SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Jorveza 1 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 1 mg of budesonide.

Excipient with known effect

Each 1 mg orodispersible tablet contains 26 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

White, round, biplane orodispersible tablets, with a diameter of 7.1 mm and height of 2.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Jorveza is indicated for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age).

4.2 Posology and method of administration

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

Posology

Induction of remission

The recommended daily dose 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.

Maintenance of remission

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

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

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 different levels of hepatic impairment is available. Patients with hepatic impairment should not be treated (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Jorveza in children and adolescents under the age of 18 years have not been established. No data are available.

Method of administration

Oral use.

The orodispersible tablet should be taken immediately once removed from the blister package.

The orodispersible tablet should be taken after a meal.
It 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 at least two minutes but can take up to 20 minutes. The effervescence process of the tablet starts after Joreveza comes into contact with saliva and stimulates the production of further saliva. The budesonide-loaded saliva should be swallowed little by little while the orodispersible tablet disintegrates. The orodispersible tablet should not be taken with liquid or food.

There should be at least 30 minutes before eating or drinking or performing oral hygiene. Any oral solutions, sprays or chewable tablets should be used at least 30 minutes before or after administration of Jorveza.

The orodispersible tablet should not be chewed or swallowed undissolved. These measures ensure optimal exposure of the esophageal mucosa to the active substance by using the adhesive characteristics of mucins in the saliva.

4.3 Contraindications

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

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.

In clinical studies conducted with Jorveza oral, oropharyngeal and esophageal candida infections have been observed with a high frequency (see section 4.8).
If indicated, symptomatic candidiasis of the mouth and throat can be treated with topical or systemic anti-fungal therapy whilst still continuing treatment with Jorveza.

Chickenpox, herpes zoster and measles can have a more serious course in patients treated with glucocorticosteroids. In patients who have not had these diseases, the

vaccination status should be checked, and particular care should be taken to avoid exposure.

Vaccines

The co-administration of live vaccines and glucocorticosteroids 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 tuberculosis, 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 glucocorticosteroid adverse reactions (see below and section 4.8) and should therefore be monitored for the occurrence of such effects.

Reduced liver function may affect the elimination of budesonide, causing higher systemic exposure. The risk of adverse reactions (systemic glucocorticosteroid effects) will be increased. However, no systematic data are available. Patients with hepatic impairment should therefore not be treated.

Systemic effects of glucocorticosteroids

Systemic effects of glucocorticosteroids (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). These adverse reactions depend on the duration of treatment, concomitant and previous glucocorticosteroid treatment and the individual sensitivity.

Angioedema
Angioedema has been reported with the use of Jorveza, mostly as part of allergic reactions which included rash and itching. If signs of angioedema are observed, the treatment should be stopped.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid 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 cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Others

Glucocorticosteroids may cause suppression of the hypothalamic–pituitary–adrenal (HPA) axis and reduce the stress response. When patients are subject to surgery or other stresses, supplementary systemic glucocorticosteroid treatment is therefore recommended.

Concomitant treatment with ketoconazole or other CYP3A4 inhibitors should be avoided (see section 4.5).

Interference with serological testing

Because adrenal function may be suppressed by treatment with budesonide, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Sodium content

Jorveza 0.5 mg and 1 mg orodispersible tablets contain 52 mg of sodium per daily dose, equivalent to 2.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 inhibitors

Co-treatment with potent CYP3A inhibitors such as ketoconazole, ritonavir, itraconazole, 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 corticosteroid adverse reactions, in which case patients should be monitored for systemic corticosteroid adverse reactions.

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

Oestrogens, oral contraceptives

Elevated plasma concentrations and enhanced effects of glucocorticosteroids 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 effect, the maximal concentration of budesonide in plasma has to be expected to be higher in the treatment with Jorveza compared to inhaled budesonide. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development (see section 5.3). The relevance of this to man has not been established.

Breast-feeding

Budesonide is excreted in human milk (data on excretion after inhalative use is available). However, only minor effects on the breast-fed child are anticipated after oral use of Jorveza within the therapeutic range. 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.

Fertility

There are no data on the effect of budesonide on human fertility. Fertility was unaffected following budesonide treatment in animal studies (see section 5.3).

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 Undesirable effects

Summary of the safety profile

Fungal infections in the mouth, pharynx and the oesophagus were the most frequently observed adverse reactions in clinical studies with Jorveza. In the clinical studies BUL-1/EEA and BUL-2/EER, a total of 44 out of 268 patients (16.4%) exposed to Jorveza experienced cases of suspected fungal infections associated with clinical symptoms, which were all of mild or moderate intensity. The total number of infections (including those diagnosed by endoscopy and histology without symptoms) was 92, occurring in 72 out of 268 patients (26.9%). Long-term treatment with Jorveza of up to 3 years (48-weeks in the BUL-2/EER followed by 96-week open-label treatment) did not increase the rate of side effects including local candidiasis.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies with Jorveza 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	Esophageal candidiasis, oral and/or oropharyngeal candidiasis		Nasopharyngitis, pharyngitis
Immune system disorders			Angioedema
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	Abdominal pain, abdominal distension, dysphagia, erosive gastritis, gastric ulcer, lip edema, gingival pain,

		herpes	
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

The following known adverse reactions of the therapeutic class (corticosteroids, budesonide) could also occur with Jorveza (frequency = not known).

MedDRA system organ class	**Adverse reactions**
Immune system disorders	Increased risk of infection
Endocrine disorders	Cushing's syndrome, adrenal suppression, growth retardation in children
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia
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)
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, contact dermatitis, ecchymosis
Musculoskeletal and connective tissue disorders	Muscle and joint pain, muscle weakness and twitching, osteoporosis, osteonecrosis
General disorders and administration site conditions	Malaise

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

4.9 Overdose

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 antiinflammatory/antiinfective agents, corticosteroids acting locally, ATC code: A07EA06

Mechanism of action

Budesonide is a non-halogenated glucocorticosteroid, which acts primarily anti-inflammatory via binding to the glucocorticoid receptor. In the treatment of EoE with Jorveza, budesonide inhibits antigen-stimulated secretion of many pro-inflammatory signal molecules such as thymic stromal lymphopoeitin, interleukin-13 and eotaxin-3 in the esophageal epithelium, which results in a significant reduction of the esophageal eosinophilic inflammatory infiltrate.

Clinical efficacy and safety

In a randomised, placebo-controlled, double-blind phase III clinical study (BUL-1/EEA) including 88 adult patients with active EoE (randomisation rate: 2:1), 1 mg budesonide given twice daily as an orodispersible tablet for 6 weeks induced clinico-pathologic remission (defined as both peak of < 16 eosinophils/mm^2 high power field in esophageal biopsies and no or only minimal symptoms of dysphagia or pain during swallowing) in 34 out of 59 patients (57.6%) versus 0/29 patients (0%) in the placebo-group. Open-label extension of the treatment with 1 mg budesonide orodispersible tablet twice daily for further 6 weeks in patients without remission in the double-blind phase increased the rate of patients with clinico-pathologic 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-pathological remission, patients were randomised to treatment with 0.5 mg budesonide twice daily (BID), 1 mg budesonide BID, or placebo (all given as orodispersible tablets) for 48 weeks. 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 nummerical rating scale, respectively), and/or histological relapse (peak of ≥ 48 eosinophils/mm^2 high power field), 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 0.5 mg BID (73.5%) group and the 1 mg BID (75.0%) group were free of treatment failure at week 48 compared to placebo (4.4%).

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 1 mg BID group (52.9%) compared to the 0.5 mg BID group (39.7%), indicating that a higher dose of budesonide is of advantage to achieve and maintain deep disease remission.
The double-blind period was followed by an optional 96-week open-label treatment with a recommended dose of 0.5 mg budesonide BID or up to 1 mg budesonide BID. More than 80% of the patients maintained clinical remission (defined as weekly Eosinophilic Esophagitis Activity Index-Pro $\leq$ 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 high power field 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, following a 48-week double-blind maintenance treatment with Jorveza) no loss of efficacy was observed.

For information about the observed adverse reactions, see section 4.8.

5.2 Pharmacokinetic properties

Absorption

Following administration of Jorveza, budesonide is rapidly absorbed. Pharmacokinetic data following administration of single doses of 1 mg budesonide 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 hours (range 0.50 - 2.00 hours). The mean peak plasma concentration 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 (range 0.81 - 5.14 hr*ng/mL).

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

Patients 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 0.5 mg orodispersible tablets to 1 mg orodispersible tablets has been demonstrated.

Distribution

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

Biotransformation

Metabolism of budesonide is decreased in EoE patients 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 to metabolites of low glucocorticosteroid activity. The glucocorticosteroid 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.

Elimination

The median elimination half-life is 2 - 3 hours in healthy subjects (receiving 1 mg budesonide) and 4 - 5 hours in EoE patients (receiving 4 mg budesonide). 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 only in marginal if any amounts by the kidney. No budesonide, but only budesonide metabolites were detected in urine.

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.

5.3 Preclinical safety data

Preclinical data in acute, subchronic and chronic toxicological studies with budesonide showed atrophies of the thymus gland and adrenal cortex and a reduction especially of lymphocytes.

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

A slightly increased number of basophilic hepatic foci were observed in chronic rat studies with budesonide, and in carcinogenicity studies, an increased incidence of primary hepatocellular neoplasms, astrocytomas (in male rats) and mammary tumours (female rats) were observed. These tumours are probably due to the specific steroid receptor action, increased metabolic burden and anabolic effects on the liver, effects which are also known from other glucocorticosteroids in rat studies and therefore represent a class effect in this species.

Budesonide had no effect on fertility in rats. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause foetal death and abnormalities of foetal development (smaller litter size, intrauterine growth retardation of foetuses and skeletal abnormalities). Some glucocorticoids have been reported to produce cleft palate in animals. The clinical relevance of these findings to man has not been established (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Jorveza 0.5 mg and 1 mg orodispersible tablets

Disodium hydrogen citrate
Docusate sodium
Macrogol (6000)
Magnesium stearate
Mannitol (E 421)
Anhydrous monosodium citrate
Povidone (K25)
Sodium hydrogen carbonate
Sucralose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Alu/Alu-blister.

Pack sizes of 20, 30, 60, 90, 100 or 200 orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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