SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dzuveo 30 micrograms sublingual tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 30 micrograms of sufentanil (as citrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet.

Blue-coloured flat-faced tablet with round edges and a diameter of 3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dzuveo is indicated for the management of acute moderate to severe pain in adult patients.

4.2 Posology and method of administration

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 and administered by healthcare professionals who are experienced in the management of opioid therapy; particularly opioid adverse reactions, such as respiratory depression (see section 4.4).

Posology

Dzuveo is provided in a disposable single-dose applicator, to be administered by a healthcare provider as needed by the individual patient, but no more than once every hour, resulting in a maximum dose of 720 micrograms /day. Patients with a higher pain intensity at one hour after sufentanil 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.

Elderly

No specific dose adjustment is required in elderly patients. However, elderly patients should be observed closely for adverse reactions of sufentanil (see section 5.2).

Hepatic or renal impairment

Sufentanil 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 sufentanil in children and adolescents below 18 years have not been established. No data are available.

Method of administration

For sublingual use only.

Dzuveo is to be administered by a healthcare professional from a disposable single-dose applicator (see section 6.6). The applicator is used as a placement aid for the healthcare professional to deliver the tablet under the tongue, on an as needed basis, per patient request, with a minimum of 1 hour between doses.

The dispensed sublingual tablet should dissolve under the tongue and should not be chewed or swallowed. If swallowed, the oral bioavailability of Dzuveo is only 9% which would result in a sub- therapeutic dose. Patients should not eat or drink and should minimise talking for 10 minutes after each dose of sufentanil 30 mcg sublingual tablet. 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.

See section 6.6 for instructions regarding handling of the Dzuveo sublingual tablet and applicator.

4.3 Contraindications

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

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).

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicinal products

Concomitant use of sufentanil and sedative medicines such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible, or when sufentanil is used in an emergency setting.

Intracranial pressure

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.

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 sufentanil 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).

Tolerance and Opioid Use Disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids.

Abuse or intentional misuse of Dzuveo may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).
Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Gastrointestinal effects

Sufentanil as a μ-opioid receptor agonist may slow the gastrointestinal motility. Therefore, sufentanil 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, sufentanil should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Opioid induced hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of sufentanil, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or discontinuation of sufentanil treatment or treatment review may be indicated.

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.

Excipients This medicine contains 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 (Cmax) 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. itraconazole, ritonavir) cannot be excluded. Any change in efficacy/tolerability associated with the increased exposure would be compensated in practice by an increase in the amount of time between doses (see section 4.2).

Interaction with calcium channel and/or beta blockers

The incidence and degree of bradycardia and hypotension with sufentanil may be greater in patients on chronic calcium channel and/or beta blocker therapy.

Caution should be exercised in patients on these concomitant medicinal products and they should be closely monitored.

Central nervous system (CNS) depressants

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

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

When considering the use of sufentanil in a patient taking a CNS depressant, the duration of use of the CNS depressant and the patient's response should be assessed, including the degree of tolerance that has developed to CNS depression. If the decision to begin sufentanil is made, the patient should be closely monitored and a lower dose of the concomitant CNS depressant should be considered.

Co-administration of sufentanil with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), or Monoamine Oxidase Inhibitors (MAOIs), may increase the risk of serotonin syndrome, a potentially life threatening condition. Monoamine Oxidase Inhibitors must not be taken in the 2 weeks before or at the same time as Dzuveo is given.

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 are no or limited amount of data from the use of sufentanil in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Sufentanil should not be used in pregnancy, because it crosses the placenta and the foetal

respiratory center is sensitive to opiates. If sufentanil is administered to the mother during this time, an antidote for the child should be readily available. Following long-term treatment sufentanil may cause withdrawl symptoms in the newborn. Sufentanil is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Sufentanil is excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sufentanil therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of sufentanil on fertility. Studies in rats have revealed reduced fertility and enhanced embryo mortality (see section 5.3).

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 sufentanil. Patients should only drive and use machines if sufficient time has elapsed after the last administration of sufentanil.

Driving in the UK:
This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:
• The medicine is likely to affect your ability to drive
• Do not drive until you know how the medicine affects you
• It is an offence to drive while under the influence of this medicine
• However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reaction of sufentanil is respiratory depression, which occurred at a rate of 0.6% in sufentanil clinical trials.

The most commonly reported adverse reactions seen in clinical trials and from post marketing experience with sufentanil containing products were nausea, vomiting and pyrexia (≥1/10 patients) (see section 4.4).

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 to <1/10
Uncommon ≥1/1 000 to <1/100
Rare ≥1/10 000 to <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**
Infections and infestations			Bronchitis Conjunctivitis infective Pharyngitis	
Neoplasm benign, malignant and unspecified (including cysts and polyps)			Lipoma	
Blood and lymphatic system disorders		Anaemia Leukocytosis	Thrombocytopenia	
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders		Hypocalcaemia Hypoalbuminaemia Hypokalaemia Hyponatraemia	Hypomagnesaemia Hypoproteinaemia Hyperkalaemia Diabetes mellitus Hyperglycaemia Hyperlipidaemia Hypophosphataemia Hypovolaemia	
Psychiatric disorders		Insomnia Anxiety Confusional state	Agitation Apathy Conversion disorder Disorientation Euphoric mood Hallucination Mental status changes Nervousness	

MedDRA system organ class	Very common	Common	Uncommon	Not known
Nervous system disorders		Headache Dizziness Somnolence Sedation	Tremor Ataxia Dystonia Hyperreflexia Tremor Burning sensation Presyncope Paraesthesia Hypoaesthesia Lethargy Memory impairment Migraine Tension headache	Convulsions Coma
Eye disorders			Eye pain Visual disturbance	Miosis
Cardiac disorders		Tachycardia Sinus tachycardia	Bradycardia Angina pectoris Atrial fibrillation Ventricular extrasystoles	
Vascular disorders		Hypotension Hypertension	Orthostatic hypertension Flushing Diastolic hypotension Orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		Hypoxia Pharyngolaryngeal pain Respiratory Depression	Bradypnoea Epistaxis Hiccups Apnoea Atelectasis Hypoventilation Pulmonary embolism Pulmonary oedema Respiratory distress Respiratory failure Wheezing	Respiratory arrest
Gastrointestinal disorders	Nausea Vomiting	Constipation Dyspepsia Flatulence Dry Mouth	Diarrhoea Eructation Retching Abdominal discomfort Abdominal distension Abdominal Pain upper Epigastric discomfort Gastritis Gastroesophageal reflux disease Hypoaesthesia oral	
Hepatobilary disorders			Hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Pruritus	Hyperhidrosis Hypoaesthesia facial Pruritus generalized Blister Rash Dry Skin	Erythema

MedDRA system organ class	Very common	Common	Uncommon	Not known
Musculoskeletal and connective tissue disorders		Muscle spasms Muscle twitching	Back Pain Musculoskeletal pain Musculoskeletal chest pain Pain in extremity	
Renal and urinary disorders		Urinary retention	Urinary hesitation Oliguria Renal failure Urinary tract pain	
General disorders and administration site conditions	Pyrexia		Feeling hot Fatigue Asthenia Chills Local swelling Non-cardiac chest pain Chest discomfort	Drug withdrawal syndrome
Investigations		Oxygen saturation decreased Body temperature increased	Blood pressure increased Respiratory rate decreased Blood glucose increased Blood bilirubin increased Urine output decreased Aspartate aminotransferase increased Blood urea increased Electrocardiogram T wave abnormal Electrocardiogram abnormal Hepatic enzyme increased Liver function test abnormal	
Injury, poisoning and procedural complications		Anaemia postoperative	Procedural nausea Postoperative ileus Procedural vomiting Gastrointestinal stoma complication Procedural pain	

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:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 sufentanil 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 that of 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: Anesthetics, opioid anesthetics, 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

The efficacy of Dzuveo was evaluated in two double-blind, placebo-controlled trials involving 221 patients with moderate-to-severe acute postoperative pain (pain intensity of ≥ 4 on a 0-10 scale) after abdominal (studied up to 48 hours) or orthopedic (bunionectomy) surgery (studied up to 12 hours). Of the 221 patients, 147 received active treatment and 74 received placebo. Patients were predominantly female (63%), mean age was 41 years (range 18-74 years), BMI 15.8 to 53.5 kg/m^2, race was predominately White (69%) and Black or African American (21%). Mean (SEM) baseline intensity in these trials was 6.48 (0.21) for the 12-hour bunionectomy trial in the sufentanil-treated patients and 5.98 (0.30) for placebo-treated patients. In the abdominal surgery trial, mean baseline pain intensity was 5.61 (0.13) for sufentanil-treated patients and 5.48 (0.18) for placebo-treated patients.

In both trials, the primary efficacy endpoint was the time-weighted sum of pain intensity difference (SPID) to baseline (measured on an 11-point NRS) over 12 hours (SPID12). Patients using Dzuveo had a mean SPID12 score that was superior to patients using placebo (25.8 vs. 13.1) in abdominal surgery patients ($p<0.001$) and (5.93 vs. -6.7) in bunionectomy patients ($p=0.005$) respectively.

Rescue analgesia was allowed in both studies, with a higher proportion of patients in the placebo group requiring rescue medication due to inadequate analgesia (64.8%, 100%; abdominal, bunionectomy) than in the sufentanil group (27.1%, 70.0%;. abdominal, bunionectomy). Onset of analgesia, as measured by pain intensity difference to baseline scores, was greater ($p<0.05$) for sufentanil versus placebo by 15 minutes after the first dose in the abdominal study and 30 minutes in the bunionectomy study. The majority (>90%) of healthcare professionals found Dzuveo easy to use.

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.

Respiratory depression

Analgesic doses of sufentanil resulted in respiratory depressive effects in some patients in the clinical trials, however, no patient treated with Dzuveo required use of an opioid reversal drug (e.g. naloxone).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of sufentanil after administration of Dzuveo can be described as a two- compartment model with first-order absorption. This route of administration results in higher absolute bioavailability than oral (swallowed) administration by avoiding intestinal and first-pass liver 3A4 enzyme metabolism. Mean absolute bioavailability after a single sublingual administration of the sufentanil tablet relative to a one-minute intravenous sufentanil infusion of the same dose was 53%.

In a study of a sufentanil 15 microgram sublingual tablet (with the same formulation as the 30 microgram tablet), a substantially lower bioavailability of 9% after oral intake (swallowed) was observed. Buccal administration 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 60 minutes after a single dose; this is shortened to approximately 40 minutes following repeated hourly dosing. When Dzuveo is administered every hour, steady-state plasma concentrations are achieved by 7 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

With Dzuveo, first dose clearance in the typical patient of weight 78.5 kg and age 47 years is 84.2 L/hr. Steady-state clearance is 129.3 L/hr. Patient weight and age are key covariates on clearance.

After single administration of Dzuveo, mean terminal phase half-live of 13.4 hours (range of 2.5 to 34.4 hours) was observed. After multiple administrations, a longer mean terminal half-life of 12.68 hours (range 5.30 to 26.91 hours) was observed, 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.

Pharmacokinetic/Pharmacodynamic Relationship

With administration of Dzuveo, clinical duration of analgesia is largely determined by the time for the sufentanil plasma concentration to drop from Cmax to 50% of Cmax after discontinuation of dosing (context sensitive half-time or CST½) rather than by the terminal half-life. Following either a single dose or multiple doses hourly over 12 hours, the median CST½ remained 2.3 hours: the sublingual delivery route thus substantially extends the duration of action associated with intravenous sufentanil administration (CST½ of 0.1 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.

Patients requested dosing with Dzuveo to maintain plasma sufentanil concentrations averaging 40- 50 pg/ml at 12 hours, with no effect based on age or body mass index (BMI), or mild to moderate renal or liver impairment.

Special populations

Renal impairment

A population pharmacokinetic analysis of plasma sufentanil concentrations following usage of Dzuveo did not identify renal function as a significant covariate for clearance. However, due to the limited number of patients with severe renal impairment studied, Dzuveo should be used with caution in such patients (see section 4.4).

Hepatic impairment

Based on the population pharmacokinetic analysis for Dzuveo, 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, Dzuveo should be used with caution in such patients (see section 4.4).

Paediatric population

No pharmacokinetic data exist for sufentanil in paediatric patients.

Elderly

No special population studies were performed using Dzuveo in the elderly. For Dzuveo, population pharmacokinetic analysis showed an effect of age, with an 18% decrease in clearance in the elderly (above 65 years of age).

Effect of BMI on dosing

Population pharmacokinetic analysis with weight as a covariate showed that patients with a higher BMI dosed more frequently.

5.3 Preclinical safety data

Reproductive toxicity

Fertility and early embryonic development studies were conducted in male and female rats. Increased mortality was noted in all treatment groups.

Lower pregnancy rates were noted following treatment of males suggesting the potential for an adverse effect on fertility in males. Increased resorption of foetuses and reduced litter size was noted in the high dose females suggesting the potential for foetotoxicity, likely due to maternal toxicity.

Mutagenicity

The Ames test revealed no mutagenic activity of sufentanil.

Carcinogenicity

Carcinogenicity studies have not been conducted with 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 sufentanil 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
Indigo carmine -E132
Stearic acid
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Dzuveo is packaged in a polypropylene single-dose applicator, which is packaged in a polyester film/LDPE/aluminium foil/LDPE sachet with an oxygen absorber.

Dzuveo will be available in cartons of 5 and 10. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for use of Single Dose Applicator (SDA)

Single-Use Product / Do Not Reuse

Do Not Use if Pouch Seal is Broken

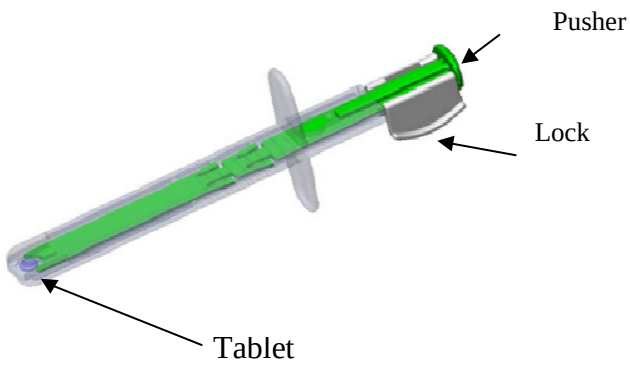
Do not use if the Single Dose Applicator (SDA) is damaged

Instruct the patient to not chew or swallow the tablet.

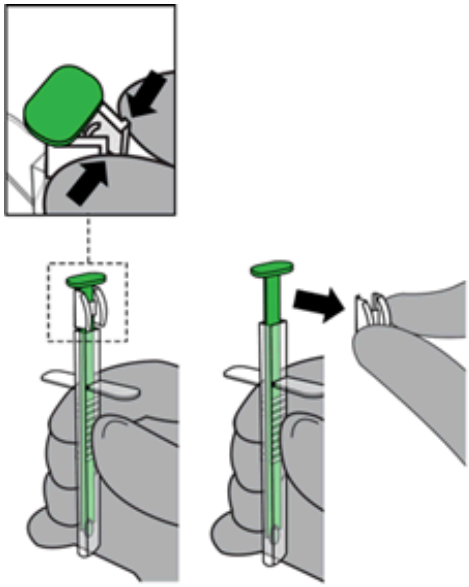
Instruct the patient to not eat or drink and minimize talking for 10 minutes after receiving the tablet.

1. When ready to administer the medicine, tear open the slit-notched pouch across the top. The pouch contains one clear plastic SDA with a single blue-colored tablet housed in the tip, and an oxygen absorber packet. The oxygen absorber packet should be discarded.

Contents of the pouch are shown below:



2. Remove the white Lock from the green Pusher by squeezing the sides together and detaching from Pusher. Discard the Lock.

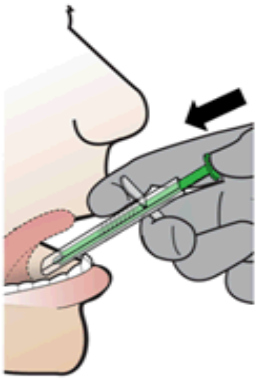


3. Tell the patient to touch their tongue to the roof of their mouth if possible.

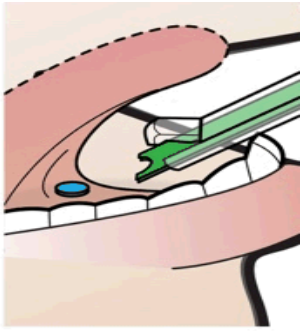
4. Rest the SDA lightly on the patient's teeth or lips.

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.



The single-dose applicator (SDA) must be discarded in accordance to the institutional policies and local requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire Aguettant
1, rue Alexander Fleming
69007 Lyon
France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 14434/0051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/06/2023

10 DATE OF REVISION OF THE TEXT

29/07/2024