ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zalviso 15 micrograms sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 15 micrograms sufentanil (as citrate).

Excipient(s) with known effect

Each sublingual tablet contains 0.074 mg sunset yellow FCF Aluminium Lake (E110).
Each sublingual tablet contains 0.013 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet.

Zalviso sublingual tablets of 3 mm diameter are orange-coloured flat-faced tablets with rounded edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zalviso is indicated for the management of acute moderate to severe post-operative pain in adult patients.

4.2 Posology and method of administration

Zalviso is to be administered in a hospital setting only. Zalviso should only be prescribed by physicians who are experienced in the management of opioid therapy, particularly opioid adverse reactions such as respiratory depression (see section 4.4).

Posology

Zalviso sublingual tablets are to be self-administered by the patient in response to pain using the Zalviso administration device. The Zalviso administration device is designed to deliver a single sufentanil 15 micrograms sublingual tablet, on a patient-controlled as needed basis, with a minimum of 20 minutes (lockout interval) between doses, over a period of up to 72 hours, which is the maximum recommended treatment duration. See section “Method of administration”.

Elderly
No special population studies were performed using sufentanil sublingual tablets in elderly patients. In clinical trials approximately 30 % of enrolled patients were 65 to 75 years of age. The safety and efficacy in elderly patients was similar to that observed in younger adults (see section 5.2).

Hepatic or renal impairment

No special population studies were performed using sufentanil sublingual tablets in hepatic and renal impaired patients. Only limited data are available for the use of sufentanil in such patients. Zalviso should be administered with caution to patients with moderate to severe hepatic or severe renal impairment (see section 4.4).

Paediatric population
The safety and efficacy of Zalviso in children aged below 18 years have not been established. No data are available.

Method of administration

For sublingual use only.

The Zalviso sublingual tablets are to be self-administered using the Zalviso administration device which should only be actuated by the patient in response to pain (see section 6.6).

The dispensed sublingual tablet should dissolve under the tongue and should not be crushed, chewed, or swallowed. Patients should not eat or drink and minimize talking for 10 minutes after each dose of Zalviso.
The maximum amount of sublingual sufentanil that can be delivered via the Zalviso administration device over an hour is 45 micrograms (3 doses).

In the event of repeated maximal usage by the patient, one cartridge will last for a period of 13 hours 20 minutes. Additional Zalviso cartridges may be utilized if needed.

For instructions on the setup and handling of the Zalviso administration device before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Significant respiratory depression.

4.4 Special warnings and precautions for use

Respiratory depression

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. Patients at higher risk are those with respiratory impairment or reduced respiratory reserve. 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 (see section 4.9).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Intracranial pressure

Sufentanil should be used with caution in patients who may be particularly susceptible to the cerebral effects of CO_2 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.

Cardiovascular effects

Sufentanil may produce bradycardia. Therefore, it should be used with caution in patients with previous or pre-existing bradyarrhythmias.
Sufentanil may cause hypotension, especially in hypovolemic patients. Appropriate measures should be taken to maintain stable arterial pressure.

Impaired hepatic or renal function

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. Only limited data are available for the use of Zalviso in such patients. Patients with moderate to severe hepatic or severe renal impairment should be monitored carefully for symptoms of sufentanil overdose (see section 4.9).

Abuse potential and tolerance

Sufentanil has potential for abuse. This should be considered when prescribing or administering sufentanil where there is concern about an increased risk of misuse, abuse or diversion.

Patients on chronic opioid therapy or opioid addicts may require higher analgesic doses than the Zalviso administration device can deliver.

Gastrointestinal effects

Sufentanil as a μ-opioid receptor agonist may slow the gastrointestinal motility. Therefore, Zalviso should be used with caution in patients at risk of ileus.

Sufentanil as a μ-opioid receptor agonist may cause spasm of the sphincter of Oddi. Therefore, Zalviso should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Risk from concomitant use of sedating medicinal products such as benzodiazepines or related substances

Concomitant use of Zalviso and sedating medicinal products such as benzodiazepines or related substances may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Zalviso concomitantly with sedating medicinal products the duration of the concomitant treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Other

Before use, the health-care professional should ensure that the patients have been appropriately instructed on how to operate the Zalviso administration device to self-administer tablets as needed to manage their pain post-operatively. Only patients who are able to understand and follow the instructions to operate the administration device should use Zalviso. The health-care professional should take into consideration the ability (e. g. visual or cognitive) of the patient to use the device appropriately.

Excipients

Zalviso sublingual tablets contain the azo colouring agent sunset yellow FCF Aluminium Lake (E110), which may cause allergic reactions.
Zalviso sublingual tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with cytochrome P450-3A4 enzyme

Sufentanil is primarily metabolised by the human cytochrome P450-3A4 enzyme. Ketoconazole, a potent CYP3A4 inhibitor, can significantly increase the systemic exposure to sublingual sufentanil (maximal plasma levels (C_{max}) increase of 19 %, overall exposure to the active substance (AUC) increase of 77 %) and prolong the time to reach maximum concentration by 41 %. Similar effects with other potent CYP3A4 inhibitors (e. g. itraconazol, ritonavir) cannot be excluded. Any change in efficacy/tolerability associated with the increased exposure would be compensated in practice by an alteration in dosing frequency (see section 4.2).

Central nervous system (CNS) depressants

The concomitant use of CNS depressants, including barbiturates, neuroleptics or other opioids, halogen gases or other non-selective CNS depressants (e.g. alcohol) may enhance respiratory depression.

Sedating medicinal products such as benzodiazepines or related substances

The concomitant use of opioids with sedating medicinal products such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The duration of the concomitant use should be limited (see section 4.4).

Monoamine oxidase (MAO) inhibitors

Discontinuation of MAO inhibitors is generally recommended 2 weeks before treatment with Zalviso, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Others

Interaction with other sublingually administered products or products intended to dilute/establish an effect in the oral cavity were not evaluated and simultaneous administration should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is insufficient data on the use of sufentanil during human pregnancy to evaluate its potential harmful effects. There are no indications to date that the use of sufentanil during pregnancy increases the risk of congenital abnormalities.
Sufentanil crosses the placenta.
Reproductive toxicity has been shown in animal studies (see section 5.3).

Zalviso is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Sufentanil is excreted in human milk when applied intravenously; therefore caution is advised when Zalviso is administered to breast-feeding women. Breastfeeding is not recommended when sufentanil is administered, due to the risk of opioid effects or toxicity in the breastfed newborns/infants (see section 4.9).

Fertility

There are no data on the effects of sufentanil on fertility in women or men.

4.7 Effects on ability to drive and use machines

Sufentanil has major influence on the ability to drive and use machines. Patients should be advised not to drive or operate machinery if they experience somnolence, dizziness, or visual disturbance while taking or after the treatment with Zalviso. Patients should only drive and use machines if sufficient time has elapsed after the last administration of Zalviso.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reaction of sufentanil is respiratory depression, potentially leading to apnoea and respiratory arrest (see section 4.4).
Based on the combined safety data from these clinical studies, nausea and vomiting were the most frequently reported adverse reactions (≥1/10 frequency).

Tabulated list of adverse reactions

Adverse reactions identified either from clinical studies or from post-marketing experience with other medicinal products containing sufentanil are summarised in the table below. The frequencies are defined as:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000
Not known	Cannot be estimated from the available data

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Not known**
Immune system disorders			Hypersensitivity*	Anaphylactic shock
Psychiatric disorders		Confusional state	Apathy* Nervousness*	
Nervous system disorders		Dizziness Headache Sedation	Somnolence Paraesthesia Ataxia* Dystonia* Hyperreflexia*	Convulsions Coma
Eye disorders			Vision disturbances	Miosis

Cardiac disorders		Heart rate increased	Heart rate decreased*	
Vascular disorders		Blood pressure increased Blood pressure decreased		
Respiratory, thoracic and mediastinal disorders		Respiratory depression	Apnoea	Respiratory arrest
Gastrointestinal disorders	Nausea Vomiting	Constipation Dyspepsia	Dry mouth	
Skin and subcutaneous tissue disorders		Pruritus	Hyperhidrosis Rash Dry skin*	Erythema
Musculoskeletal and connective tissue disorders		Involuntary muscle spasms Muscle twitching*		
Renal and urinary disorders		Urinary retention		
General disorders and administration site conditions	Pyrexia		Chills Asthenia	Drug Withdrawal Syndrome

* see "Description of selected adverse reactions"

Description of selected adverse reactions

After prolonged use of other substances with μ-opioid receptor activity, symptoms of withdrawal were observed after abrupt interruption of the treatment.
Some adverse reactions were not observed in the clinical trials with Zalviso. Their frequencies were established based on data from intravenous administration of sufentanil: common – muscle twitching; uncommon – hypersensitivity, apathy, nervousness, ataxia, dystonia, hyperreflexia, heart rate decreased and dry skin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms

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.

Management

Management of overdose should be focused on treating symptoms of μ-opioid receptor agonism, including administration of oxygen. Primary attention should be given to obstruction of airways and the necessity of assisted or controlled ventilation.
An opiate antagonist (e.g. naloxone) should be administered in the event of respiratory depression. This does not rule out more direct countermeasures. The shorter duration of activity of the opiate antagonist compared to sufentanil should be taken into account. In that case, the opioid antagonist can be administered repeatedly or by infusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, opioid anaesthetics, ATC Code: N01AH03

Mechanism 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.

Primary pharmacodynamics effects

Analgesia
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.

Secondary pharmacodynamics effects

Respiratory depression
Sufentanil may cause respiratory depression (see section 4.4) and also suppresses the cough reflex.

Other CNS effects
High doses of intravenously administered sufentanil 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.

Gastrointestinal effects
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 (see section 4.4).

Cardiovascular effects
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 (see section 4.4).

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.

Clinical efficacy and safety

Analgesia
Efficacy of Zalviso for patient-controlled analgesia was demonstrated in 3 Phase III clinical trials in acute post-surgical nociceptive and visceral pain (post-surgical pain following major abdominal or orthopaedic surgery): 2 trials were double-blind placebo-controlled (Zalviso N = 430 patients; placebo N = 161 patients) and 1 was an open-label active-controlled (Zalviso N = 177 patients; morphine N = 180 patients) trial.

Patients were treated using the Zalviso dosing regimen of 15 micrograms sufentanil sublingually as needed with a minimum 20 minute lock-out interval over a period of 72 hours.

Superiority over placebo was demonstrated in the Phase III placebo-controlled trials for the primary endpoint time-weighted sum of pain intensity difference from baseline over 48 hours (SPID48; P ≤0.001), and the secondary endpoints, time-weighted SPID (P ≤0.004), total pain relief (TOTPAR; P ≤0.004), and patients global assessment (P ≤0.007) over 24, 48 and 72 hours. After 48 hours more than half of the subjects in the Zalviso group had a relevant pain reduction (30 % responder rate) in these trials (visceral pain 60 %, nociceptive pain 54.9 %).

A significantly higher proportion of patients (78.5 %) rated the method of pain control as “good” or “excellent” with Zalviso than with intravenous morphine patient-controlled analgesia method (65.5 %) (primary endpoint at 48 hours; P = 0.007). Patients reported in all the 3 Phase III trials a clinically meaningful pain relief within the first hour of treatment with Zalviso (pain intensity difference to baseline and total pain response >1 NRS). Zalviso was also considered to be easier to use by health-care professionals (P = 0.017).

As demonstrated in the active-controlled trial, the average time between Zalviso doses was approximately double as long as compared to intravenous morphine patient-controlled analgesia (approximately 80 minutes compared to approximately 45 minutes) over the first 48 hours.
Patients who were treated with Zalviso between 48 and 72 hours in the three controlled trials used a wide range of the available 216 doses, with a mean of 49 doses/patient (range of 8-153 doses) with the majority of patients (69.7 %) using between 24 to 72 doses.

Respiratory depression
Analgesic doses of Zalviso resulted in respiratory depressive effects in some patients in the clinical trials. In the Phase III active-controlled trial, the magnitude of decrease in oxygen saturation was comparable between Zalviso and i.v. patient-controlled morphine groups. However, there was a statistically significant lower percentage of patients who experienced oxygen desaturation episodes following the administration of Zalviso sublingual tablets (19.8 %) with the administration device than in the IV PCA morphine group (30.0 %). Clinical trials have shown that sufentanil administered intravenously causes less respiratory depression when compared with equianalgesic doses of fentanyl.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of sufentanil after sublingual administration can be described as a three-compartment model with first-order absorption. This route of administration results in higher absolute bioavailability by avoiding intestinal and first-pass liver 3A4 enzyme metabolism.
Mean absolute bioavailability after a single sublingual administration of Zalviso relative to a one-minute intravenous sufentanil infusion of 15 micrograms was 59 %. This compares to a substantially

lower bioavailability of 9 % after oral intake (swallowed). In clinical trials during repeated administrations the bioavailability decreased to 37.6 %.
Buccal administration study showed an increased bioavailability of 78 % when the tablets were placed in front of the front lower teeth.
Maximum concentrations of sufentanil are achieved approximately 50 minutes after a single dose; this is shortened to approximately 20 minutes following repeat dosing. When Zalviso was administered every 20 minutes, steady state plasma concentrations were achieved after 13 doses.

Distribution

The central volume of distribution after intravenous application of sufentanil is approximately 14 litres and the volume of distribution at steady state is approximately 350 litres.

Biotransformation

Biotransformation takes place primarily in the liver and the small intestine. Sufentanil is mainly metabolised in humans by the cytochrome P450-3A4 enzyme system (see section 4.5). Sufentanil is rapidly metabolised to a number of inactive metabolites, with oxidative N- and O-dealkylation being the major routes of elimination.

Elimination

The total plasma clearance after single intravenous administration is about 917 l/min.
Approximately 80 % of the intravenously administered dose of sufentanil is excreted within 24 hours. Only 2 % of the dose is excreted in unchanged form. Clearance is not affected by race, sex, renal parameters, hepatic parameters, or concomitant CYP3A4 substrates.

Clinically relevant plasma levels are largely determined by the time for the sufentanil plasma concentration to drop from C_{max} to 50 % of C_{max} after discontinuation of dosing (context sensitive half-time or CST½) rather than by the terminal half-life. After a single dose, the median CST½ was 2.2 hours, increasing to a median value of 2.5 h after multiple dosing: the sublingual delivery route thus substantially extends the duration of action associated with intravenous sufentanil administration (CST½ of 0.14 hours). Similar CST½ values were observed following both single and repeated administration demonstrating that there is a predictable and consistent duration of action after multiple dosing of the sublingual tablet.
After single administration of a 15 micrograms sufentanil sublingual tablet, mean terminal phase half-lives in the range of 6 to 10 hours have been observed. After multiple administrations, a longer mean terminal half-life of up to 18 hours was determined, owing to the higher plasma concentrations of sufentanil achieved after repeated dosing and due to the possibility to quantify these concentrations over a longer time period.

Special populations

Renal impairment
A population pharmacokinetic analysis of plasma sufentanil concentrations following usage of Zalviso in patients and healthy volunteers (N = 700), which included 75 patients with moderate and 7 patients with severe renal impairment, did not identify renal function as a significant covariate for clearance. However, due to the limited number of patients with severe renal impairment studied, Zalviso should be used with caution in such patients (see section 4.4).

Hepatic impairment
Based on the population pharmacokinetic analysis for Zalviso in patients and healthy volunteers (N = 700), which included 13 patients with moderate and 6 patients with severe hepatic impairment, hepatic function was not identified as a significant covariate for clearance. Due to the limited number of patients with moderate to severe hepatic impairment, a potential effect of hepatic dysfunction as

covariate on clearance may not have been detected. Therefore, Zalviso should be used with caution in such patients (see section 4.4).

Paediatric population
No pharmacokinetic data exist for the Zalviso in paediatric patients.
There is limited pharmacokinetic data available in children after intravenous sufentanil administration.

Elderly
No special population studies were performed using Zalviso in the elderly. Pharmacokinetic data from intravenous sufentanil administration did not reveal age related differences. In the placebo-controlled Phase 3 trials, approximately 20 % of enrolled patients were elderly (≥ 75 years of age) and approximately 30 % of enrolled patients were 65 to 75 years of age. The population pharmacokinetic analysis showed an effect of age with a 27 % decrease in clearance in the elderly people (above 65 years of age). Since this decrease related to age is smaller than the observed inter-subject variability of 30-40 % in exposure parameters for sufentanil, this effect is not considered to be of clinical relevance, particularly given that Zalviso is only used on an 'as-needed' basis.

Population pharmacokinetics

When patients titrated themselves to analgesic effect with Zalviso, plasma sufentanil concentrations averaged 60-100 pg/ml over two days of use, with no effect based on age or body mass index (BMI), or mild to moderate renal or liver impairment.

Patients with BMI > 30 kg/m^2

Population pharmacokinetic analysis with a BMI as covariate showed that patients with a BMI > 30 kg/m^2 dosed more frequently.

5.3 Preclinical safety data

Repeat-dose toxicity

Sufentanil has been shown to induce opioid-like effects in a variety of laboratory animals (dogs, rats, guinea pigs, hamsters) at doses above those inducing analgesia and in two repeat-dose studies with sufentanil sublingual tablets administered buccally in Golden Syrian hamster.

Reproductive toxicity

Sufentanil was not teratogenic in rats and rabbits. Sufentanil caused embryolethality in rats and rabbits who were treated for 10-30 days during pregnancy with 2.5 times the maximum human dose by intravenous administration. The embryolethal effect was considered secondary to the toxicity for the mother animal.
No negative effects were observed in another study in rats that were treated with 20times the maximum human dose in the period of organogenesis. The preclinical effects were only observed following administrations of levels significantly above the maximum human dose, which are therefore of little relevance for clinical use.

Mutagenicity

The Ames test revealed no mutagenic activity of sufentanil. In the micronucleus test in female rats, single intravenous doses of sufentanil as high as 80 µg/kg (approximately 2.5 times the upper human intravenous dose) produced no structural chromosome mutations.

Carcinogenicity

Carcinogenicity studies have not been conducted on sufentanil.

Local tolerance

Two local tolerance studies were conducted in the hamster cheek pouch with the sufentanil sublingual tablets. It was concluded from these studies that Zalviso sublingual tablets have no or minimal potential for local irritation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Calcium hydrogen phosphate,
Hypromellose
Croscarmellose sodium
Stearic acid
Magnesium stearate
Sunset yellow FCF Aluminium Lake (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Zalviso is provided in a polycarbonate cartridge, each of which contains 40 sublingual tablets and is packed in a polyester film/LDPE/aluminium foil/LDPE sachet with an oxygen absorber.
Zalviso is available in pack sizes of 1 and 10, 20 cartridges and multipacks containing 40 (2 packs of 20), 60 (3 packs of 20) and 100 (5 packs of 20) cartridges, equivalent to 40, 400, 800, 1,600, 2,400 and 4,000 sublingual tablets, respectively.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The cartridge should be used only with the Zalviso administration device, consisting of a controller and a dispenser to ensure the proper use of this system.
After removing from the sachet, the cartridge should be placed into the Zalviso administration device immediately.

The device should be used as recommended in the information provided by the device manufacturer.

The instructions for setting up the Zalviso administration device by a healthcare professional must be followed carefully.
The Zalviso administration device should not be used if any component is visibly damaged.

The fully charged Zalviso administration device will operate without recharging for up to 72 hours.

After treatment discontinuation the health-care professional has to remove the cartridge from the device and any unused and/or not completely empty cartridges have to be disposed by the health-care professional in accordance with local laws and requirements for controlled substances. Any other waste material must be discarded in accordance to the institutional policies and local requirements.

7. MARKETING AUTHORISATION HOLDER

FGK Representative Service GmbH
Heimeranstrasse 35
80339 Munich
Germany
Tel. +49 89 89 3119 22

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1042/001
EU/1/15/1042/002
EU/1/15/1042/003
EU/1/15/1042/004
EU/1/15/1042/005
EU/1/15/1042/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2015
Date of latest renewal: 24 September 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Grunenthal GmbH
Zieglerstr. 6
D-52078 Aachen
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Zalviso in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Zalviso is launched all healthcare professionals who are expected to prescribe Zalviso are informed through an information letter on having access to / are provided with the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet
- Educational materials for the healthcare professionals

The Educational material shall contain the following key messages:

- Inform about the indication and how to appropriately select patients;
- Use Zalviso according to the guidance in the SmPC to ensure appropriate use and minimize risks.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON for 1, 10 and 20 cartridges

1. NAME OF THE MEDICINAL PRODUCT

Zalviso 15 micrograms sublingual tablets
sufentanil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 15 micrograms sufentanil (as citrate).

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF Aluminium Lake (E110), contains sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 cartridge of 40 sublingual tablets
10 cartridges of 40 sublingual tablets each
20 cartridges of 40 sublingual tablets each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
To be used only with the Zalviso administration device.
Place immediately into the Zalviso administration device after removal from sachet.
Do not crush, chew, or swallow the tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

FGK Representative Service GmbH
Heimeranstrasse 35
80339 Munich
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1042/001 1 cartridge of 40 sublingual tablets
EU/1/15/1042/002 10 cartridges of 40 sublingual tablets each
EU/1/15/1042/003 20 cartridges of 40 sublingual tablets each

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Zalviso 15 micrograms sublingual tablets
sufentanil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 15 micrograms sufentanil (as citrate).

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF Aluminium Lake (E110), contains sodium. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

800 sublingual tablets (20 cartridges of 40 sublingual tablets each). Component of multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
To be used only with the Zalviso administration device.
Place immediately into the Zalviso administration device after removal from sachet.
Do not crush, chew, or swallow the tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

FGK Representative Service GmbH
Heimeranstrasse 35
80339 Munich
Germany

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX)
MULTIPACKS ONLY

1. NAME OF THE MEDICINAL PRODUCT

Zalviso 15 micrograms sublingual tablets
sufentanil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 15 micrograms sufentanil (as citrate).

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF Aluminium Lake (E110), contains sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 1600 sublingual tablets [40 (2 packs of 20) cartridges of 40 sublingual tablets each]
Multipack: 2400 sublingual tablets [60 (3 packs of 20) cartridges of 40 sublingual tablets each]
Multipack: 4000 sublingual tablets [100 (5 packs of 20) cartridges of 40 sublingual tablets each]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
To be used only with the Zalviso administration device.
Place immediately into the Zalviso administration device after removal from sachet.
Do not crush, chew, or swallow the tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

FGK Representative Service GmbH
Heimeranstrasse 35
80339 Munich
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1042/004 2 x 20 cartridges of 40 sublingual tablets each
EU/1/15/1042/005 3 x 20 cartridges of 40 sublingual tablets each
EU/1/15/1042/006 5 x 20 cartridges of 40 sublingual tablets each

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Zalviso 15 micrograms sublingual tablets
sufentanil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 15 micrograms sufentanil (as citrate).

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF Aluminium Lake (E110), contains sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 cartridge of 40 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
To be used only with the Zalviso administration device.
Place immediately into the Zalviso administration device after removal from sachet.
Do not crush, chew, or swallow the tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP see page 1
EXP see reverse

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

FGK Representative Service GmbH
Heimeranstrasse 35
80339 Munich
Germany

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot
Lot see page 1
Lot see reverse

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zalviso 15 micrograms sublingual tablets
sufentanil
Sublingual use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 sublingual tablets

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zalviso 15 micrograms sublingual tablets
sufentanil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zalviso is and what it is used for

The active substance of Zalviso is sufentanil, which belongs to a group of strong pain-relieving medicines called opioids.

Zalviso is used to treat acute moderate to severe pain after an operation in adults.

2. What you need to know before you take Zalviso

Do not take Zalviso:
- if you are allergic to sufentanil or any of the other ingredients of this medicine (listed in section 6).
- if you have severe breathing problems.

Warnings and precautions
Talk to your doctor or nurse before taking Zalviso.

Tell your doctor or nurse before treatment if you:
- are suffering from any condition that affects your breathing (such as asthma, wheezing, or shortness of breath). As Zalviso may affect your breathing, your doctor or nurse will check your breathing during treatment;
- have a head injury or brain tumour;
- have problems with your heart and circulation, especially slow heart rate, irregular heart beats, low blood volume or low blood pressure;
- have moderate to severe liver or severe kidney problems, as these organs have an effect on the way in which your body breaks down and eliminates the medicine;
- have a history of medicine or alcohol abuse;
- are regularly using a prescribed opioid medicine (e.g. codeine, fentanyl, hydromorphone, oxycodone);
- have abnormally slow bowel movements;
- have a disease of the gall bladder or pancreas.

Sleep-related breathing disorders
Zalviso contains an active substance that belongs to the group of opioids. Opioids can cause sleep-related breathing disorders, for example central sleep apnea (shallow/pause of breathing during sleep) and sleep-related hypoxemia (low level of oxygen in the blood).
The risk of experiencing central sleep apnea is dependent on the dose of opioids. Your doctor may consider decreasing your total opioid dosage if you experience central sleep apnea.

Children and adolescents
Zalviso should not be used in children and adolescents below 18 years.

Other medicines and Zalviso
Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor if you are taking any of the following:
- Any medicines that might have an effect on the way in which your body breaks down Zalviso e.g. ketoconazole, which is used for the treatment of fungal infections.
- Any medicines to treat anxiety, tranquillisers or other opioid medicines, as they can increase the risk of severe breathing problems.
- Medicines for the treatment of severe depression (monoamine-oxidase (MAO) inhibitors), even if you have taken them in the last 2 weeks. The use of MAO inhibitors must be stopped for at least 2 weeks prior to use of Zalviso.
- Other medicines which are also taken sublingually (medicines that are placed under the tongue where they dissolve) or medicines which dilute or take effect in your mouth (e.g. nystatin, a liquid or pastilles you hold in your mouth to treat fungus infections), as the effect on Zalviso has not been studied.

Concomitant use of Zalviso and sedating medicines such as benzodiazepines or related medicines increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.
However, if your doctor prescribes Zalviso together with sedating medicines the duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all sedating medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Zalviso with alcohol
Do not drink alcohol while using Zalviso. It can increase the risk of experiencing severe breathing problems.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Zalviso should not be used during pregnancy or if you are a woman of childbearing potential not using contraception.

Sufentanil passes into breast milk and can cause side effects in the breast-fed child. Breastfeeding is not recommended when you take Zalviso.

Driving and using machines
Zalviso affects your ability to drive or use machines as it may cause sleepiness, dizziness or visual disturbances. You should not drive or operate machinery if you experience any of these symptoms whilst or after being treated with Zalviso. You should only drive and use machines if sufficient time as elapsed after your last dose of Zalviso.

Zalviso contains sunset yellow FCF Aluminium Lake (E110)

Zalviso contains the colouring agent sunset yellow FCF Aluminium Lake (E110), which may cause allergic reactions.

Zalviso contains sodium
Zalviso contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

3. How to take Zalviso

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The sublingual tablets are taken using the Zalviso administration device, which is a system that delivers a single dose upon activation.

Before you start using Zalviso, your doctor or nurse will show you how to use the Zalviso administration device. You will then be able to take a tablet as needed to relieve your pain. Follow the instructions carefully. Talk to your doctor or nurse if you did not fully understand the instructions or are unsure about the correct handling of the administration device.

After receiving a dose you will not be able to release another dose for 20 minutes and you will not be able to take more than 3 doses in one hour.

The device will work for 3 days (72 hours), which is also the maximum recommended duration of your treatment.

Zalviso is placed under the tongue using the Zalviso administration device. You can control your treatment and should only activate the device when in need of pain relief.

The tablets dissolve under your tongue and should not be crushed, chewed, or swallowed. You should not eat or drink and should talk as little as possible for 10 minutes after each dose.

Zalviso is only to be taken in a hospital setting. It is only prescribed by physicians who are experienced in the use of strong pain killers like Zalviso and know the effects it may have on you, in particular on your breathing (see "Warnings and precautions" above).

Do not use the device if any component is visibly damaged.

After your treatment the medical staff will take the Zalviso administration device and dispose of any unused tablets accordingly. The device is constructed so that you will not be able to open it.

If you take more Zalviso than you should
The administration device will make you wait 20 minutes between doses to prevent you from taking more Zalviso than you should. However, symptoms of overdose include severe breathing problems like slow and shallow breathing, loss of conciousness, extreme low blood pressure, collapse and muscle rigidity. If these start to develop, tell a doctor or nurse immediately.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effects are severe breathing problems like slow and shallow breathing, which may even lead to stopping breathing or inability to breathe.

In case you experience any of the above mentioned side effects, stop taking Zalviso and tell your doctor or nurse immediately.

Very common side effects (may affect more than 1 in 10 people): nausea, vomiting, fever.

Common side effects (may affect up to 1 in 10 people):
confusion, dizziness, headache, drowsiness, increased heart rate, high blood pressure, low blood pressure, constipation, indigestion, itching of the skin, involuntary muscle cramps, muscle twitching, difficulty passing urine.

Uncommon side effects (may affect up to 1 in 100 people): allergic reactions, lack of interest or emotion, nervousness, sleepiness, abnormal sensation of the skin, problems coordinating muscle movements, muscle contractions, exaggeration of reflexes, vision disturbances, decreased heart rate, dry mouth, excessive sweating, rash, dry skin, chills, weakness.

Frequency not known (frequency cannot be estimated from the available data): severe allergic reactions (anaphylactic shock), convulsion (fits), coma, small pupil size, redness of the skin, withdrawal syndrome.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Zalviso

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and sachet after EXP.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask the medical staff how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zalviso contains
- The active substance is sufentanil. Each sublingual tablet contains 15 micrograms sufentanil (as citrate).
- The other ingredients are mannitol (E421), calcium hydrogen phosphate, hypromellose, croscarmellose sodium, stearic acid, magnesium stearate, sunset yellow FCF Aluminium Lake (E110) (see section 2 “What you need to know before you take Zalviso”)

What Zalviso looks like and contents of the pack
Zalviso sublingual tablets are orange-coloured flat-faced tablets with rounded edges. The sublingual tablets measure 3 mm in diameter.

The sublingual tablets are supplied in cartridges; each cartridge contains 40 sublingual tablets. One cartridge is packed in a sachet including an oxygen absorber.
Zalviso sublingual tablets are available in pack sizes of 1, 10 and 20 cartridges and in multipacks containing 40 (2 packs of 20), 60 (3 packs of 20) and 100 (5 packs of 20) cartridges, equivalent to 40, 400, 800, 1,600, 2,400 and 4,000 sublingual tablets, respectively.
Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.