can be reduced. Adjuvants are often used in combination with analgesics in the management of some types of pain.

Opioids are the most effective centrally acting analgesic drugs for the treatment of pain. The opioids most often used for the treatment of pain include morphine, hydromorphone, methadone, oxycodone, fentanyl, sufentanil, alfentanil, buprenorphine, pethidine (meperidine) and tramadol (Bujedo *et al*. 2012), although the use of opioid analgesics differs by country. Modes of administration include spinal opioids (epidural, intrathecal), patient-controlled analgesia (IV, subcutaneous, epidural), IV infusions, sublingual, oral, transmucosal, rectal, nasal, intra-articular and transdermal.

Concomitant Medications:

Medicinal products often used to treat pain are described under treatment options. Analgesics are often co-administered with adjuvant analgesics which are medicinal products not originally indicated for pain but have been found to be effective in some painful conditions that may be difficult to manage with conventional analgesics. Commonly used adjuvants include corticosteroids, antipsychotics, antidepressants, anticonvulsants, and bisphosphonates. Other adjuvant therapies used include radiation, intrathecal and epidural analgesia, nerve blocks and surgery (Leppert and Luczak 2005).

Other concomitant medications used by patients with moderate to severe acute pain will depend on the underlying cause of the pain and concurrent conditions. Pre-operatively a patient may receive an analgesic such as a parenteral opioid, while post-operatively patients may also need to receive oxygen during the initial stages of recovery, anti-inflammatory products such as corticosteroids and antibiotics. A healthy adult undergoing a knee replacement surgery will have a completely different medication profile compared with an elderly patient undergoing a hip replacement; elderly patients are more likely to have rheumatoid arthritis (RA), osteoarthritis (OA), diabetes, hypertension, hepatic and renal impairment in addition to cognitive impairment leading to polypharmacy.

Important co-morbidities:

Co-morbidities in the target population may be related to their underlying condition or consequential to inadequate pain relief. Patients with moderate to severe acute pain may have a multitude of co-morbidities depending on the underlying cause of the pain. Pain can be caused by trauma or a surgical procedure and is often the symptom of a disease or condition with its associated morbidity and mortality. The patient may be suffering from cancer, HIV, diabetes, RA, OA, multiple sclerosis, or a surgical patient may have hypertension, renal impairment, or obesity, all of which need to be accounted for to determine the appropriate course of treatment. Post-operative or trauma patients may experience inflammation and infection of the wound or site of incision.

Functional impairment of the excretory organs is common in the elderly and consequently they may have comorbidities due to underlying conditions or adverse reactions related to polypharmacy. The elderly are more likely to suffer from hepatic and renal impairment in addition to cognitive impairment, confusion, memory loss either from pathology or medication and these may be confounded by sight and hearing impairment. This can lead to problems of compliance and also to difficulties reporting or describing pain or adverse events (Closs 2005) and may ultimately result in overtreatment or undertreatment leading to adverse reactions or the development of tolerance (Pergolizzi *et al*. 2008).

Importantly, unrelieved pain has considerable consequences as inadequate pain control post-operatively can result in increased morbidity and length of hospital stay and may lead to chronic pain (Raksamani et al. 2013). For example, pain after abdominal surgery can restrict the patient's ability to take a deep breath, cough or sit out of bed leading to an increased risk of respiratory and thromboembolic complications (Duncan 2011). It is known that uncontrolled pain and post-operative complications, adverse reactions to medications such as nausea and vomiting, persistent ileus, fatigue, the presence of drains, and stress-induced organ dysfunction all affecting the length of time people stay in hospital (Delaney et al. 2001).

Unrelieved severe pain can result in physiological changes that include pituitary-adrenal activation which in turn may produce a weakened immune response (Hutchison 2007). There is also sympathetic activation in association with pain which may result in cardiovascular, GI and renal changes. In addition, unrelieved acute post-operative pain results in avoidance of movement and ambulation on the part of patients which may often be key elements in their early surgical recovery. All of the above may contribute to deep vein thrombosis (DVT), pulmonary embolism (PE), coronary ischaemia, myocardial infarction (MI), pneumonia, poor wound healing, reduced immune response to surgery and chronic pain

syndrome. Unrelieved acute post-operative pain may also have important psychological sequelae including stress, anxiety, demoralisation and depression (Hutchison 2007). Chronic severe pain has also been associated with significant functional impairment, medical and psychiatric comorbidities, and abuse behaviours (Sheu et al. 2008).

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

Section omitted – not required for hybrid medicinal products application according to GVP – Module V (Rev2).

Part II: Module SIII - Clinical trial exposure

The clinical development program for the sufentanil 30 mcg sublingual tablet product consisted of 1 Phase 1 pharmacokinetic (PK) study (SAP101) conducted in naltrexone-blocked volunteers, 1 Phase 2 study (SAP202), and 3 Phase 3 studies (SAP301, SAP302 and SAP303). Studies SAP202 (post-bunionectomy) and SAP301 (post-abdominal surgery) were randomized, double-blind, placebo-controlled studies; SAP302 (emergency room setting) and SAP303 (post-operative patients $\geq$ 40 years of age) were both single-arm, open-label studies. A total of 363 patients are included in the primary sufentanil 30 microgram sublingual tablet safety database, with the majority of patients having been administered multiple doses as needed for pain management, subject to a 1-hour minimum dosing interval.

Safety data collected from studies conducted with sufentanil 15 mcg sublingual tablet licenced in the EU as part of the Zalviso MAA will also be used to support a safety assessment of sufentanil 30 microgram sublingual tablet (Supporting Studies). These studies include 3 Phase 2 studies (ARX-C001, ARX-C004, and ARX-C005) and 3 Phase 3 studies (IAP309, IAP310, and IAP311). The use of Zalviso data is based on the establishment of bioequivalence of 1 sufentanil 30 mcg sublingual tablet with 2 sufentanil 15 mcg sufentanil tablets dosed within 20 minutes of each other as well as PK modelling, which concludes that this equivalence is expected if the dosing interval between 2 SST 15 mcg tablets is increased from 20 to 25 minutes. A total of 323 patients who received active study drug met this criterion.

Table 2: Duration of active drug exposure (patients receiving sufentanil 30 mcg [n=363] and patients receiving sufentanil 15 mcg [n=323])

Cumulative for all indications (person time)	
Duration of exposure (at least)	**No. of Subjects**
≥ 1 Minute	686
≥ 30 Minutes	585
≥ 1 Hour	581
≥ 2 Hours	556
≥ 4 Hours	525
≥ 6 Hours	514
≥ 8 Hours	474
≥ 12 Hours	349
≥ 16 Hours	330
≥ 20 Hours	315
≥ 24 Hours	251
≥ 32 Hours	221
≥ 40 Hours	206

Cumulative for all indications (person time)	
Duration of exposure (at least)	**No. of Subjects**
≥ 48 Hours	102

Table 3: Age group and gender

Age (years)	**No. of Subjects (%)**
< 55	312 (45.5%)
55 - < 65	174 (25.4%)
65 - < 75	128 (18.7%)
≥ 75	72 (10.4%)
Total	**686 (100%)**
Gender	
Male	279 (40.7%)
Female	407 (59.3%)
Total	**686 (100%)**

Table 4: Dose

Total number of doses used	**No. of Subjects**	
	Sufentanil 30 mcg	**Sufentanil 15 mcg**
< 6	268	15
6 - 12	81	43
13 - 24	14	61
25 - 48	0	93
> 48	0	111
Total	**363**	**323**

Table 5: Race and Ethnic origin

Race	**No. of Subjects (%)**
American Indian or Alaska Native	6 (0.9%)
Asian	7 (1.0%)
Black or African American	118 (17.2%)
Native Hawaiian or Other Pacific Islander	2 (0.3%)
White	543 (79.2%)
Other	10 (1.4%)
Total	**686 (100%)**
Ethnic Origin	
Hispanic or Latino	91 (13.3%)
Not Hispanic or Latino	595 (86.7%)
Total	**686 (100%)**

Table 6: Body Mass Index (BMI) kg/m2

BMI (kg/m2)	**No. of Subjects (%)**
< 30	403 (59.1%)
30 - 40	229 (33.6%)

> 40	50 (7.3%)
Total	682 (100%)

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

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Patients with an allergy or hypersensitivity to opioids

Reason for exclusion: Similar to all medicinal products patients should not be administered sufentanil 30 mcg sublingual tablets if they are known to be hypersensitive to sufentanil or to any of the excipients because of the risk of hypersensitivity or anaphylactic type reactions.

Is it considered to be included as missing information?: No

Rationale: This risk is important identified risk

Subjects with chronic obstructive pulmonary disease, any other respiratory condition that would cause carbon dioxide (CO2) retention, sleep apnoea that was documented by a sleep laboratory study, or use of continuous positive airway pressure.

Patients who were receiving oxygen therapy at the time of screening.

Reason for exclusion: Patients with significant respiratory depression are contraindicated from using sufentanil. Sufentanil is associated with a known increased risk of respiratory depression that may be exacerbated in the elderly and debilitated patients, the very young, those with underlying pulmonary conditions such as chronic bronchitis, multiple sclerosis, chronic obstructive pulmonary disease, apnoea or those who receive other CNS drugs that affect ventilation.

The sufentanil 30 mcg sublingual tablet SmPC contains a warning about the risk of respiratory depression in section 4.4.

Is it considered to be included as missing information?: No

Rationale: This risk is important identified risk

Subjects who were pregnant or breastfeeding.

Female subjects with a positive pregnancy test at screening (serum) or check in (urine).

Reason for exclusion: Similar to the majority of medicinal products the clinical trials excluded female subjects who were pregnant or breast feeding.

Is it considered to be included as missing information?: Yes

Patients with a positive drug of abuse urine screen unless the positive test result was consistent with a prescribed medication.

Patients with a history of opioid dependence within two years before the start of the study, defined as meeting the DSM-IV- TR™ Criteria for Substance Dependence.

Patients who had used any illicit drugs of abuse within 5 years before the start of the study. Patients who had abused any prescription medication or alcohol within one year before the start of the study.

Reason for exclusion: Sufentanil is known to have the potential for abuse.

Is it considered to be included as missing information?: No

Rationale: This is important potential risk

Patient had clinically significant renal or liver impairment that could affect metabolism or clearance of sufentanil.

Reason for exclusion: This exclusion criterion only applied to the initial Phase 1 and 2 studies. In the Phase 3 studies no significant difference was observed between patients with mild to moderate hepatic impairment based upon raised aminotransferases or total bilirubin with respect to sufentanil plasma levels or between patients with mild to moderate renal impairment with respect to either sufentanil plasma levels or to the AE profile. Additionally, in the population PK studies clearance was not affected by hepatic or renal parameters.

Is it considered to be included as missing information?: Yes

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare or uncommon adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Table 7: Exposure of special populations included or not in clinical trials development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Hepatic dysfunction was assessed based on the maximum severity of baseline liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. Most patients had normal hepatic function (ie, liver function tests below or equal to upper limit of normal range) (n = 364); 79 patients had mild, 13 had moderate, and 6 had severe hepatic dysfunction. In the clinical trials renal dysfunction was assessed based on the maximum severity of baseline renal function tests (creatinine and glomerular filtration rate estimate). Most patients had normal renal function (n = 418) (ie, creatinine below or equal to upper limit of normal range); 15 patients had mild, 25 had moderate, and 4 had severe renal dysfunction.

Type of special population	Exposure
Population with relevant different ethnic origin	Since the majority of patients were Caucasian (77.9%), a comparison of Caucasian and non-Caucasian patients was performed. Of the Caucasian patients, 72.1% experienced AEs, and the most common (≥ 4%) were nausea 46.4%), vomiting (14.6%), headache (8.2%), dizziness (6.4%), pyrexia (6.0%), anaemia (5.6%), and pruritus (4.7%). Of the non-Caucasian patients, 63.2% experienced AEs, and the most common (≥ 4%) were nausea (39.2%), headache (11.2%), dizziness (7.2%), vomiting (6.4%), pruritus (6.4%), somnolence (4.8%), and hypertension (4.0%)
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Sufentanil 30 mcg sublingual tablet has not been studied in paediatrics in the clinical development program

Part II: Module SV - Post-authorisation experience

Section omitted – not required for hybrid medicinal products application according to GVP – Module V (Rev2).

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

Potential for misuse for illegal purposes

Opioids including sufentanil are known to be medicines at risk of abuse and diversion.

As the plasma sufentanil C_{max} that is achieved with the sublingual route is approximately 10% of that seen with IV bolus administration, this PK profile is considered less desirable for abusers. Nonetheless, drug abuse and drug diversion are considered an important potential risk for Sufentanil 30 µg Sublingual Tablet.

Several features of the Dzuveo are developed to reduce the risk of overdose and related risk of abuse and diversion. Some of them make the abuse less convenient.

- Dzuveo is intended only for use in medically monitored settings and is to be administered only by HCPs; it is not intended for use in non-medically monitored settings or for dosing by patients. The restricted distribution of the product only to certified medically monitored settings should help reduce diversion.
- The C_{max} of Dzuveo is more than 17-fold lower than the C_{max} of dose equivalent Sufenta (63.14 vs. 1073 pg/mL respectively, SAP101), thus, the reinforcing properties (e.g., the amount of opioid euphoric effects) of Dzuveo, if taken as labeled, should be less than IV sufentanil.

- Only a single dose of Dzuveo will be available in each package. Dzuveo will be packaged as a single dose of a sufentanil sublingual tablet 30 mcg preloaded in a SDA which is contained in a tamper-evident, laminate foil pouch. The SDA is used to aid in placing the tablet in the patient's sublingual space by the HCP, after which it is to be disposed.
- The tablet can be seen in the clear plastic SDA so visual verification is possible that the dose is present when removed from the foil pouch. Furthermore, when the tablet is dispensed from the SDA, the pusher portion of the SDA has been designed so it will not retract such that a counterfeit/dummy tablet could not be inserted, and the SDA reassembled.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Nausea, Vomiting, Flatulence, Dry Mouth, Pruritus, Eye pain, Visual disturbance, Insomnia, Apathy, Miosis, Flushing, Hiccups, Lethargy, Agitation, Wheezing

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Constipation, Diarrhoea, Eructation, Gastritis, Hypoaesthesia oral, Confusional state, Conversion disorder, Disorientation, Euphoric mood, Hallucination, Nervousness, Orthostatic hypertension, Orthostatic hypotension, Pharyngolaryngeal pain, Hypoxia, Hyperhidrosis, Hypoaesthesia facial, Pruritus generalized, Muscle spasms, Pain in extremity, Feeling hot, Asthenia, Chest discomfort, Procedural nausea, Procedural vomiting, Gastrointestinal stoma complication, Thrombocytopenia, Anaemia, Leukocytosis, Hypocalcaemia, Hypoalbuminaemia, Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypoproteinaemia, Hyperkalaemia, Diabetes mellitus, Hyperglycaemia, Hyperlipidaemia, Hypophosphataemia, Hypovolaemia, Paraesthesia, Atelectasis, Hypoventilation, Pulmonary embolism, Pulmonary oedema, Hyperbilirubinaemia

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Presyncope, Burning sensation, Hypoaesthesia, Sedation, Tension headache, Anxiety, Tachycardia, Sinus tachycardia, Hypertension, Coma, Memory impairment, Urinary retention, Drug withdrawal syndrome, Pyrexia

Known risks that do not impact the risk-benefit profile:

Headache, Dizziness, Somnolence, Erythema, Back Pain, Musculoskeletal pain, Musculoskeletal chest pain

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Respiratory depression:

Risk-benefit impact: Respiratory depression may be life-threatening if left untreated. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Hypersensitivity:

Risk-benefit impact: Allergic reactions may be mild, or they may be damaging, uncomfortable, or occasionally fatal. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Drug abuse and drug diversion:

Risk-benefit impact: Compulsive drug abuse by addicts typically leads to asocial, illegal and self-destructive behaviour. Illegal use for recreational purposes may lead to further abuse. Low impact on risk-benefit balance is expected.

Overdose:

Risk-benefit impact: In overdose, a patient may experience respiratory depression, ranging from hypoventilation to respiratory arrest, loss of consciousness, coma, cardiovascular shock and muscle rigidity. These effects may be life threatening or reversible. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Bradycardia:

Risk-benefit impact: Bradycardia may be life-threatening if left untreated. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Hypotension:

Risk-benefit impact: Severe hypotension may be life-threatening if left untreated. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Paralytic ileus:

Risk-benefit impact: Paralytic ileus is uncomfortable, leads to nausea and vomiting, delays return to enteral nutrition, and prolongs the stay in the hospital. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Spasm of the sphincter of Oddi:

Risk-benefit impact: The pain associated with Oddi disorder is usually debilitating requiring emergency treatment. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Use in patients with raised intracranial pressure:

Risk-benefit impact: Raised intracranial pressure may be life-threatening if left untreated. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Convulsion:

Risk-benefit impact: Convulsion may be life-threatening if left untreated. The medicinal product is proposed to be used in medically monitored setting. Low impact on risk-benefit balance is expected.

Use during pregnancy and lactation:

Risk-benefit impact: Sufentanil is not recommended during pregnancy and in women of childbearing potential not using contraception. Sufentanil is excreted in the human milk and recommends not to use it in breastfeeding women.

Use in patients with hepatic impairment:

Risk-benefit impact: Sufentanil is primarily metabolised in the liver and excreted in the urine and faeces. The duration of activity may be prolonged in patients with severe hepatic and renal impairment.

Use in patients with renal impairment:

Risk-benefit impact: Sufentanil is primarily metabolised in the liver and excreted in the urine and faeces. The duration of activity may be prolonged in patients with severe hepatic and renal impairment.

Use beyond 48 hours:

Risk-benefit impact: Dzuveo was not studied when used for longer than 48 hours.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Based on PRAC recommendations, and consistently with the Good pharmacovigilance practices (GVP) Module V Rev. 2, the list of safety concerns should be updated:

Summary of safety concerns	
Important identified risks	Respiratory depression ~~Hypersensitivity~~
Important potential risks	Drug abuse and drug diversion Overdose ~~Bradycardia~~ Hypotension ~~Paralytic ileus~~ ~~Spasm of the sphincter of Oddi~~ Use in patients with raised intracranial pressure Convulsion
Missing information	~~Use during pregnancy and lactation~~ ~~Use in patients with hepatic impairment~~ ~~Use in patients with renal impairment~~ Use beyond 48 hours

Indeed, these safety concerns are well-known and documented, they do not require further characterization and are not concerned by additional risk minimization measures or additional pharmacovigilance activities. Besides, some of these risks (like hypersensitivity) are not specific and common to all active substances.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Respiratory depression:

Potential mechanisms: Respiratory depression is mediated via the μ-opioid receptor and with full agonists such as morphine and fentanyl there is a clear dose-dependent effect which at high doses or combined

with other CNS depressants, progresses to apnoea (Dahan *et al*. 2010; Regnard and Pelham 2003). Respiratory depression is rare in opioid naïve patients if low starting doses and proper titration are used.

Evidence source(s) and strength of evidence: Sufentanil may cause respiratory depression, for which the degree/severity is dose related. The respiratory effects of sufentanil should be assessed by clinical monitoring, e.g., respiratory rate, sedation level and oxygen saturation.

Respiratory depression caused by sufentanil can be reversed by opioid antagonists. Repeat antagonist administration may be required as the duration of respiratory depression may last longer than the duration of the effect of the antagonist.

Characterisation of the risk: Respiratory depression describes any condition which causes a patient's respiration rate to fall or that fails to provide full ventilation of the lungs. Respiratory depression may be life-threatening if left untreated. Respiratory depression is a listed ADR with common frequency.

Risk factors and risk groups: Patients at higher risk are those with respiratory impairment or reduced respiratory reserve. Respiratory depression is a particular concern in very elderly and debilitated patients and those with underlying pulmonary conditions such as chronic bronchitis, multiple sclerosis, chronic obstructive pulmonary disease, or those who receive other CNS drugs that affect ventilation (Pergolizzi *et al*. 2008). CNS depressants such as benzodiazepines, barbiturates, antidepressants, phenothiazine derivatives, and alcohol increase the risk of respiratory depression if taken with any opioid analgesia (Dahan and Teppema 2003, Pergolizzi *et al*. 2008) this may progress to apnoea.

Preventability: This effect is preventable by HCP awareness about the possible risk of severe breathing problems in the summary of product characteristics and by consulting with the physician if sign and symptoms appeared. However, the Healthcare Professional Guide has been developed in order to inform HCPs about the importance of 1-hour interval between doses. Moreover, Minimum 1 hour dosing interval has been added to the pouch and outer carton labels. Dzuveo is indicated for use only in a medically monitored setting with equipment and personnel trained to detect and manage hypoventilation, and with the availability of supplemental oxygen and opioid antagonists, such as naloxone. This should ensure early detection and management of signs of respiratory depression.

Impact on the risk-benefit balance of the product: Respiratory depression may be life-threatening if left untreated. The Healthcare Professional Guide has been developed in order to mitigate the risk of respiratory depression. The medicinal product is intended to be used only in a medically monitored setting with appropriate monitoring equipment and trained personnel. Low impact on risk-benefit balance is expected.

Public health impact: The public health impact is unknown.

Drug abuse and drug diversion:

Potential mechanisms: The repeated use of drugs changes the biochemistry and physiology of the brain. One danger of drug abuse is that virtually all abused drugs have the potential for causing addiction. Drug addiction is a brain disorder with the main manifestation of this disorder is compulsive drug-seeking behaviour.

Evidence source(s) and strength of evidence: Similar to all opioids, sufentanil is known to have a risk of abuse (misuse) and diversion (illegal use for recreational purposes). Dzuveo is administered by the HCP to the patient. However, it is known that due to the nature of the medicine some people may try to use sufentanil for illegal purposes. The product information warns about the potential risk of abuse and diversion with sufentanil.

Characterisation of the risk: Abuse and diversion not only leads to asocial, illegal, and self-destructive behaviour in patients themselves but can profound effects on close friends and family members trying

to support the patient and society as a whole. Patients who start abusing opioids are at risk of addiction, dependence and overdose that may have life-threatening consequences.

Risk factors and risk groups: Patients with a high potential for abuse include those with a history of substance abuse or psychiatric issues.

Preventability: Scheduling is an accepted method to prevent unlimited access to a drug with abuse potential. Dzuveo is intended for medically monitored settings only, it is not intended for outpatient use.

Several features of the Dzuveo are developed to reduce the risk of overdose and related risk of abuse and diversion. Some of them make the abuse less convenient.

- Dzuveo is intended only for use in medically monitored settings and is to be administered only by HCPs; it is not intended for use in non-medically monitored settings or for dosing by patients. The restricted distribution of the product only to certified medically monitored settings should help reduce the risk of abuse and diversion.
- The C_{max} of Dzuveo is more than 17-fold lower than the C_{max} of dose equivalent Sufenta (63.14 vs. 1073 pg/mL respectively, SAP101), thus, the reinforcing properties (e.g., the amount of opioid euphoric effects) of Dzuveo, if taken as labeled, should be less than IV sufentanil.
- Only a single dose of Dzuveo will be available in each package. Dzuveo will be packaged as a single dose of a sufentanil sublingual tablet 30 mcg preloaded in an SDA which is contained in a tamper-evident, laminate foil pouch. The SDA is used to aid in placing the tablet in the patient's sublingual space by the HCP, after which it is to be disposed.
- The tablet can be seen in the clear plastic SDA so visual verification is possible that the dose is present when removed from the foil pouch. Furthermore, when the tablet is dispensed from the SDA, the pusher portion of the SDA has been designed so it will not retract such that a counterfeit/dummy tablet could not be inserted, and the SDA reassembled.

Impact on the risk-benefit balance of the product: Compulsive drug use by addicts typically leads to asocial, illegal, and self-destructive behaviour. Low impact on risk-benefit balance is expected.

Public health impact: Increased abuse of prescription opioids has widespread consequences including an increase in drug-related emergency department admissions and deaths, worsening of emotional and mental health problems and an increased risk of criminal behaviour. Another consequence is a reluctance by physicians to initiate prescription opioids leading to under treatment or inadequate treated pain.

Overdose:

Potential mechanisms: In general, increased age is associated with increased body fat and reduction in total body water, a combined effect of which increases the volume of distribution of lipophilic drugs. In the elderly patients with chronic hepatic disease dosage reductions or longer dosing intervals are required to prevent drug accumulation. Accumulation of drug or active drug metabolites can increase the risk of toxicity and the severity of drug-related adverse events in patients with renal impairment.

Evidence source(s) and strength of evidence: Patients with moderate to severe hepatic or severe renal impairment should be monitored carefully for symptoms of sufentanil overdose.

Management of sufentanil overdose should be focused on treating symptoms of μ-opioid receptor agonism including administration of oxygen and opioid antagonists. Primary attention should be given to obstruction of airways and the necessity of assisted or controlled ventilation.

Characterisation of the risk: Sufentanil overdose is manifested by an exaggeration of its pharmacological effects. Depending on individual sensitivity, the clinical picture is determined by the degree of respiratory depression. This may range from hypoventilation to respiratory arrest. Other symptoms that may occur

are loss of consciousness, coma, cardiovascular shock, and muscle rigidity. Overdose can be life-threatening but is treatable through administration of oxygen, mechanic ventilation and opioid antagonist (e.g., naloxone) in the event of respiratory depression.

Risk factors and risk groups: Opioid overdose has been associated with a history of depression or substance abuse and is related to the dose prescribed. Elderly patients and patients with renal impairment are also at increased risk. Sufentanil should also be used with caution in patients with previous or pre-existing bradyarrhythmias as sufentanil in overdose is known to cause bradycardia. In hypovolemic patients sufentanil in overdose may cause hypotension and appropriate measures should be taken to maintain stable arterial pressure.

Preventability: Overdose can be managed through appropriate dose titration and not using concomitant drugs known to enhance respiratory depression such as CNS depressants or use in patients at risk of such conditions. Dzuveo is indicated for use only in a medically monitored setting with equipment and personnel trained to detect and manage overdose, and with the availability of supplemental oxygen and opioid antagonists, such as naloxone, enabling early detection and management of signs of overdose. The risk of overdose from the use of Dzuveo is expected to be low, given that only a single 30 mcg tablet is available in each single dose applicator. Dzuveo 30 mcg is approximately equivalent in potency to a 15 mg oral morphine tablet. The label for Dzuveo requires a minimum one-hour dosing interval between doses if additional analgesia is required. The administration of each tablet by an HCP should limit the possibility of overdose: it is expected that patients will either have adequate analgesia from Dzuveo or become drowsy or sleepy and therefore stop asking for additional doses before an overdose would occur. A Healthcare Professional Guide (HPG) has been developed to inform HCPs about the importance of a minimum 1-hour interval between doses. Additionally red text highlighting the minimum 1-hour dosing interval has been added to the pouch and outer carton labels.

Impact on the risk-benefit balance of the product: In overdose, a patient may experience respiratory depression, ranging from hypoventilation to respiratory arrest, loss of consciousness, coma, cardiovascular shock, and muscle rigidity. These effects may be life threatening or reversible. The Healthcare Professional Guide has been developed in order to mitigate the risk of overdose. The medicinal product is proposed to be used medically monitored setting. Low impact on risk-benefit balance is expected.

Public health impact: The public health impact is unknown. Nevertheless, the risk of fatal or otherwise unfavourable outcome of an occurrence of respiratory depression should be reduced due to the administration of sufentanil sublingual tablets in a hospital setting and by the in-built features of the Dzuveo administration device.

Hypotension:

Potential mechanisms: Opioids can modulate the stress response through receptor-mediated actions on the hypothalamic-pituitary-adrenal axis. Most opioids reduce sympathetic and enhance vagal and parasympathetic tone. If not countered by indirect effects (e.g.e.g., catecholamine release) or the co-administration of drugs with anticholinergic or sympathomimetic activity (e.g.e.g., atropine, ephedrine, or pancuronium), use of opioids can result in hypotension. High doses of morphine produce peripheral vasodilation and frequently significant hypotension that are thought to be due, in part, to the release of histamine with differences on the peripheral vascular system between morphine and fentanyl (Rosow *et al*. 1982). In contrast to treatment with morphine intravenous sufentanil does not induce histamine release (Flacke *et al*. 1987).

Evidence source(s) and strength of evidence: Sufentanil may cause hypotension, especially in hypovolemic patients. Appropriate measures should be taken to maintain stable arterial pressure.

Characterisation of the risk: Blood pressure is regulated by the autonomic nervous system using receptors, nerves, and hormones to balance the effects of the sympathetic and parasympathetic nervous systems. Hypotension is generally mild and reversible unless underlying conditions increase its severity. Hypotension is a listed ADR with a common frequency.

Risk factors and risk groups: Hypovolemic patients are at increased risk of hypotension.

Preventability: This effect is preventable by HCP awareness about the possible risk of hypotension in the summary of product characteristics. Dzuveo is indicated for use only in a medically monitored setting enabling early detection and management of signs of hypotension.

Impact on the risk-benefit balance of the product: Severe hypotension may be life-threatening if left untreated. The medicinal product is proposed to be used medically monitored setting. Low impact on risk-benefit balance is expected.

Public health impact: The public health impact is unknown.

Use in patients with raised intracranial pressure:

Potential mechanisms: Opioids change cerebral blood flow in relation to the background cerebrovascular resistance before opioid infusion. With such elevations, opioids may increase cerebral blood flow. Increases in intracranial pressure after opioid infusion are associated with decreases in arterial blood pressure. This suggests that increases in intracranial pressure are due to autoregulatory cerebrovascular dilation and a concomitant increase in cerebral blood volume secondary to systemic hypotension (Werner and Kochs 1996).

Evidence source(s) and strength of evidence: Warning to use sufentanil with caution in patients who may be particularly susceptible to the cerebral effects of CO_2 and patients with brain tumours is included in SmPC.

Characterisation of the risk: Opioids such as sufentanil can cause small and transient increases in intracranial pressure (de Nadal *et al*. 1998, Scholz *et al*. 1994), although others have shown that sufentanil exerts no effects on intracranial pressure (Weinstabl *et al*. 1991). Raised intracranial pressure (ICP) in brain trauma patients directly correlates with poor outcome (Orlando Regional Healthcare, 2004). ICP is very likely to cause severe harm and may be fatal if it rises too high (Dawodu 2005). An increase in pressure can lead to intracranial haematoma or cerebral oedema, can crush brain tissue, shift brain structures, contribute to hydrocephalus, cause brain herniation, and restrict blood supply to the brain (Graham and Gennareli 2000).

Risk factors and risk groups: Patients who are particularly susceptible are those with impaired consciousness, head injuries or brain tumours.

Preventability: Sufentanil should be used with caution in patients who may be particularly susceptible to the cerebral effects of CO2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Sufentanil may obscure the clinical course of patients with head injury. Sufentanil should be used with caution in patients with brain tumours. This effect is preventable by HCP awareness about the possible risk of raised intracranial pressure in the summary of product characteristics. Dzuveo is indicated for use only in a medically monitored setting enabling early detection and management of signs of raised intracranial pressure.

Impact on the risk-benefit balance of the product: Raised intracranial pressure may be life-threatening if left untreated. The medicinal product is proposed to be used medically monitored setting. Low impact on risk-benefit balance is expected.

Public health impact: The public health impact is unknown.

Convulsion:

Potential mechanisms: Compounds with μ-opioid receptor agonist activity in general are known to have excitatory effects on the CNS (Duthie and Nimmo 1987). Mechanisms that have been postulated include opioids blocking cortical inhibitory pathways, thus allowing lower centres to express excitability resulting in clonus, or that the motor activity induced by opioids could represent a form of exaggerated muscle rigidity that may sometimes resemble seizures (Manninen 1997). Meanwhile pethidine has a norpethidine metabolite well known to cause seizures when it accumulates. Unlike morphine, hydromorphone, or pethidine, sufentanil has no metabolites that may cause either analgesic or non-analgesic effects (nausea and neuroexcitatory activity such as allodynia, myoclonus, and seizures) (Smith 2000, Verbeeck and Musuamba 2009).

Evidence source(s) and strength of evidence: Compounds with μ-opioid receptor agonist activity in general are known to have excitatory effects on the CNS (Duthie and Nimmo 1987).

Characterisation of the risk: Convulsions involve muscles contracting and relaxing rapidly and repeatedly, resulting in an uncontrolled shaking of the body. Convulsions can range in duration and intensity, but generally non-epileptic seizures are not life-threatening or cause long-term adverse outcomes. Opioids are known to cause convulsions but generally these do not have electroencephalogram (EEG) activity associated with epileptic seizures (Manninen 1997). The convulsion is listed ADR with unknown frequency.

Risk factors and risk groups: For opioids with active metabolites, such as pethidine, codeine, morphine, and (to a lesser degree) hydromorphone, use of the opioid for a period greater than a few days may increase the risk of convulsions when the dose of the metabolite builds up (Gallagher 2007). Factors such as dehydration, infection, or adding drugs that depress the CNS can increase the risk of convulsions in the elderly.

Preventability: This effect is preventable by HCP awareness about the possible risk of convulsion in the summary of product characteristics. Dzuveo is indicated for use only in a medically monitored setting enabling early detection and management of signs of convulsion.

Impact on the risk-benefit balance of the product: Convulsion may be life-threatening if left untreated. The medicinal product is proposed to be used medically monitored setting. Low impact on risk-benefit balance is expected.

Public health impact: The public health impact is unknown.

SVII.3.2. Presentation of the missing information

Use beyond 48 hours:

Evidence source: Sufentanil 30 micrograms sublingual tablet was not studied beyond 48 hours.

Population in need of further characterisation: Patients using Dzuveo beyond 48 hours

Part II: Module SVIII - Summary of the safety concerns

Table 8: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Respiratory depression
Important potential risks	Drug abuse and drug diversion Overdose Hypotension

Summary of safety concerns	
	Use in patients with raised intracranial pressure Convulsion
Missing information	Use beyond 48 hours

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

There are no specific routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

III.2 Additional pharmacovigilance activities

Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional)

Study short name and title:

Dzuveo HPG Effectiveness Survey.

Rationale and study objectives:

A survey consisting in an in-house questionnaire containing around 10 to 15 questions on the actual use of Dzuveo will be performed to assess whether the HCP followed the guidance provided in the educational materials and capture the understanding of appropriate use of the product.

The survey will be initiated when the market penetration is considered as sufficient (at least 20% of prescriber centers in at least 4 EU countries). A center is considered to be prescribing when it is ordering routinely.

III.3 Summary table of additional pharmacovigilance activities

Table 9: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional) Planned	The survey should contain questions on the actual use of Dzuveo and assess whether the HCP followed the guidance provided in the educational materials.	Respiratory depression Overdose	Study to be initiated once market penetration is achieved	Study results to be submitted within 12 months of the end of data collection (GVP VIII.B.4.3.2)

Part IV: Plans for post-authorisation efficacy studies

No additional post-authorisation efficacy studies applicable to generics were identified by the Applicant in the publicly available information on the reference product Sufenta. Therefore, no additional post-authorisation efficacy studies were proposed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 10: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Respiratory depression	Routine risk communication: *SmPC section 4.2, 4.3, 4.4, 4.5, 4.8, 5.1* *PL section 2, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for monitoring the respiratory effects is included in SmPC sections 4.4* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine Minimum 1 hour dosing interval on the pouch and outer carton labels
Drug abuse and drug diversion	Routine risk communication: *SmPC section 4.4* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Overdose	Routine risk communication: *SmPC section 4.4, 4.9* *PL section 3* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for management the overdose are included in SmPC sections 4.9* *how to detect early signs and symptoms of overdose in PL section 3* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine Minimum 1 hour dosing interval on the pouch and outer carton labels

Safety concern	Routine risk minimisation activities
Hypotension	Routine risk communication: *SmPC section 4.4, 4.8* *PL section 2, 4* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Use in patients with raised intracranial pressure	Routine risk communication: *SmPC section 4.4* *PL section 2* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Convulsion	Routine risk communication: *SmPC section 4.8* *PL section 4* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Use beyond 48 hours	Routine risk communication: *SmPC section 4.2, 5.1* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine

V.2 Additional Risk Minimisation Measures

Healthcare Professional Guide

A Healthcare Professional Guide (HPG) will be made available to educate prescribers and other Healthcare Professionals who may be administering Dzuveo. The guide will cover critical information for the safe and effective use of Dzuveo, covering the method of use of the novel device, the recommended minimum interval between doses and the methods for reducing the risk of respiratory depression and overdose.

Objectives:

The HPG is intended to increase the Healthcare Professionals understanding of the intended use of Dzuveo, specifically to re-iterate the information in the SmPC with regards to the minimum duration between dosing (minimum 1-hour interval) and how to minimise the both the risk of overdose and the risk of respiratory depression.

Rationale for the additional risk minimisation activity:

To remind prescribers about the risk of respiratory depression and overdose and specify importance of 1-hour interval between doses. The second objective is to remind prescribers on how to counsel patients on the risks.

Target audience and planned distribution path:

The HPG is going to target those HCPs likely to use the drug, i.e., hospital pharmacies and physicians and nurses in the appropriate settings. The way of distribution would be the website (where applicable) and accompanied by printed material (where necessary). Second emailing campaign will be repeated after one year and afterwards as necessary. The direct distribution paths will be communicated with the

national competent authorities when necessary prior launch of the product on the market. Direct distribution and re-distribution strategy to HCPs will be considered as per local practice and when necessary approved by national competent authorities. The receipt of the HPG will be closely monitored and documented. The evaluation of proposed process indicators is planned within PSUR and will be evaluated as per PSUR frequency.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Process evaluation is proposed as follows:

(1) A survey containing non-leading questions on the actual use of Dzuveo will assess whether the HCP followed the guidance provided in the educational materials and capture the understanding of appropriate use of the product. This will represent the process indicator number of HCPs understanding and/or using the HPG vs. number of HCPs with lower level of understanding.

Outcome evaluation is proposed as follows:

The planned routine pharmacovigilance measures will determine whether there are any incidences of overdose and/or respiratory depression due to incorrect dosage interval or other medication errors and usability issues. The criteria for success will be measured as reported incidence of respiratory depression and overdose in comparison to that of other opioids used in similar indications and medically supervised settings. This evaluation will be performed via routine signal detection and will be assessed cumulatively within PSUR. The EVDAS will be used as one of the tools of signal detection and incidence of overdose and/or respiratory depression due to incorrect dosage interval or other medication errors and usability issues will be calculated. The incidence of abnormal high rate of respiratory adverse events and use of reversal agents will be monitored, in order to assess the effectiveness of the risk minimization measures.

V.3 Summary of risk minimisation measures

Table 11: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Respiratory depression	Routine risk minimisation measures: *SmPC section 4.2, 4.3, 4.4, 4.5, 4.8, 5.1* *SmPC section 4.4 where advice is given on monitoring the respiratory effects* *PL section 2, 4* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimisation measures: *Healthcare Professional Guide*	Additional pharmacovigilance activities: *Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional)*
Drug abuse and drug diversion	Routine risk minimisation measures: *SmPC section 4.4* *Prescription only medicine*	None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Overdose	Routine risk minimisation measures: *SmPC section 4.4, 4.9* *SmPC section 4.9 where advice is given on management of overdose* *PL section 3* *PL section 3 where advice is given how to detect sign and symptoms of overdose* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimisation measures: *Healthcare Professional Guide*	Additional pharmacovigilance activities: *Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional)*
Hypotension	Routine risk minimisation measures: *SmPC section 4.4, 4.8* *PL section 2, 4* *Prescription only medicine*	None
Use in patients with raised intracranial pressure	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2* *Prescription only medicine*	None
Convulsion	Routine risk minimisation measures: *SmPC section 4.8* *PL section 4* *Prescription only medicine*	None
Use beyond 48 hours	Routine risk minimisation measures: *SmPC section 4.2, 5.1* *Prescription only medicine*	None

Part VI: Summary of the risk management plan

Summary of risk management plan for Dzuveo (Sufentanil (as citrate))

This is a summary of the risk management plan (RMP) for Dzuveo. The RMP details important risks of Dzuveo, how these risks can be minimised, and how more information will be obtained about Dzuveo risks and uncertainties (missing information).

Dzuveo summary of product characteristics (SmPC) and its package leaflet give essential information to Healthcare Professionals and patients on how Dzuveo should be used.

This summary of the RMP for Dzuveo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Dzuveo RMP.

I. The medicine and what it is used for

Dzuveo is an opioid pain medicine used to treat moderate to severe pain in adults. It is a 'hybrid medicine'. This means that it is similar to a 'reference medicine' (called Sufenta Forte) containing the same active substance. The difference between the products is that Dzuveo is available as sublingual tablets (tablets to be dissolved under the tongue) while the reference medicine is a solution for injection. Dzuveo contains the active substance sufentanil.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Dzuveo, together with measures to minimise such risks and the proposed studies for learning more about Dzuveo risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and Healthcare Professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Dzuveo, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Dzuveo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Dzuveo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dzuveo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 12: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Respiratory depression
Important potential risks	Drug abuse and drug diversion Overdose Hypotension Use in patients with raised intracranial pressure Convulsion
Missing information	Use beyond 48 hours

II.B Summary of important risks

Important identified risk: Respiratory depression	
Evidence for linking the risk to the medicine	Sufentanil may cause respiratory depression, for which the degree/severity is dose-related. The respiratory effects of sufentanil should be assessed by clinical monitoring, e.g., respiratory rate, sedation level and oxygen saturation. Respiratory depression caused by sufentanil can be reversed by opioid antagonists. Repeat antagonist administration may be required as the duration of respiratory depression may last longer than the duration of the effect of the antagonist.
Risk factors and risk groups	Patients at higher risk are those with respiratory impairment or reduced respiratory reserve. Respiratory depression is a particular concern in very elderly and debilitated patients and those with underlying pulmonary conditions such as chronic bronchitis, multiple sclerosis, chronic obstructive pulmonary disease, or those who receive other CNS drugs that affect ventilation (Pergolizzi et al. 2008). CNS depressants such as benzodiazepines, barbiturates, antidepressants, phenothiazine derivatives, and alcohol increase the risk of respiratory depression if taken with any opioid analgesia (Dahan and Teppema 2003, Pergolizzi *et al*. 2008) this may progress to apnoea.
Risk minimisation measures	Routine risk minimisation measures

	SmPC section 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 *SmPC section 4.4 where advice is given on monitoring the respiratory effects* *PL section 2, 4* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimization measures *Healthcare Professional Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Drug abuse and drug diversion	
Evidence for linking the risk to the medicine	Similar to all opioids, sufentanil is known to have a risk of abuse (misuse) and diversion (illegal use for recreational purposes). Dzuveo is administered by the HCP to the patient. However, it is known that due to the nature of the medicine some people may try to use sufentanil for illegal purposes. The product information warns about the potential risk of abuse and diversion with sufentanil.
Risk factors and risk groups	Patients with a high potential for abuse include those with a history of substance abuse or psychiatric issues.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *Prescription only medicine*
Important potential risk: Overdose	
Evidence for linking the risk to the medicine	Patients with moderate to severe hepatic or severe renal impairment should be monitored carefully for symptoms of sufentanil overdose. Management of sufentanil overdose should be focused on treating symptoms of μ-opioid receptor agonism including administration of oxygen and opioid antagonists. Primary attention should be given to obstruction of airways and the necessity of assisted or controlled ventilation.
Risk factors and risk groups	Opioid overdose has been associated with a history of depression or substance abuse and is related to the dose prescribed. Elderly patients and patients with renal impairment are also at increased risk. Sufentanil should also be used with caution in patients with

	previous or pre-existing bradyarrhythmias as sufentanil in overdose is known to cause bradycardia. In hypovolemic patients sufentanil in overdose may cause hypotension and appropriate measures should be taken to maintain stable arterial pressure.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, 4.9* *SmPC section 4.9 where advice is given on management of overdose* *PL section 3* *PL section 3 where advice is given how to detect sign and symptoms of overdose* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimization measures *Healthcare Professional Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Hypotension	
Evidence for linking the risk to the medicine	Sufentanil may cause hypotension, especially in hypovolemic patients. Appropriate measures should be taken to maintain stable arterial pressure.
Risk factors and risk groups	Hypovolemic patients are at increased risk of hypotension.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, 4.8* *PL section 2, 4* *Prescription only medicine*
Important potential risk: Use in patients with raised intracranial pressure	
Evidence for linking the risk to the medicine	Warning to use sufentanil with caution in patients who may be particularly susceptible to the cerebral effects of CO_2 and patients with brain tumours is included in SmPC.
Risk factors and risk groups	Patients who are particularly susceptible are those with impaired consciousness, head injuries or brain tumours.
Risk minimisation measures	Routine risk minimisation measures

	SmPC section 4.4 *PL section 2* *Prescription only medicine*
Important potential risk: Convulsion	
Evidence for linking the risk to the medicine	Compounds with μ-opioid receptor agonist activity in general are known to have excitatory effects on the CNS (Duthie and Nimmo 1987).
Risk factors and risk groups	For opioids with active metabolites, such as pethidine, codeine, morphine, and (to a lesser degree) hydromorphone, use of the opioid for a period greater than a few days may increase the risk of convulsions when the dose of the metabolite builds up (Gallagher 2007). Factors such as dehydration, infection, or adding drugs that depress the CNS can increase the risk of convulsions in the elderly.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8* *PL section 4* *Prescription only medicine*
Missing information: Use beyond 48 hours	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 5.1* *Prescription only medicine*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Dzuveo.

II.C.2 Other studies in post-authorisation development plan

Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional): Study short name and title:

Dzuveo HPG Effectiveness Survey.

Purpose of the study: A survey consisting in an in-house questionnaire containing around 10 to 15 questions on the actual use of Dzuveo to assess whether the HCP followed the guidance provided in the educational materials.

The survey will be initiated when the market penetration is considered as sufficient (at least 20% of prescriber centers in at least 4 EU countries). A center is considered to be prescribing when it is ordering routinely.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

None proposed

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Draft key messages of the additional risk minimisation measures of the Healthcare Professional educational material

- The Summary of Product Characteristics
- Guide for Healthcare Professionals

Guide for Healthcare Professionals

- To inform the Healthcare Professionals about the indication and important information for use;
    - DZUVEO (sublingual sufentanil) is indicated for the management of acute moderate to severe pain in adult patients
    - DZUVEO should only be used by Healthcare Professionals, who are experienced, knowledgeable, and skilled in the management of opioid therapy and particularly the management of opioid adverse reactions, such as respiratory depression.
    - DZUVEO is not intended for home or long-term use.
    - DZUVEO is to be administered by a Healthcare Professional in a medically monitored setting only. A medically monitored setting must have equipment and personnel trained to detect and manage hypoventilation, and availability of supplemental oxygen and opioid antagonists, such as naloxone.
    - DZUVEO is to be administered **no more frequently than once per hour** (minimum dosing interval is 1 sublingual tablet per hour).
    - The Healthcare Professional should visually inspect that the DZUVEO tablet has been successfully delivered to the patient's sublingual space and is visible under the patient's tongue.
    - DZUVEO must never be dispensed for pain management at home or continued after the patient is discharged or released from the medically monitored healthcare facility or service.
- To remind the Healthcare Professionals the contraindication
    - Do not prescribe if the patient is allergic to any of the ingredients or excipients
    - DZUVEO is contraindicated in significant respiratory depression
- When prescribing/using DZUVEO
    - Before prescribing DZUVEO, review other medications that the patient takes or has already taken. In particular inhibitors of CYP3A4, calcium channel or beta blocker and CNS depressants as these can increase the systemic exposure to sufentanil, increases the incidence and degree of bradycardia and hypotension or may enhance respiratory depression and therefore lead to an overdose and life-threatening condition.
    - Reassess the appropriateness of the usage of DZUVEO at regular intervals.
    - Have respiratory emergency kit and opioid antagonist (e.g., naloxone) readily available
- Monitoring the effects of DZUVEO

As with other opioids patients receiving DZUVEO should be evaluated at regular intervals for level of pain, alertness and vital signs, including rate and quality of respiration. Particular attention should be paid to the first 24 hours, especially at night when hypoventilation and nocturnal hypoxia may occur.

- Patients should be monitored for signs and symptoms of respiratory depression
- Patients on chronic opioid therapy or with a history of opioid use may require higher (or more frequent) analgesic doses than are available with DZUVEO. Therefore, these patients should be evaluated frequently to ensure they are receiving adequate analgesia. **DZUVEO should not be administered more frequently than once per hour.**
- If the frequency of DZUVEO's administration is less than one-hour, high risk of respiratory depression and overdose is expected.
- Respiratory depression describes any condition which causes a patient's respiration rate to fall or that fails to provide full ventilation of the lungs. Respiratory depression may be life-threatening if left untreated. Respiratory depression is a listed ADR with common frequency. Patients at higher risk are those with respiratory impairment or reduced respiratory reserve. Respiratory depression is a particular concern in very elderly and debilitated patients and those with underlying pulmonary conditions such as chronic bronchitis, multiple sclerosis, chronic obstructive pulmonary disease, or those who receive other CNS drugs that affect ventilation. CNS depressants such as benzodiazepines, barbiturates, antidepressants, phenothiazine derivatives, and alcohol increase the risk of respiratory depression if taken with any opioid analgesia this may progress to apnoea.
- Sufentanil overdose is manifested by an exaggeration of its pharmacological effects. This may range from hypoventilation to respiratory arrest. Overdose can be life-threatening but is treatable through administration of oxygen, mechanic ventilation and opioid antagonist (e.g., naloxone) in the event of respiratory depression. Opioid overdose has been associated with a history of depression or substance abuse and is related to the dose prescribed. Elderly patients and patients with renal impairment are also at increased risk. Sufentanil should also be used with caution in patients with previous or pre-existing bradyarrhythmias as sufentanil in overdose is known to cause bradycardia. In hypovolemic patients sufentanil in overdose may cause hypotension and appropriate measures should be taken to maintain stable arterial pressure.
- Healthcare Professionals should follow an appropriate protocol for overdose management and have respiratory emergency kit and opioid antagonist (e.g., naloxone) readily available.
- Primary attention should be given to hypoventilation and the necessity of assisted or controlled ventilation.
- Repeat antagonist administration or infusion may be required as the duration of respiratory depression may last longer than the duration of the effect of the antagonist.

- Remind the patient information about DZUVEO administration
  - sublingual tablet should be dissolved under the tongue and should not be chewed or swallowed.
  - Patients should not eat or drink and should minimise talking for 10 minutes after each dose of DZUVEO.
  - In the case of an excessive dry mouth, patients may be given ice cubes.

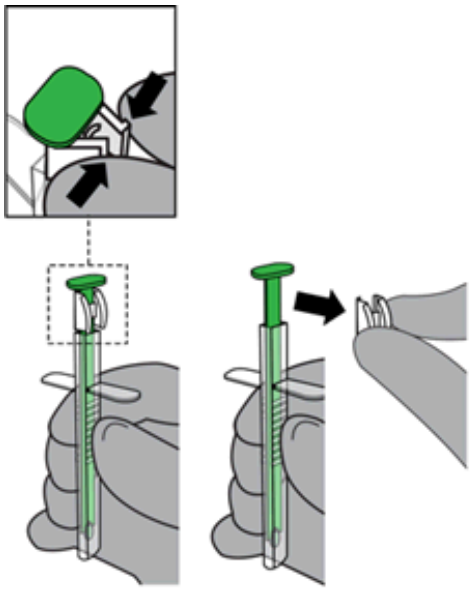
- Some insoluble excipients of the tablet may remain in the mouth after dissolution is complete; this is normal and does not indicate lack of absorption of sufentanil from the tablet.

- Instruct and monitor the patient for signs and symptoms of respiratory depression:
  - Unusual tiredness and daytime sleepiness
  - Shortness of breath and slow and shallow breathing
  - Bluish lips, toes and/or fingers
  - Confusion
  - Headache
  - Seizures
  - Some people may experience faster breathing
- Be vigilant for other sign and symptoms of the sufentanil overdose
  - Loss of consciousness
  - Coma
  - Cardiovascular shock
  - Muscle rigidity

- Healthcare Professionals are reminded of the importance of reporting any suspected adverse reactions, including overdose and respiratory depression, to the national reporting system listed in Appendix V.

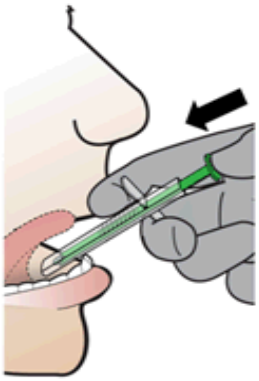
- Healthcare Professionals are reminded that the Instructions for Use are described in the SmPC and Package Leaflet

1. When ready to administer the medication, tear open the slit-notched pouch across the top. The pouch contains one clear plastic single-dose applicator (SDA) with a single, blue-colored tablet housed in the tip, and a StabilOx® oxygen absorber packet. Discard the StabilOx packet)
2. Remove the white Lock from the green Pusher by squeezing the sides together and detaching from Pusher. Discard the Lock.

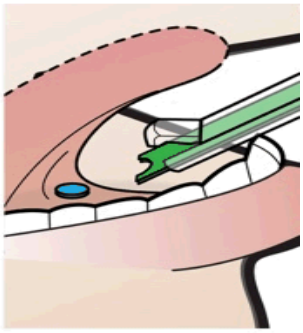


3. Tell the patient to touch their tongue to the roof of their mouth if possible.
4. Rest the SDA lightly on the patient's teeth or lips.
5. Place the SDA tip under the tongue and aim at the floor of the patient's mouth.

NOTE: Avoid direct mucosal contact with the SDA tip.



6. Depress the green Pusher to deliver the tablet to the patient's sublingual space and confirm tablet placement.



Annex 7 - Other supporting data (including referenced material)

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