▼ This medicine is subject to additional monitoring due to approval of an extension of indications. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. You can report side effects to your doctor, or directly at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – JORVEZA® (BUDESONIDE) ORALLY DISINTEGRATING TABLETS AND ORAL SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

Budesonide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orally disintegrating tablet contains either 0.5 mg or 1 mg of budesonide.

Each mL of oral suspension contains 0.2 mg of budesonide.

Excipients with known effect

Each budesonide orally disintegrating tablet also contains sucralose and sodium.

The budesonide oral suspension also contains sucrose and sodium benzoate.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Orally disintegrating tablet

Jorveza® 0.5 mg tablet: White or almost white, round, biplane orally disintegrating tablet with '0.5' debossed on one side.

Jorveza® 1 mg tablet: White or almost white, round, biplane orally disintegrating tablet.

Oral Suspension

Jorveza 0.2 mg/mL oral suspension is a whitish, viscous suspension with a blackcurrant flavour.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Jorveza® orally disintegrating tablets are indicated for the treatment of eosinophilic oesophagitis (EoE) in adults.

Jorveza 0.2 mg/mL oral suspension is indicated for the treatment of EoE in paediatric patients aged 2 to 17 years.

4.2 DOSE AND METHOD OF ADMINISTRATION

The treatment with this medicinal product should be initiated by a physician experienced in the diagnosis and treatment of eosinophilic oesophagitis.

Dosage

Orally disintegrating tablets
The recommended daily dose for induction treatment is 2 mg budesonide as one 1 mg tablet in the morning and one 1 mg tablet in the evening.

The usual duration of induction treatment is 6 weeks. For patients who are not appropriately responding during 6 weeks, the treatment can be extended to up to 12 weeks.

If a dose is missed, treatment should be continued at the prescribed dosage. A double dose should not be used to make up for a forgotten dose.

The recommended daily dose for maintenance of remission is 1 mg budesonide as one 0.5 mg tablet in the morning and one 0.5 mg tablet in the evening, or 2 mg budesonide as one 1 mg tablet in the morning and one 1 mg tablet in the evening, depending on the individual clinical requirement of the patient.

The maintenance dose of 1 mg budesonide twice daily is recommended for patients with a long-standing disease history and/or high extent of oesophageal inflammation in their acute disease state, see also section 5.1 PHARMACODYNAMIC PROPERTIES.

The duration of maintenance therapy is determined by the treating physician.

Oral Suspension

Induction of remission

Children 2 to 11 years of age
The recommended daily dose is 1 mg budesonide to be administered as two separate doses: one 2.5 mL dose of oral suspension (corresponding to 0.5 mg budesonide) in the morning and one 2.5 mL dose of oral suspension (corresponding to 0.5 mg budesonide) in the evening.

Adolescents 12 to 17 years of age
The recommended daily dose is 2 mg budesonide to be administered as two separate doses: one 5 mL dose of oral suspension (corresponding to 1 mg budesonide) in the morning and one dose 5 mL of oral suspension (corresponding to 1 mg budesonide) in the evening.

The usual duration of induction treatment is 12 weeks. For patients who are not appropriately responding within 12 weeks, the treatment can be extended to up to 24 weeks.

If a dose is missed, treatment should be continued at the prescribed dosage. A double dose should not be used to make up for a forgotten dose.

Maintenance of remission

Children 2 to 11 years of age
The recommended daily dose is 0.5 mg budesonide to be administered as one 2.5 mL dose of oral suspension (corresponding to 0.5 mg budesonide) in the morning, depending on the individual clinical requirement of the patient.

For patients with a long-standing history and/or high extent of oesophageal inflammation in their acute disease state, the recommended daily dose for maintenance of remission is 1.0 mg budesonide (corresponding to 5 mL of the suspension), to be administered as two separate doses: one 2.5 mL dose of oral suspension (corresponding to 0.5 mg budesonide) in the morning and one 2.5 mL dose of oral

suspension (corresponding to 0.5 mg budesonide) in the evening, see also section 5.1 PHARMACODYNAMIC PROPERTIES.

Adolescents 12 to 17 years of age
The recommended daily dose is 1 mg budesonide to be administered as one 5 mL dose of oral suspension (corresponding to 1 mg budesonide) in the morning, depending on the individual clinical requirement of the patient.

For patients with a long-standing history and/or high extent of oesophageal inflammation in their acute disease state, the recommended daily dose for maintenance of remission is 2.0 mg budesonide (corresponding to 10 mL of the suspension), to be administered as two separate doses: one 5 mL dose of oral suspension (corresponding to 1 mg budesonide) in the morning and one 5 mL dose of oral suspension (corresponding to 1 mg budesonide) in the evening, see also section 5.1 PHARMACODYNAMIC PROPERTIES.

The duration of maintenance therapy is determined by the treating physician. Tapering of the dose is required after prolonged treatment. It is recommended to perform control endoscopies if symptoms persist or return. Follow-up endoscopies are recommended in line with current clinical guidelines because symptoms did not reliably predict the histological outcome in the clinical study.

Method of administration

Orally disintegrating tablets

Jorveza® orally disintegrating tablet should be taken after a meal.

The orally disintegrating tablet should be placed on the tip of the tongue and gently pressed against the top of the mouth, where it will disintegrate. This will usually take between two and five minutes, but can take up to 10 minutes or longer in some patients. The effervescence process starts after the orally disintegrating tablet comes into contact with saliva and stimulates the production of further saliva in which the released budesonide mixes and which the patient is instructed to swallow slowly. This enables the surface of the oesophagus to be exposed to comparatively high concentrations of budesonide over a relatively long period of time from this budesonide-loaded saliva. Therefore, the saliva, with its mucoadhesive properties, acts like a biologic vehicle, facilitating optimal targeting of the budesonide from the orally disintegrating tablet at the site of the inflammation in the oesophagus of patients with EoE.

Jorveza® orally disintegrating tablet should not be taken with liquid or food.

There should be at least 30 minutes after dosing before eating or drinking or performing oral hygiene. Any oral solutions, sprays or chewable tablets should also not be used for at least 30 minutes before or after administration of Jorveza® orally disintegrating tablet.

Jorveza® orally disintegrating tablet should not be chewed or swallowed if not disintegrated.

The above measures ensure optimal exposure of the oesophageal mucosa to budesonide.

Jorveza® orally disintegrating tablet should be taken immediately once removed from the blister package.

Oral Suspension

Jorveza® oral suspension should be taken after a meal.
Only use the syringe provided as a measuring device to dose the Jorveza oral suspension. Do not use any other measuring device.

Shake the suspension well before use. To open the bottle, push the child-resistant cap down firmly whilst turning it anti-clockwise to remove. Insert the syringe into the bottle until a tight seal forms and push the plunger fully inside the syringe, so it is completely down. Turn the bottle upside-down and hold the syringe firmly whilst gently drawing back the plunger in the syringe to the required level, based on the mL graduations on the syringe. Turn the bottle upright and gently remove the syringe by twisting it from the bottle. Immediately afterwards, place the tip of the syringe in the patient's mouth and press the plunger all the way down to dose. The patient should now completely swallow the suspension contained in the syringe.

The patient should not drink, eat, brush their teeth or rinse their mouth for at least for at least 30 minutes after taking Jorveza® oral suspension. They should not use any oral solutions, sprays or chewable tablets for at least 30 minutes before or after taking the Jorveza® oral suspension. The above measures ensure optimal exposure of the oesophageal mucosa to budesonide.

Jorveza® oral suspension should be administered immediately after the required dose is drawn up into the syringe.
After dosing, screw the cap back onto the bottle and store. Immediately remove the plunger from the barrel of the syringe. Rinse both inside the syringe and the plunger with cold water and allow to air dry. (Do not use any other liquid other than cold water to rinse the syringe and plunger). Once fully dry, insert the plunger back into the barrel and store with the suspension bottle for the next dose.

Special populations

Renal impairment
There are currently no data available for patients with renal impairment. Because budesonide is not excreted via the kidneys, patients with mild to moderate impairment may be treated with caution with the same doses as patients without renal impairment. Budesonide is not recommended for use in patients with severe renal impairment.

Hepatic impairment
During treatment of patients with hepatic impairment with other budesonide containing medicinal products, budesonide levels were increased. However, no systematic study investigating the impact of different degrees of hepatic impairment on the bioavailability of budesonide has been conducted. In the absence of these data, patients with hepatic impairment should not be treated with Jorveza® (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Jorveza® is contraindicated in patients with uncontrolled infections or active tuberculosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infections
Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. Symptoms of infections can be atypical or masked.
Jorveza® should not be used in patients with active tuberculosis or uncontrolled infection.

In clinical studies conducted with either Jorveza® orally disintegrating tablets or Jorveza® oral suspension, the observed frequency of oral, oropharyngeal and oesophageal candida infections was common or very common (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

If indicated, symptomatic candidiasis of the mouth and throat can be treated with topical or systemic anti-fungal therapy whilst continuing treatment with Jorveza® orally disintegrating tablets or Jorveza®oral suspension.

Chickenpox, herpes zoster and measles can have a more serious course in patients treated with glucocorticoids. In patients who have not had these diseases, the vaccination status should be checked, and particular care should be taken to avoid exposure. If patients are infected or suspected of being infected, consider reduction or discontinuation of glucocorticoid treatment.

Vaccines
The co-administration of live vaccines and glucocorticoids should be avoided as this is likely to reduce the immune response to vaccines. The antibody response to other vaccines may be diminished.

Special populations
Patients with infections, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataract, family history of diabetes or family history of glaucoma may be at higher risk of experiencing systemic glucocorticoid adverse reactions, especially from systemically acting glucocorticoids (see below and section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and should therefore be monitored for the occurrence of such effects. In these patients, caution should be exercised and the benefits of a topical glucocorticoid , such as Jorveza®, must be weighed against its risk.

Use in Hepatic Impairment
Reduced liver function may affect the elimination of budesonide, causing higher systemic exposure. The risk of adverse reactions (systemic glucocorticoid effects) will be increased. However, no systematic data are available. In the absence of these data, patients with hepatic impairment should therefore not be treated with Jorveza®.

Renal impairment
There are currently no data available for patients with renal impairment. Because budesonide is not excreted via the kidneys, patients with mild to moderate impairment may be treated with caution with the same doses as patients without renal impairment. In the absence of specific data, Jorveza® is not recommended for use in patients with severe renal impairment.

Use in the elderly
There are insufficient data concerning the use of Jorveza® orally disintegrating tablets in patients aged ≥65 years. Caution should be exercised in elderly patients due to the potential for decreased hepatic, renal or cardiac function, or due to other intercurrent conditions or diseases as well as the administration of specific concomitant therapies (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Systemic effects of glucocorticoids
Systemic effects of glucocorticoids (e.g., Cushing's syndrome, adrenal suppression, growth retardation, cataract, glaucoma, decreased bone mineral density and a wide range of psychiatric effects) may occur (see also section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), particularly when prescribed at high doses and for prolonged periods, especially with systemically acting glucocorticoids. These adverse reactions also depend on concomitant and previous glucocorticoid treatment, the individual sensitivity and the glucocorticoid levels achieved in the systemic circulation with the administered medicine. The risk of these events occurring with the topically acting Jorveza® orally disintegrating tablets or Jorveza®oral suspension is anticipated to be lower, relative to systemically acting glucocorticoids, consistent with the extensive biotransformation of budesonide and lower systemic absorption (see section 5.2 PHARMACOKINETIC PROPERTIES).

Visual disturbance
Visual disturbance may be reported with systemic and topical glucocorticoid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include a cataract, glaucoma or rare ocular diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical glucocorticoids.

Angioedema
Cases of angioedema and/or contact dermatitis have been reported with the use of Jorveza®, mostly as part of an allergic reaction which include rash and itching.

Treatment with Jorveza® should be stopped if a patient develops signs of angioedema, such as swelling of the face, particularly around the mouth (lips, tongue or throat) and/or difficulties to breathe or swallow.

Growth and monitoring
It is recommended that the height of children receiving prolonged treatment with budesonide is regularly monitored. If growth is slowed, the benefits of glucocorticoid treatment and the potential risks of growth impairment should be considered carefully. If it is decided to continue budesonide treatment, the dose should be reduced to the lowest dose at which effective control of the disease is maintained.

Effects on the hypothalamic–pituitary–adrenal (HPA) axis
Glucocorticoids may cause suppression of the HPA axis and reduce the stress response. When patients are subject to surgery or other stresses, supplementary systemic glucocorticoid treatment is therefore recommended. It is unclear whether this supplementary treatment would be required for a patient receiving Jorveza® orally disintegrating tablets or Jorveza®oral suspension owing to the low systemic absorption of budesonide (see section 5.2 PHARMACOKINETIC PROPERTIES**).**

CYP3A4 inhibitors
Concomitant treatment with ketoconazole or other CYP3A4 inhibitors should be avoided in patients receiving glucocorticoids (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Effects on laboratory tests
No data available.

Interference with ACTH stimulation test
Because adrenal function may be suppressed by treatment with a glucocorticoid, especially one which is systemically acting, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Excipient with known effect
The Jorveza® 0.5 mg and 1 mg tablets each contain 26 mg of sodium. Therefore, the maximum daily dose of sodium intake from either strength is 52 mg per day, if taken as recommended as either 2 x 0.5 mg tablet or 2 x 1 mg tablet (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). This is equivalent to 2.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Each mL of Jorveza® oral suspension contains 100 mg sucrose and 0.86 mg sodium benzoate.
Each mL of Jorveza® oral suspension contains 0.26 mg of sodium. Therefore, the maximum daily dose of sodium intake from a dose of 5 mL is 1.3 mg and from a dose of 10 mL is 2.6 mg of sodium.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

CYP3A4 inhibitors
While no formal drug interaction studies have been conducted with Jorveza®, based on studies with budesonide administered in enteric capsules, concomitant treatment with potent CYP3A inhibitors such as ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin, cobicistat and grapefruit juice may cause a marked increase of the plasma concentration of budesonide and is expected to increase the risk of systemic adverse reactions. Therefore, concomitant use should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid adverse reactions, in which case patients should be monitored for these adverse reactions.

Ketoconazole 200 mg once daily orally increased the plasma concentration of budesonide (single dose of a 3 mg budesonide enteric capsule) approximately 6-fold during concomitant administration. When ketoconazole was administered approximately 12 hours after the budesonide capsule, the plasma concentration of budesonide increased approximately 3-fold.

Oestrogens, oral contraceptives
Elevated plasma concentrations and enhanced effects of glucocorticoids have been reported in women also receiving oestrogens or oral contraceptives. No such effect has been observed with budesonide and concomitant intake of low-dose combination oral contraceptives.

Cardiac glycosides
The action of glycoside can be potentiated by potassium deficiency which is a potential and known adverse reaction of glucocorticoids.

Saluretics
Concommitant use of glucocorticoids may result in enhanced potassium excretion and aggravated hypokalaemia.

Drug Food Interactions
Inhibitors of CYP3A4 such as grapefruit juice may cause a marked increase of the plasma concentration of budesonide. In the absence of specific data for Jorveza® concomitant use should be avoided.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
There are no data on the effect of budesonide on human fertility. Subcutaneous administration of budesonide to rats at doses of up to 20 µg/kg/day did not affect fertility.

Use in Pregnancy – Category B3
Administration during pregnancy should be avoided unless there are compelling reasons for therapy with Jorveza®. There are few data of pregnancy outcomes after oral administration of budesonide in humans. Although data on the use of inhaled budesonide in a large number of exposed pregnancies indicate no adverse effects, the maximal concentration of budesonide in plasma is expected to be higher in the treatment with Jorveza®, compared to inhaled budesonide. In pregnant animals, budesonide, like other glucocorticoids, has been shown to cause abnormalities of fetal development (smaller litter size, intrauterine growth retardation of fetuses and skeletal and visceral abnormalities). Some glucocorticoids have been reported to produce cleft palate in animals. The clinical relevance of these findings to humans has not been established.

Use in Lactation
There is currently no experience with the administration of Jorveza® in breast-feeding mothers. However, budesonide is known to be excreted in human milk when administered by inhalation. In the

absence of specific experience, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Jorveza® therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Jorveza® has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Adults 18 years and older with EoE

Fungal infections in the mouth, pharynx and the oesophagus were the most frequently observed adverse reactions in clinical studies with Jorveza® orally disintegrating tablets in adults with EoE In the clinical studies BUL-1/EEA and BUL-2/EER, a total of 44 out of 268 patients (16.4%) exposed to Jorveza® orally disintegrating tablets experienced cases of suspected fungal infections associated with clinical symptoms, which were all of mild or moderate intensity and which did not interfere with their daily activities. The total of 92 infections (including those without symptoms diagnosed by endoscopy and histology through proactive investigation required in the study protocol) was reported in 72 of 268 patients (26.9%). The frequency of the fungal infections was not dose-related. All patients received oral antifungal treatment or no medical intervention. None of the patients needed to cease or otherwise modify their Jorveza® orally disintegrating tablet regimen due to a local fungal infection during the two studies, including while they received oral antifungal treatment.

Long-term treatment with Jorveza® orally disintegrating tablets for up to 3 years (6-12 weeks of induction treatment followed by 48-weeks of maintenance treatment, with a further 96-weeks of open-label treatment) did not increase the rate of adverse effects observed, including local candidiasis or abnormally low morning serum cortisol levels.

Children and adolescents with EoE aged 2-17 years

In the paediatric clinical study PEDEOS 1 (BUU-5/EEA) the most frequently reported adverse drug reactions in patients receiving Jorveza® 0.2 mg/mL oral suspension, were oropharyngeal and/or oesophageal candidiasis (8%), blood cortisol decreased (2.7%) and vomiting (2.7%). Local fungal infection (candidiasis, clinically manifested or confirmed by histology) occurred across all budesonide dosage groups, with no dose-related effect. All cases of candidiasis were non-serious, generally of mild intensity, and did not generally interfere with normal daily activities.

In the 24-week open label extension (OLE) phase of study PEDEOS 1 (BUU-5/EEA), for those patients achieving histologic remission and a clinical response after induction therapy, oropharyngeal candidiasis (3.2%) was the most frequently reported adverse reaction.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies with Jorveza® 0.5 mg and 1 mg orally disintegrating tablets and Jorveza® 0.2 mg/mL oral suspension* are listed in the table below, by MedDRA system organ class and frequency. 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) or not known (cannot be estimated from the available data).

MedDRA system organ class	Very common	Common	Uncommon
Infections and infestations	Oesophageal candidiasis, oral and/or		Nasopharyngitis, pharyngitis

MedDRA system organ class	Very common	Common	Uncommon
	oropharyngeal candidiasis		
Immune system disorders			Hypersensitivity reactions including angioedema and contact dermatitis
Psychiatric disorders		Sleep disorder	Anxiety, agitation
Nervous system disorders		Headache, dysgeusia	Dizziness
Eye disorders		Dry eyes	
Vascular disorders			Hypertension
Respiratory, thoracic and mediastinal disorders			Cough, dry throat, oropharyngeal pain
Gastrointestinal disorders		Gastroesophageal reflux disease, nausea, oral paraesthesia, dyspepsia, upper abdominal pain, dry mouth, glossodynia tongue disorder, oral herpes	Abdominal pain, abdominal distension, dysphagia, erosive gastritis, gastric ulcer, lip oedema, gingival pain
Skin and subcutaneous tissue disorders			Rash, urticaria
General disorders and administration site conditions		Fatigue	Sensation of foreign body
Investigations		Blood cortisol decreased	Osteocalcin decreased, weight increased

* Not all the ADRs listed in the table have been observed in paediatric populations.

The following known adverse reactions of the therapeutic class (glucocorticoids), especially for those which are systemically acting, however, may also occur with the topically acting Jorveza® (frequency = not known).

MedDRA system organ class	Adverse reactions
Immune system disorders	Immune suppression (e.g. increased risk of infection)
Endocrine disorders	Cushing's syndrome, moon-face, truncal obesity, adrenal suppression, growth retardation in children, disturbance of sex hormone secretion (e.g. amenorrhea, hirsutism, impotence)
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia, reduced glucose tolerance, diabetes mellitus, sodium retention with oedema
Psychiatric disorders	Depression, irritability, euphoria, psychomotor hyperactivity, aggression
Nervous system disorders	Pseudotumor cerebri including papilloedema in adolescents
Eye disorders	Glaucoma, cataract (including subcapsular cataract), blurred vision, central serous chorioretinopathy (CSCR) (see also section 4.4 Special Warnings and Precautions for Use; Visual disturbance)

MedDRA system organ class	Adverse reactions
Vascular disorders	Increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy)
Gastrointestinal disorders	Duodenal ulcers, pancreatitis, constipation
Skin and subcutaneous tissue disorders	Allergic exanthema, petechiae, delayed wound healing, ecchymosis, steroid acne, red striae
Musculoskeletal and connective tissue disorders	Muscle and joint pain, muscle weakness and twitching, osteoporosis, osteonecrosis
General disorders and administration site conditions	Malaise

Post-Market Adverse Reactions
Adverse reactions seen with Jorveza® orally disintegrating tablets during post-market safety reporting

Nervous system disorders: Dysgeusia

Reporting of suspected adverse reactions
Reporting suspected adverse effects after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

In case of short-term overdose no emergency medical treatment is required. There is no specific antidote. Subsequent treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antidiarrheals, intestinal anti-inflammatory/anti-infective agents, glucocorticoids acting locally, ATC code: A07EA06

Mechanism of action
Budesonide is a non-halogenated glucocorticoid, which acts primarily as anti-inflammatory via binding to the glucocorticoid receptor. The exact mechanism of action in the treatment of EoE is not fully understood. In the treatment of EoE with Jorveza® orally disintegrating tablets or Jorveza® oral suspension, budesonide may inhibit antigen-stimulated secretion of many pro-inflammatory signal molecules such as thymic stromal lymphopoeitin, interleukin-13 and eotaxin-3 in the oesophageal epithelium, which may result in a significant reduction of the oesophageal eosinophilic inflammatory infiltrate.

Pharmacodynamics
The primary pharmacodynamic effect of budesonide is its anti-inflammatory activity. Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to glucocorticoid receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

Effect on hypothalamus-pituitary-adrenal and endogenous cortisol levels
Treatment with systemically active glucocorticoid is associated with a suppression of endogenous cortisol concentrations and impairment of the HPA axis function.

Following 48 weeks of Jorveza® orally disintegrating tablets (1 mg BID or 0.5 mg BID) treatment in adult patients with EoE, the rate of patients with morning serum cortisol levels below the lower limit of normal (LLN) was 2.9% (4/136) for both Jorveza® treatment regimens vs. 0% for the placebo group. None of these patients had symptoms of adrenal insufficiency.

In the paediatric clinical study BUU-5/EEA in children and adolescents with EoE treated with the Jorveza® oral suspension, one case each of adrenal suppression and adrenal insufficiency were observed based on abnormal ACTH test results only. However, no clinical symptoms of adrenal insufficiency were reported, and outcome of both events was specified as resolved. Three adverse events of cortisol decreased under treatment with Jorveza® oral suspension were reported in study BUU-5/EEA. However, cortisol levels in these patients normalised under treatment or, at the latest, during follow-up.

The above observations are consistent with the extensive biotransformation of budesonide and thus its low systemic absorption of budesonide when administered as Jorveza® (see section 5.2 PHARMACOKINETIC PROPERTIES).

Clinical Trials

Adults 18 years and older with EoE

In a randomised, placebo-controlled, double-blind phase III clinical study (BUL-1/EEA) in 88 adult patients with active symptomatic and histological EoE (randomisation rate: 2:1), Jorveza® 1 mg BID orally disintegrating tablets for 6 weeks induced clinico-histologic remission (defined as peak of < 16 eosinophils/mm^2 high power field (hpf); < 5 eos/hpf in oesophageal biopsies, with no or only minimal symptoms of dysphagia or pain during swallowing on each day in week prior to week 6 visit) in 34 out of 59 patients (57.6%) *versus* 0/29 patients (0%) in the placebo-group (p< 0.0001). Open-label extension of the treatment with Jorveza® 1 mg BID for a further 6 weeks in 23 Jorveza®-treated patients without remission in the preceding double-blind phase increased the rate of patients with clinico-histologic remission to 84.7%.

In a randomised, placebo-controlled, double-blind phase III clinical study (BUL-2/EER) including 204 adult patients with EoE in clinico-histological remission, induced by prior treatment with Jorveza® 1 mg BID, were randomised to treatment with Jorveza® 1 mg BID, Jorveza® 0.5 mg BID, or placebo (all given as orally disintegrating tablets) for 48 weeks (n=68 for all treatment groups). Primary endpoint was the rate of patients free of treatment failure, with treatment failure defined as clinical relapse (severity of dysphagia or pain during swallowing of ≥4 points on a 0-10 numerical rating scale, respectively), and/or histological relapse (peak of ≥ 48 eosinophils/mm^2 hpf; >15 eos/hpf), and/or food impaction requiring endoscopic intervention, and/or need of an endoscopic dilation, and/or premature withdrawal for any reason. Significantly more patients in the Jorveza® 1 mg BID (75.0%) group and the Jorveza® 0.5 mg BID (73.5%) group were free of treatment failure at week 48, compared to placebo (4.4%); p<0.0001; both treatments. The median time to clinical relapse was 86 days for the placebo group, compared to over 330 days for the two Jorveza dose groups (p <0.0001 versus placebo; both treatments).

The most stringent secondary endpoint “deep disease remission”, i.e., deep clinical, deep endoscopic and histological remission, showed a clinically relevant higher efficacy in the Jorveza® 1 mg BID group (52.9%) compared to the Jorveza® 0.5 mg BID group (39.7%), indicating the utility of the higher dose of Jorveza® to achieve and maintain deep disease remission.

At the end of the 48-week double-blind period in BUL-2/EER, all patients free of treatment failure were invited to enter an optional 96-week open-label phase, each receiving either Jorveza® 0.5 mg BID, or Jorveza®1 mg BID, based on decision of the treating physician. More than 80% of the patients maintained clinical remission (defined as weekly Eosinophilic Esophagitis Activity Index-Pro ≤ 20) over the 96-week period, while only 2/166 patients (1.2%) experienced a food impaction. In addition,

40/49 patients (81.6%) maintained deep histological remission (0 eosinophils/mm^2 hpf in all biopsies) from baseline of study BUL-2/EER to the end of treatment of the 96-week open-label period.

Over a period of up to 3 years (i.e., 96-week open-label treatment with Jorveza® orally disintegrating tablets, following the 48-week randomised, double-blind maintenance treatment and the preceding 6-12 week induction treatment with Jorveza® orally disintegrating tablets), no loss of efficacy was observed.

Children and adolescents aged 2-17 years

A 12 week, randomised, placebo-controlled, double-blind (DB), phase II/III clinical study BUU-5/EEA (PEDEOS-1) was conducted in 76 paediatric patients (aged 2-17 years) with active EoE, to evaluate the safety and efficacy of two different daily doses of the Jorveza® oral suspension versus placebo, stratified by age: 1) high dose (2-11 years: 0.5 mg budesonide BID; 12-17 years: 1.0 mg budesonide BID); 2) low dose (2-11 years: 0.5 mg budesonide OD; placebo OD; 12-17 years: 1.0 mg budesonide OD; placebo OD); 3) placebo (placebo BID).

The primary composite endpoint was the rate of patients with histologic remission (peak eos < 16 eos/mm^2 hpf [i.e. <5 eos/hpf]) and with a clinical response (≥30% decrease in the total score of PEESS v2.0) at week 12 in the DB phase. At week 12, significantly more patients in the high dose (69.2%) and low dose (46.2%) groups achieved the primary endpoint versus placebo (0.0%) (FAS-DB, p<0.0001).

When the rate of histologic remission alone at week 12 was evaluated, a significantly larger proportion of patients (88.5%) in the high dose group achieved this endpoint compared to the low dose (61.5%) and placebo (0%) groups. This outcome was independent of the location, extent, or severity of the oesophageal inflammation, or the age stratification.

Biopsies of each patient blindly scored using the EoE Histology Scoring System showed a dose-dependent improvement for parameters defining both the severity and extent of the pathology in the oesophagus, with a statistically significant difference for both active dose regimens vs placebo.

The BUU-5/EEA protocol permitted patients who had not achieved a clinical response by week 8, or who did not achieve histologic remission at week 12 during the DB induction phase, to enter an optional 12-week open-label induction (OLI) phase in which patients in the high and low dose groups received 1 mg BID or 0.5 mg BID of open label Jorveza® suspension, respectively. Forty five of 52 patients (86.5%) achieved both histologic remission and a clinical response.

Patients achieving both histologic remission and a clinical response after induction treatment could enter an open label extension (OLE) phase over 24 weeks, in which all patients initially received the low dose regimen, stratified by age, with the option to escalate to the high dose, if required, at the discretion of the investigator.

The rate of clinical remission (defined by the PEESS v2 score) at the start of the OLE phase was 62.9%. At the end of the OLE phase 67.7% of patients remained in clinical remission. Minimal or no dysphagia or odynophagia, reported by 87.1% and 91.9% of patients, respectively, at the start of the OLE was maintained in 93.5% and 96.8% of patients, respectively, at the end of the OLE. During the OLE phase, no patient had a food bolus obstruction requiring endoscopic intervention or required dilatation.

For information about the observed adverse reactions, see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

5.2 PHARMACOKINETIC PROPERTIES

Single doses and multiple doses of up to 4 mg/day were evaluated in the pharmacokinetic studies of the Jorveza®orally disintegrating tablets in healthy subjects and in patients with EoE. The results showed that systemic cumulative budesonide exposure after administration of the orally disintegrating tablets was lower than after the reference capsule (3 mg budesonide gastro-resistant capsule), while budesonide absorption was faster after the orally disintegrating tablets, relative to the reference capsule.

Absorption

Orally disintegrating tablets
Following administration of Jorveza®orally disintegrating tablet, budesonide is rapidly absorbed. Pharmacokinetic data following administration of single doses of a 1 mg Jorveza® orally disintegrating tablet to fasted healthy subjects in two different studies show a median lag time of 0.17 hours (range 0.00 – 0.52 hours) and a median time to peak plasma concentration of 1.00 - 1.22 hour (range 0.50 – 2.00 hours). The mean peak plasma concentration (± standard deviation) was 0.44 – 0.49 ng/mL (range 0.18 – 1.05 ng/mL) and the area under the plasma-concentration–time curve ($AUC_{0-\infty}$) was 1.50 – 2.23 hr*ng/mL (0.81 – 5.14 hr* ng/mL).

Single dose pharmacokinetic data in fasted patients with EoE are also available with a 4 mg budesonide orally disintegrating tablet, with a median lag-time of 0.00 hours (range 0.00 – 0.17 hours), median time to peak plasma concentration of 1.00 hour (range 0.67 – 2.00 hours); peak plasma concentration of 2.56 ± 1.36 ng/mL, and AUC_{0-12} of 8.96 ± 4.21 hr*ng/mL.

Patients with active EoE showed a 35% increase in peak plasma concentrations and a 60% increase in AUC_{0-12} compared to healthy subjects.

Dose proportionality of the systemic exposure (C_{max} and AUC) from the 0.5 mg orally disintegrating tablets to the 1 mg budesonide orally disintegrating tablets has been demonstrated.

There was little to no accumulation of budesonide upon repeated dosing (daily 4 mg doses for 7 days) with the orally disintegrating tablets.

Oral suspension
Following administration of Jorveza® 0.2 mg/mL oral suspension, budesonide is rapidly absorbed. Pharmacokinetic data after administration of a single 1 mg dose to fasted healthy subjects in two different studies show a median lag time of 0.00 – 0.08 hours (range 0,00 - 0.17 hours) and a median time to peak plasma concentration of 0.75-1.00 hours (range 0.33- 1.75 hours). The mean peak plasma concentration (C_{max}) was 0.39-0.41 ng/mL (range 0.09 - 0.90 ng/mL) and the area under the plasma-concentration-time curve ($AUC_{0-\infty}$) was 1.47-1.49 hr*ng/mL (range 0.53-3.85 hr*ng/mL).

After administration of Jorveza 0.2 mg/mL oral suspension under fed conditions in healthy subjects, the C_{max} of budesonide decreased by 36%- 41% while the T_{max} increased by 0.90-1.25 h when compared to the administration under fasting conditions. No effect of food intake was noted on $AUC_{0-\infty}$.

In a multiple dose study over 7 days, healthy subjects received a 1mg BID regimen of Jorveza® oral suspension. In this study, budesonide accumulation was documented at a rate of approximately 15% for the extent of exposure (AUC0-24,ss), relative to levels recorded in the single dose study.

In paediatric EoE patients (2-17 years), with active disease, the bioavailability of budesonide following the administration of a single dose of Jorveza 0.2 mg/mL oral suspension was shown to be approximately 60% lower than that documented in adult healthy volunteers. In this paediatric patient cohort, the subgroup aged between 2 to 5 years showed slightly higher median exposure parameters (AUC and C_{max}) versus the older age groups, while the range of exposure in younger children was fully within that simulated for the other age groups.

In contrast, adult EoE patients with active disease treated with Jorveza orally disintegrating tablets showed a 35% increase in peak plasma concentrations and a 60% increase in AUC_{0-12} compared to adult healthy subjects.

Distribution
The apparent volume of distribution following oral administration of 1 mg Jorveza® orally disintegrating tablet to healthy subjects was 35.52 ± 14.94 L/kg and 42.46 ± 23.90 L/kg following administration of 4 mg budesonide orally disintegrating tablets to adult patients with EoE.
Plasma protein binding is on average 85-90%.

Biotransformation
Metabolism of budesonide is decreased in adult EoE patients with active disease compared to healthy subjects resulting in increased plasma concentrations of budesonide.

Budesonide undergoes extensive biotransformation by CYP3A4 in the mucosa of the small intestine and in the liver with only 10-15% of administered dose reaching the systemic circulation. The remaining proportion of the dose is transformed by CYP34A to metabolites of low glucocorticoid activity. The glucocorticoid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. CYP3A5 does not contribute significantly to the metabolism of budesonide. This is consistent with the low rate of systemic adverse events, including the absence of clinically relevant reductions in serum cortisol levels, in the clinical studies in EoE patients (see Section 5.1 PHARMACODYNAMIC PROPERTIES)

Elimination
The median elimination half-life is 2 – 3 hours in healthy subjects (receiving 1 mg Jorveza® orally disintegrating tablets) and 4 – 5 hours in EoE patients (receiving 4 mg budesonide orally disintegrating tablets). Clearance of budesonide is about 13 – 15 L/hour/kg in healthy subjects and 6.54 ± 4.4 L/hour/kg in EoE patients. Budesonide is eliminated by the kidney in marginal amounts, if at all. Budesonide was not detected in the urine; only budesonide metabolites were detected.

Hepatic impairment
A relevant proportion of budesonide is metabolised in the liver by CYP3A4. The systemic exposure of budesonide is considerably increased in patients with severely impaired hepatic function. No studies have been conducted with Jorveza® in patients with impaired liver function. In the absence of data, Jorveza® should not be used in patients with hepatic impairment.

Renal impairment
The effect of renal impairment on budesonide pharmacokinetics was not evaluated in a dedicated clinical study.Therefore budesonide is not recommended for use in patients with severe renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Budesonide had no mutagenic effects in a number of *in vitro* and *in vivo* tests.

Carcinogenicity

The carcinogenic potential of budesonide has been assessed in mice and rats at respective oral doses of up to 200 and 50 μg/kg/day. No oncogenic effect was noted in mice. One study showed an increased incidence of malignant gliomas in male Sprague-Dawley rats given budesonide 50 μg/kg/day. As this was not confirmed in further studies in male Sprague-Dawley and Fischer rats, it was concluded that budesonide does not increase the incidence of brain tumours in rats. In male rats dosed with 10, 25 and 50 μg/kg/day of budesonide, those receiving 25 and 50 μg/kg/day regimens showed an increased

incidence of primary hepatocellular tumours. However, this was also observed in rats treated with prednisolone and triamcinolone acetonide, thus indicating a class effect of glucocorticoids in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Jorveza® 0.5 mg and 1 mg orally disintegrating tablets:

Sodium acid citrate
Docusate sodium
Macrogol 6000
Magnesium stearate
Mannitol
Sodium dihydrogen citrate
Povidone
Sodium bicarbonate
Sucralose

Jorveza 0.2 mg/mL oral suspension:

Sucrose
Purifiedwater
Sodium benzoate
Disodium edetate
Citric acid
Methylcellulose
Blackcurrant flavour PHL-146218 (ARTG# 107040)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australia Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Orally disintegrating tablets

Store below 25°C. Store in the original package in order to protect from light and moisture.

Oral suspension

Store below 25°C.

After first opening, use within 6 weeks.

6.5 NATURE AND CONTENTS OF CONTAINER

Orally disintegrating tablets

Al/Al blister.

Jorveza® 0.5 mg:

Pack sizes: 20, 60, 100 or 200 orally disintegrating tablets. Not all pack sizes may be marketed.

Jorveza® 1 mg:

Pack sizes: 20, 30, 60 or 90 orally disintegrating tablets. Not all pack sizes may be marketed.

Oral suspension

Amber glass bottle with white ribbed child-resistant cap (PP) with colourless screw closure (HDPE) and internal colourless flow limiter (LDPE). After first opening, the flow limiter remains in the bottle neck and enables the insertion of the syringe to draw the suspension.

Jorveza ® 0.2 mg/mL suspension

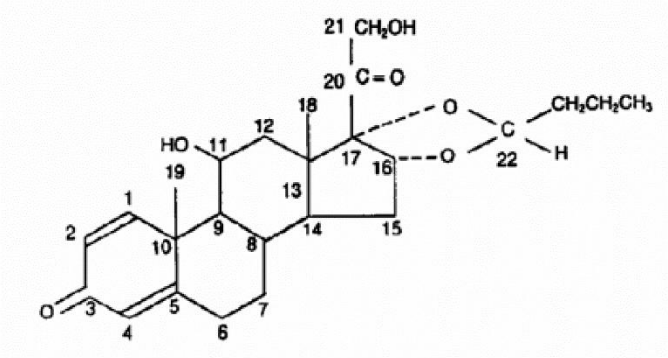
Pack size: 1 bottle containing 165 mL oral suspension. Supplied with one graduated syringe.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: 16α,17α-butylidene dioxy-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione

Molecular formula: $C_{25}H_{34}O_6$

Molecular mass: 430.5

CAS number: 51333-22-3

Physicochemical properties: Budesonide is a white or almost-white crystalline powder, with a pKa of 12.85 ± 0.10.

Budesonide is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96%).

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Dr Falk Pharma Australia Pty Ltd
Suite 205, 9 Help Street
Chatswood, NSW 2067

Phone: 1800 DRFALK (373 255)

9. DATE OF FIRST APPROVAL

15 September 2020

10. DATE OF REVISION

26 August 2026

Summary table of changes

Section changed	Summary of new information
2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.1, 6.2, 6.3, 6.4	Sections updated to include details of new dosage form Jorveza oral suspension Minor editorial changes