**ANNEX I**

**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 $CO_2$ 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 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).

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 contained in Dzuveo.

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.

## 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. 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.

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.

Monoamine oxidase (MAO) inhibitors

Discontinuation of MAO inhibitors is generally recommended 2 weeks before treatment with sufentanil, 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 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.

## 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** | **Unknown** |
|---|---|---|---|---|
| Infections and infestations | | | Bronchitis<br>Conjunctivitis infective<br>Pharyngitis | |
| Neoplasm benign, malignant and unspecified (including cysts and polyps) | | | Lipoma | |
| Blood and lymphatic system disorders | | Anaemia<br>Leukocytosis | Thrombocytopenia | |
| Immune system disorders | | Hypersensitivity | | Anaphylactic shock |
| Metabolism and nutrition disorders | | Hypocalcaemia<br>Hypoalbuminaemia<br>Hypokalaemia<br>Hyponatraemia | Hypomagnesaemia<br>Hypoproteinaemia<br>Hyperkalaemia<br>Diabetes mellitus<br>Hyperglycaemia<br>Hyperlipidaemia<br>Hypophosphataemia<br>Hypovolaemia | |
| Psychiatric disorders | | Insomnia<br>Anxiety<br>Confusional state | Agitation<br>Apathy<br>Conversion disorder<br>Disorientation<br>Euphoric mood<br>Hallucination<br>Mental status changes<br>Nervousness | |
| Nervous system disorders | | Headache<br>Dizziness<br>Somnolence<br>Sedation | Tremor<br>Ataxia<br>Dystonia<br>Hyperreflexia<br>Tremor<br>Burning sensation<br>Presyncope<br>Paraesthesia<br>Hypoaesthesia<br>Lethargy<br>Memory impairment<br>Migraine<br>Tension headache | Convulsions<br>Coma |
| Eye disorders | | | Eye pain<br>Visual disturbance | Miosis |
| Cardiac disorders | | Tachycardia | Bradycardia | |

| MedDRA system organ class | Very common | Common | Uncommon | Unknown |
|---|---|---|---|---|
| | | Sinus tachycardia | Angina pectoris<br>Atrial fibrillation<br>Ventricular extrasystoles | |
| Vascular disorders | | Hypotension<br>Hypertension | Orthostatic hypertension<br>Flushing<br>Diastolic hypotension<br>Orthostatic hypotension | |
| Respiratory, thoracic and mediastinal disorders | | Hypoxia<br>Pharyngolaryngeal pain<br>Respiratory Depression | Bradypnoea<br>Epistaxis<br>Hiccups<br>Apnoea<br>Atelectasis<br>Hypoventilation<br>Pulmonary embolism<br>Pulmonary oedema<br>Respiratory distress<br>Respiratory failure<br>Wheezing | Respiratory arrest |
| Gastrointestinal disorders | Nausea<br>Vomiting | Constipation<br>Dyspepsia<br>Flatulence<br>Dry Mouth | Diarrhoea<br>Eructation<br>Retching<br>Abdominal discomfort<br>Abdominal distension<br>Abdominal Pain upper<br>Epigastric discomfort<br>Gastritis<br>Gastroesophageal reflux disease<br>Hypoaesthesia oral | |
| Hepatobilary disorders | | | Hyperbilirubinaemia | |
| Skin and subcutaneous tissue disorders | | Pruritus | Hyperhidrosis<br>Hypoaesthesia facial<br>Pruritus generalized<br>Blister<br>Rash<br>Dry Skin | Erythema |
| Musculoskeletal and connective tissue disorders | | Muscle spasms<br>Muscle twitching | Back Pain<br>Musculoskeletal pain<br>Musculoskeletal chest pain<br>Pain in extremity | |
| Renal and urinary disorders | | Urinary retention | Urinary hesitation<br>Oliguria<br>Renal failure<br>Urinary tract pain | |
| General disorders and administration site conditions | Pyrexia | | Feeling hot<br>Fatigue<br>Asthenia<br>Chills<br>Local swelling<br>Non-cardiac chest pain<br>Chest discomfort | Drug withdrawal syndrome |
| Investigations | | Oxygen saturation decreased<br>Body temperature | Blood pressure increased<br>Respiratory rate decreased | |

| MedDRA system organ class | Very common | Common | Uncommon | Unknown |
|---|---|---|---|---|
| | | increased | Blood glucose increased<br>Blood bilirubin increased<br>Urine output decreased<br>Aspartate aminotransferase increased<br>Blood urea increased<br>Electrocardiogram T wave abnormal<br>Electrocardiogram abnormal<br>Hepatic enzyme increased<br>Liver function test abnormal | |
| Injury, poisoning and procedural complications | | Anaemia postoperative | Procedural nausea<br>Postoperative ileus<br>Procedural vomiting<br>Gastrointestinal stoma complication<br>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 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 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: NO1AH03.

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/m2, 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 sufenatil-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 15.7 hours (range 2.4 to 42.7 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 $C_{max}$ to 50% of $C_{max}$ after discontinuation of dosing (context sensitive half-time or $CST_{½}$) rather than by the terminal half-life. Following either a single dose or multiple doses hourly over 12 hours, the median $CST_{½}$ remained 2.3 hours: the sublingual delivery route thus substantially extends the duration of action associated with intravenous sufentanil administration ($CST_{½}$ of 0.1 hours). Similar $CST_{½}$ 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

3 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 and other handling

Instructions for use of Single Dose Applicator (SDA)

Single-Use Product / Do Not Reuse

**Do Not Use if Pouch Seal is Broken**

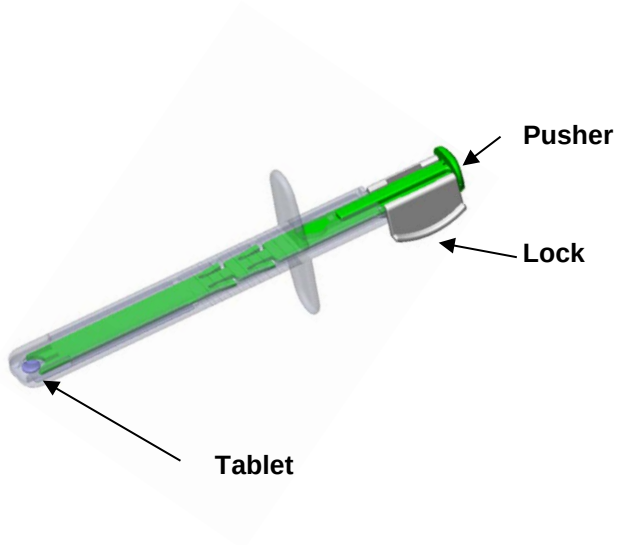
**Do not use if the Single Dose Applicator (SDA) is damaged**

Instruct the patient to not chew or swallow the tablet.

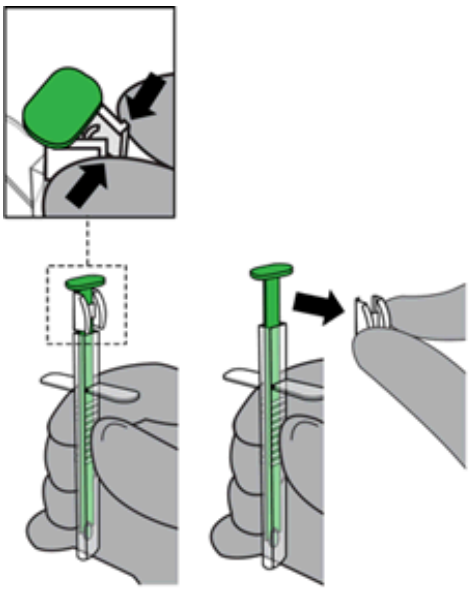
Instruct the patient to not eat or drink and minimize talking for 10 minutes after receiving the tablet.

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:

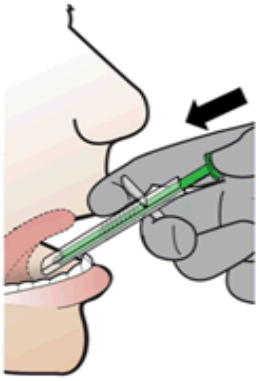



2. Remove the white Lock from the green Pusher by squeezing the sides together and detaching from Pusher. Discard the Lock.

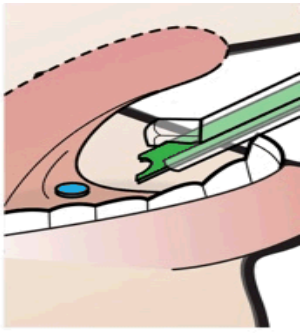


3. Tell the patient to touch their tongue to the roof of their mouth if possible.
4. Rest the SDA lightly on the patient's teeth or lips.
5. Place the SDA tip under the tongue and aim at the floor of the patient's mouth.

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

FGK Representative Service GmbH,
Heimeranstr. 35,

80339 Munich,
Germany.

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1284/001
EU/1/18/1284/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 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(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Propak Health Ltd
3-4 Ballyboggan Industrial Estate
Ballyboggan Road
Finglas
Dublin 11
Ireland

## 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.

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

The MAH shall ensure that in each MS where Dzuveo is marketed, all HCPs (i.e. physicians, hospital pharmacists, and nurses) who are expected to prescribe / administer the product are provided with a Healthcare Professional Guide, outlining critical information for the safe and effective use of Dzuveo, including:

- The method of use of the device;
- The minimum dosing interval of one sublingual tablet per hour, in order to prevent / minimise the important identified risk of respiratory depression and the important potential risk of overdose;
- The key message to convey during patients counselling, about possible respiratory depression / overdose;
- Detailed instruction on how to handle overdose / respiratory depression

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF 5 OR 10 POUCHES**

## 1. NAME OF THE MEDICINAL PRODUCT

Dzuveo 30 micrograms sublingual tablets
sufentanil

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1sublingual tablet in a single-dose applicator.
5 x 1 sublingual tablet in a single dose applicator.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use
To be used only with the single-dose applicator.
Do not chew or swallow the tablet.
Minimum 1 hour dosing interval.

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

Keep out of reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in original package to protect from light and oxygen.

## 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,
Heimeranstr. 35,
80339 Munich,
Germany.

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1284/001 5 x 1 tablets in single dose applicators
EU/1/18/1284/002 10 x 1 tablets in single dose applicators

## 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

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**POUCH**

## 1. NAME OF THE MEDICINAL PRODUCT

Dzuveo 30 micrograms sublingual tablet
sufentanil

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 single-dose applicator containing 1 sublingual tablet.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use
To be used only with the single-dose applicator.
Administer product immediately after opening pouch.
Do not chew or swallow the tablet.
Minimum 1 hour dosing interval.

## 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 original package to protect from light and oxygen.

**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,
Heimeranstr. 35,
80339 Munich,
Germany.

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/18/1284/001
EU/1/18/1284/002

**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**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**SINGLE-DOSE APPLICATOR**

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

Dzuveo 30 mcg sublingual tablet
sufentanil

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**Dzuveo 30 micrograms sublingual tablet**
sufentanil

**Read all of this leaflet carefully before you start using 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 pharmacist or nurse.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Dzuveo is and what it is used for

The active substance of Dzuveo is sufentanil, which belongs to a group of strong painkillers called opioids.

Sufentanil is used to treat sudden moderate-to-severe pain in adults in medically monitored settings such as a hospital.

## 2. What you need to know before you use Dzuveo

**Do not use Dzuveo:**
- if you are allergic to sufentanil or any of the other ingredients of this medicine (listed in section 6).
- If you have a serious lung or breathing problem

**Warnings and precautions**
Talk to your doctor or nurse before using Dzuveo. 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 Dzuveo 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 heartbeat, low blood volume or low blood pressure;
- Have moderate to severe liver problems or severe kidney problems, as these organs have an effect on the way in which your body breaks down and eliminates the medicine; have abnormally slow bowel movements;
- Have a disease of the gall bladder or pancreas;
- Have a history of medicine or alcohol abuse;

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

**Other medicines and Dzuveo**
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:

- Ketoconazole, which is used for the treatment of fungal infections this medicine may have an effect on the way in which your body breaks down sufentanil.
- Any medicines which might make you sleepy (have a sedative effect), such as sleeping pills, medicines to treat anxiety (e.g. benzodiazipines), tranquillisers or other opioid medicines, as they can increase the risk of severe breathing problems, coma and may be life-threatening.
- 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 sufentanil.
- Other medicines which are also taken sublingually (placed under the tongue where they dissolve) or medicines which 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 Dzuveo has not been studied.
- Regularly prescribed opioid medicine (e.g. morphine, codeine, fentanyl, hydromorphone, oxycodone).
- Medicines used to treat high blood pressure or angina (chest pain) known as calcium channel or beta blockers e.g. diltiazem and nifedipine.

**Dzuveo with alcohol**
Do not drink alcohol while using Dzuveo. 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.

Dzuveo should not be used during pregnancy or in women of childbearing potential not using effective contraception.

Dzuveo passes into breast milk and can cause side effects in the breast-fed child. Breastfeeding is not recommended while you are taking Dzuveo.

**Driving and using machines**
Dzuveo 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 sufentanil. You should only drive and use machines if sufficient time has elapsed after your last dose of Dzuveo.

## 3. How to use Dzuveo

This medicine must be given to you by a doctor or a nurse using the single-dose administration device. You will not give yourself this medicine.

Dzuveo is only used in a medically monitored setting, such as a hospital. It is only prescribed by a doctor who is experienced in the use of strong painkillers like sufentanil and knows the effects it may have on you, in particular on your breathing (see ‘Warnings and precautions’ above).

The recommended dose is a maximum of one 30 microgram sublingual tablet per hour. The sublingual tablet will be given to you by a healthcare professional using the disposable single-dose applicator. The applicator will help your healthcare provider place one tablet under your tongue. The tablets dissolve under your tongue and should not be chewed, or swallowed because the tablet is not effective for pain relief unless it is allowed to dissolve under your tongue. You should not eat or drink and should talk as little as possible for 10 minutes after each dose.

After receiving a dose you will not be given another dose for at least one hour. The maximum daily dose is 720 micrograms (24 tablets per day).
Dzuveo should not be used beyond 48 hours.
After your treatment the medical staff will dispose of the applicator accordingly.

**If you use more Dzuveo than you should**
The symptoms of overdose include severe breathing problems like slow and shallow breathing, loss of consciousness, extremely 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.

**Serious side effects**
The most serious side effects are severe breathing problems, like slow and shallow breathing, which may even lead to you stopping breathing.

If you experience any of the above mentioned side effects, tell your doctor or nurse immediately.

**Very common side effects** (may affect more than 1 in 10 people):
Nausea or feeling sick, vomiting or being sick and generally feeling hot.

**Common side effects (may affect up to 1 in 10 people):**
- Inability or difficulty sleeping, feeling anxious or confused, dizziness.
- Headache, drowsiness, feeling sleepy.
- Increased heart rate, high blood pressure, low blood pressure.
- Low levels of oxygen in your blood, feeling pain in the lower throat, slow shallow breathing.
- Dry mouth, flatulence (passing wind), constipation, indigestion or reflux.
- Allergic reactions, itching of the skin.
- Muscle twitching and spasms.
- Inability to pass urine.
- This medicine may also cause changes in levels of red blood cells, white blood cells, calcium, albumin, potassium and sodium in your blood which can only be identified through a blood test. If you are having a blood test ensure your doctor knows you are taking this medicine.

**Uncommon side effects (may affect up to 1 in 100 people):**
- Inflammation of the lungs, eye redness and inflammation, inflammation of the throat.
- Fatty lumps underneath skin.
- Inability to manage blood sugar (diabetes), increased cholesterol.
- Feeling agitated, lack of interest or emotion, lack of energy, disorientation, feeling elated, hallucinating or seeing things that are not there, nervousness.
- Problems coordinating muscle movements, muscle contractions, tremors or excessive shaking, exaggeration of reflex responses, burning sensation, feeling faint, abnormal sensation of the skin (tingling, skin crawling), numbness in general, tiredness, forgetfulness, migraine, tension headaches.
- Vision disturbances, eye pain.
- Decreased heart rate, irregular heartbeat, angina or other chest discomfort.
- High blood pressure or low blood pressure when standing up, skin flushing.
- Slow or difficult breathing (including when sleeping), Nose bleeds, hiccups.
- Chest pain and breathing difficulties caused by a blood clot in lung, fluid in the lungs, wheezing.
- Diarrhoea, burping or belching, inflammation of stomach lining or gastritis, bloating, acid reflux, retching, stomach pain or an uncomfortable stomach.
- Developing blisters, excessive sweating, rash, dry skinnumbness of mouth or face.
- Pain in the back, chest or other body parts, pain in the extremities.
- Difficulty urinating, strong smelling urine, pain urinating, kidney failure.
- Swelling, uncomfortable sensations in your chest, chills, and weakness (lack of energy).

This medicine may also cause changes in levels of platelets (which help your blood to clot), magnesium, protein, sugar, fats, phosphates and plasma in your blood which can only be identified through a blood test. If you are having a blood test ensure your doctor knows you are taking this medicine.

**Frequency not known (frequency cannot be estimated from the available data):**
- Severe allergic reactions (anaphylactic shock), convulsions (fits), coma, small pupil size, redness of the skin.
- Withdrawal syndrome which may include symptoms such as agitation, anxiety, muscle aches, insomnia, sweating and yawning.

**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 Dzuveo

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

Your doctor or nurse will ensure that:
- this medicine is not used after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
- is stored in the original package in order to protect from light and oxygen.
- this medicine is not used if there are signs of deterioration.

Medicines should not be thrown away via wastewater or household waste. Your healthcare provider will dispose of any waste according to hospital policies. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Dzuveo contains**
- The active substance is sufentanil. Each sublingual tablet contains 30 micrograms of sufentanil (as citrate).
- The other ingredient(s) are mannitol (E421), dicalcium phosphate, hypromellose, croscarmellose sodium, Indigo Carmine (E132), stearic acid, and magnesium stearate.

**What Dzuveo looks like and contents of the pack**
Dzuveo is a blue-coloured, flat-faced sublingual tablet with round edges. It measures 3 mm in diameter and is enclosed within a single-dose applicator (labelled [sublingual tablet]). The applicator, with the tablet inside, is enclosed within a pouch.

Each pouch contains one applicator and one sufentanil 30 micrograms tablet.
Each pack contains either 5 or 10 pouches.
Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
FGK Representative Service GmbH,
Heimeranstr. 35,
80339 Munich,
Germany.
Phone: +49 - 89-893 119 22
Fax: +49 - 89-893 119 20

Email: edgar.fenzl@fgk-rs.de

**Manufacturer**

Propak Health Ltd,
3-4 Ballyboggan Industrial Estate,
Ballyboggan Road,
Finglas, Dublin 11,
Ireland.

**This leaflet was last revised in**.

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**The following information is intended for healthcare professionals only:**

Instructions for use of Single Dose Applicator (SDA)

Single-Use Product / Do Not Reuse.

**Do Not Use if Pouch Seal is Broken.**

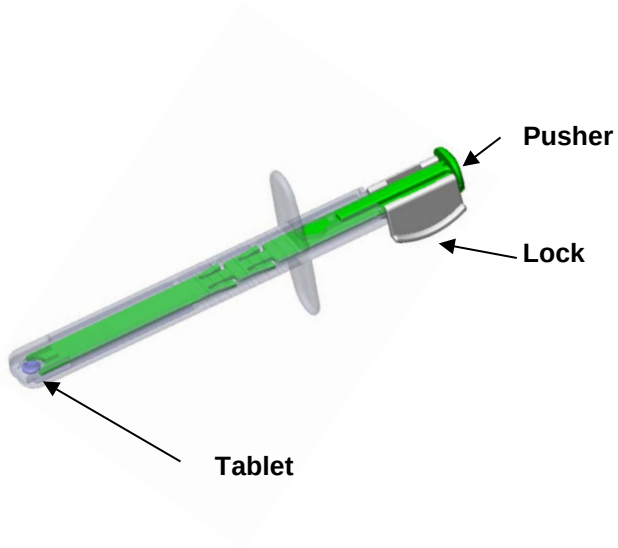
**Do not use if the Single Dose Applicator (SDA) is damaged.**

Instruct the patient to not chew or swallow the tablet.

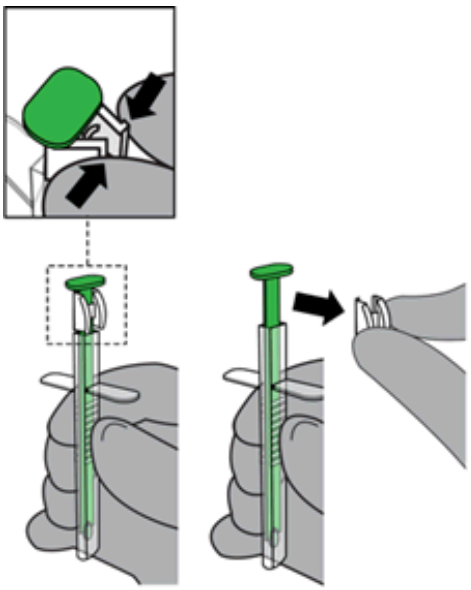
Instruct the patient to not eat or drink and minimize talking for 10 minutes after receiving the tablet.

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:

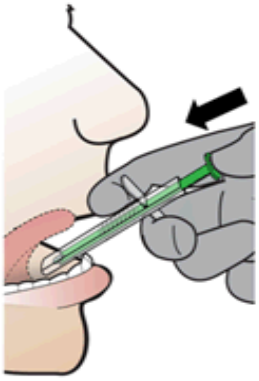



2. Remove the white Lock from the green Pusher by squeezing the sides together and detaching from Pusher. Discard the Lock.

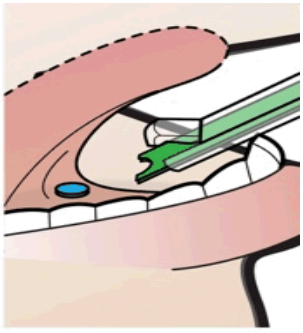


3. Tell the patient to touch their tongue to the roof of their mouth if possible.
4. Rest the SDA lightly on the patient's teeth or lips.
5. Place the SDA tip under the tongue and aim at the floor of the patient's mouth.

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.