

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Jorveza 0.5 mg orodispersible tablets  
Jorveza 1 mg orodispersible tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Jorveza 0.5 mg orodispersible tablets

Each orodispersible tablet contains 0.5 mg of budesonide.

#### *Excipient with known effect*

Each 0.5 mg orodispersible tablet contains 26 mg sodium.

### Jorveza 1 mg orodispersible tablets

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

### Jorveza 0.5 mg orodispersible tablets

White, round, biplane orodispersible tablets, with a diameter of 7.1 mm and height of 2.2 mm. They are debossed with “0.5” on one side.

### Jorveza 1 mg orodispersible tablets

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 Jorveza 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

Concomitant 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) or not known (cannot be estimated from the available data).

<b>MedDRA system organ class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>
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 herpes	Abdominal pain, abdominal distension, dysphagia, erosive gastritis, gastric ulcer, lip edema, 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

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

<b>MedDRA system organ class</b>	<b>Adverse reactions</b>
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 the national reporting system listed in [Appendix V](#).

## 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 lymphopoietin, 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<sup>2</sup> 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  $\geq 4$  points on a 0-10 numerical rating scale, respectively), and/or histological relapse (peak of  $\geq 48$  eosinophils/mm<sup>2</sup> 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<sup>2</sup> 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  $2.56 \pm 1.36$  ng/mL, and  $AUC_{0-12}$  was  $8.96 \pm 4.21$  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  $35.52 \pm 14.94$  L/kg and  $42.46 \pm 23.90$  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, 6 $\beta$ -hydroxybudesonide and 16 $\alpha$ -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  $6.54 \pm 4.4$  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.

#### Jorveza 0.5 mg orodispersible tablets

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

#### Jorveza 1 mg orodispersible tablets

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**

Dr. Falk Pharma GmbH  
Leinenweberstr. 5  
79108 Freiburg  
Germany  
Tel.: +49 (0)761 1514-0  
Fax: +49 (0)761 1514-321  
E-mail: zentrale@drfalkpharma.de

## **8. MARKETING AUTHORISATION NUMBER(S)**

### Jorveza 1 mg orodispersible tablets

EU/1/17/1254/001  
EU/1/17/1254/002  
EU/1/17/1254/003  
EU/1/17/1254/004  
EU/1/17/1254/005  
EU/1/17/1254/006

### Jorveza 0.5 mg orodispersible tablets

EU/1/17/1254/007  
EU/1/17/1254/008  
EU/1/17/1254/009  
EU/1/17/1254/010  
EU/1/17/1254/011

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

Date of first authorisation: 08 January 2018  
Date of latest renewal: 27 September 2022

## **10. DATE OF REVISION OF THE TEXT**

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

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Dr. Falk Pharma GmbH  
Leinenweberstrasse 5  
79108 Freiburg  
Germany

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to 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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON – 0.5 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Jorveza 0.5 mg orodispersible tablets  
budesonide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each orodispersible tablet contains 0.5 mg budesonide.

**3. LIST OF EXCIPIENTS**

Contains sodium. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

orodispersible tablet

20 orodispersible tablets  
60 orodispersible tablets  
90 orodispersible tablets  
100 orodispersible tablets  
200 orodispersible tablets

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

Do not chew or swallow.  
Use as directed by the physician.  
Read the package leaflet before use.  
Oral use.

**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**

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

**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**

Dr. Falk Pharma GmbH  
Leinenweberstr. 5  
79108 Freiburg  
Germany

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

EU/1/17/1254/007 (20 orodispersible tablets)  
EU/1/17/1254/008 (60 orodispersible tablets)  
EU/1/17/1254/009 (90 orodispersible tablets)  
EU/1/17/1254/010 (100 orodispersible tablets)  
EU/1/17/1254/011 (200 orodispersible tablets)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Jorveza 0.5mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS – 0.5 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Jorveza 0.5 mg orodispersible tablets  
budesonide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Dr. Falk Pharma GmbH

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON – 1 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Jorveza 1 mg orodispersible tablets  
budesonide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each orodispersible tablet contains 1 mg budesonide.

**3. LIST OF EXCIPIENTS**

Contains sodium. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

orodispersible tablet

20 orodispersible tablets  
30 orodispersible tablets  
60 orodispersible tablets  
90 orodispersible tablets  
100 orodispersible tablets  
200 orodispersible tablets

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

Do not chew or swallow. Use as directed by the physician.  
Read the package leaflet before use.  
Oral use.

**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**

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

**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**

Dr. Falk Pharma GmbH  
Leinenweberstr. 5  
79108 Freiburg  
Germany

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

EU/1/17/1254/001 (20 orodispersible tablets)  
EU/1/17/1254/002 (30 orodispersible tablets)  
EU/1/17/1254/003 (60 orodispersible tablets)  
EU/1/17/1254/004 (90 orodispersible tablets)  
EU/1/17/1254/005 (100 orodispersible tablets)  
EU/1/17/1254/006 (200 orodispersible tablets)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Jorveza 1mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN

NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS – 1 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Jorveza 1 mg orodispersible tablets  
budesonide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Dr. Falk Pharma GmbH

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**  
**Jorveza 0.5 mg orodispersible tablets**  
**Jorveza 1 mg orodispersible tablets**  
budesonide

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Jorveza is and what it is used for
2. What you need to know before you take Jorveza
3. How to take Jorveza
4. Possible side effects
5. How to store Jorveza
6. Contents of the pack and other information

**1. What Jorveza is and what it is used for**

Jorveza contains the active substance budesonide, a corticosteroid medicine that reduces inflammation.

It is used in adults (older than 18 years of age) to treat eosinophilic oesophagitis, which is an inflammatory condition of the gullet (food pipe) that causes problems with swallowing food.

**2. What you need to know before you take Jorveza**

**Do not take Jorveza**

- if you are allergic to budesonide or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**

Talk to your doctor or pharmacist before taking Jorveza if you have:

- tuberculosis
- high blood pressure
- diabetes, or if somebody in your family has diabetes
- weakening of the bones (osteoporosis)
- ulcers in the stomach or first part of the small intestine (peptic ulcer)
- increased pressure in your eye (which can cause glaucoma) or eye problems such as clouding of the lens (cataracts) or if somebody in your family has glaucoma
- liver disease.

If you have any of the conditions mentioned above you may be at increased risk of side effects. Your doctor will decide on the appropriate measures and if it is still all right for you to take this medicine.

If you develop swelling of your face, particularly around your mouth (lips, tongue or throat) and/or difficulties to breathe or swallow, stop taking Jorveza and contact your doctor immediately. These may be signs of an allergic reaction, which may also include rash and itching (see also section 4).

Jorveza may cause typical side effects of corticosteroid medicines and may affect all parts of the body, particularly when you take this medicine at high doses and over a long time (see section 4).

#### *Further precautions during treatment with Jorveza*

- Contact your doctor if you get blurred vision or have other problems with your vision.

Take the following precautions during treatment with Jorveza because your immune system may be weakened:

- Tell your doctor if you get fungal infections in the mouth, throat and gullet or if you think you have any infection during treatment with this medicine. Symptoms of fungal infection can be white spots in the mouth and throat and difficulty in swallowing. The symptoms of some infections can be unusual or less noticeable.
- Keep away from people who have chickenpox or herpes zoster (shingles) if you have not had these infections. The effects of these illnesses can be much more severe during treatment with this medicine. If you do come into contact with chickenpox or shingles, see your doctor straight away. Please also report your vaccination status to your doctor.
- Tell your doctor if you have not yet had measles and/or if and when you have received your last vaccination for this disease.
- If you need to be vaccinated please speak to your doctor first.
- If you know that you are due to have an operation please tell your doctor that you are taking Jorveza.

Jorveza could affect the results of adrenal function tests (ACTH stimulation test) ordered by your doctor or in hospital. Tell your doctors that you are taking Jorveza before you have any tests.

#### **Children and adolescents**

Jorveza should not be used in children and adolescents under 18 years of age. The use of this medicine in children younger than 18 years of age has not yet been studied.

#### **Other medicines and Jorveza**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Some of these medicines may increase the effects of Jorveza and your doctor may wish to monitor you carefully if you are taking these medicines.

In particular:

- ketoconazole or itraconazole (to treat fungal infections)
- clarithromycin, an antibiotic medicine used to treat infections
- ritonavir and cobicistat (to treat HIV infections)
- oestrogens (used for hormone replacement therapy or contraception)
- cardiac glycosides such as digoxin (medicines used to treat heart conditions)
- diuretics (to remove excess fluid from the body).

#### **Jorveza with food and drink**

You should not drink grapefruit juice whilst you are taking this medicine as this can worsen its side effects.

#### **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 or pharmacist for advice before taking this medicine.

Do not take this medicine during pregnancy without checking with your doctor first.

Do not take this medicine if you are breast-feeding unless you have checked with your doctor. Budesonide passes in small amounts into the breast milk. Your doctor will help you decide whether you should continue treatment and not breast-feed or if you should stop treatment over the period your baby is being breast-fed.

### **Driving and using machines**

Jorveza is not expected to affect your ability to drive or use machines.

### **Jorveza contains sodium**

This medicine contains 52 mg sodium (main component of cooking/table salt) per daily dose. This is equivalent to 2.6% of the recommended maximum daily dietary intake of sodium for an adult.

### **3. How to take Jorveza**

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

The recommended dose for treatment of acute episodes is two 1 mg orodispersible tablets (2 mg budesonide) per day. Take one 1 mg orodispersible tablet in the morning and one 1 mg orodispersible tablet in the evening.

The recommended dose for prevention of further episodes is two 0.5 mg orodispersible tablets (1 mg budesonide) per day or two 1 mg orodispersible tablets (2 mg budesonide) per day, depending on your body's response to the treatment. Take one orodispersible tablet in the morning and one orodispersible tablet in the evening.

### **Method of administration**

Take the orodispersible tablet immediately once removed from the blister package.

Take the orodispersible tablet after a meal.

Place the orodispersible tablet on the tip of your tongue and close your mouth. Press it gently against the roof of your mouth with your tongue until it has disintegrated completely (this usually takes at least two minutes but may take up to 20 minutes). Swallow the disintegrated material with saliva little by little, as the orodispersible tablet breaks up.

Do NOT take any liquid with the orodispersible tablet.

Do not chew or swallow the undisintegrated orodispersible tablet.

Do not eat, drink, brush your teeth or rinse your mouth for at least 30 minutes after you have taken the orodispersible tablet. Do not use any oral solutions, sprays or chewable tablets for at least 30 minutes before or after administration of the orodispersible tablet. This will ensure that your medicine works properly.

### *Kidney and liver problems*

If you have any problem with your kidney or liver, talk to your doctor. If you have a kidney problem, your doctor will decide if Jorveza is suitable for you. In case your kidney problems are severe, you should not take Jorveza. If you have any liver disease, you should not take Jorveza.

### **Duration of treatment**

Initially, your treatment should last about 6 to 12 weeks.

After treatment of the acute episode, your doctor will decide how long and with which dose you are to continue the treatment, depending on your condition and your response to the treatment.

### **If you take more Jorveza than you should**

If you have taken more orodispersible tablets than you should, take your next dose as prescribed. Do not take a smaller amount. Ask your doctor or pharmacist if you are in doubt. Take the carton and this leaflet with you if possible.

### **If you forget to take Jorveza**

If you miss a dose, just take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

#### **If you stop taking Jorveza**

Speak to your doctor if you want to interrupt or end your treatment early. It is important that you do not stop taking your medicine without talking to your doctor. Keep taking your medicine until your doctor tells you to stop, even if you feel better.

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

#### **4. Possible side effects**

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

Stop using Jorveza and seek medical attention immediately if you notice any of the following symptoms:

- swelling of the face, particularly of the eyelids, lips, tongue or throat (angioedema) which may be symptoms of an allergic reaction.

The following side effects have been reported during the use of Jorveza:

##### **Very common: may affect more than 1 in 10 people**

- fungal infections in the gullet (which can cause pain or discomfort when swallowing)
- fungal infections in the mouth and throat (symptoms can be white spots)

##### **Common: may affect up to 1 in 10 people**

- headache
- heartburn
- indigestion
- feeling sick (nausea)
- tingling or numbness in your mouth, dry mouth
- taste disorder, burning tongue
- upper abdominal (belly) pain
- tiredness
- decreased amount of the hormone cortisol in your blood
- dry eyes.
- difficulty in sleeping
- problems with tongue
- cold sore (oral herpes)

##### **Uncommon: may affect up to 1 in 100 people**

- anxiety, agitation
- dizziness
- high blood pressure
- cough, dry throat, sore throat, common cold
- abdominal (belly) pain, abdominal distension (bloating)
- difficulty swallowing
- inflammation of the stomach, ulcers in the stomach
- swelling of the lips
- rash, itching rash
- sensation of foreign body
- pain in the mouth or throat
- painful gums,

- decreased level of osteocalcin, weight gain.

The following side effects have been reported and are typical with medicines similar to Jorveza (corticosteroids), and can therefore also occur with this medicine. The frequency of these events is currently not known:

- increased risk of infection
- Cushing’s syndrome, which is associated with too much corticosteroid and causes roundness of the face, weight gain, high blood sugar, build-up of fluid in the tissues (e.g. swollen legs), reduced potassium level in the blood (hypokalaemia), irregular periods in women, unwanted body hair in women, impotence, stretch marks on the skin, acne.
- slowed growth in children
- mood changes, such as depression, irritability or euphoria
- restlessness with increased physical activity, aggression
- increased pressure in the brain, possibly with increased pressure in the eye (swelling of the optic disk) in adolescents
- blurred vision
- increased risk of blood clots, inflammation of the blood vessels (which can happen when the medicine is stopped after long-term use)
- constipation, ulcers in the small intestine
- inflammation of the pancreas, which causes severe pain in the belly and back
- rash, red spots from bleeding in the skin, delayed wound healing, skin reactions such as contact dermatitis, bruising
- muscle and joint pain, muscle weakness, muscle twitching
- weakening of the bones (osteoporosis), bone damage due to poor circulation of blood (osteonecrosis)
- general feeling of being ill.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. 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 Jorveza**

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

Do not take this medicine after the expiry date which is stated on the carton and blister after “EXP”. The expiry date refers to the last day of that month.

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

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

## 6. Contents of the pack and other information

### What Jorveza contains

#### Jorveza 0.5 mg orodispersible tablet

- The active substance is budesonide. Each orodispersible tablet contains 0.5 mg of budesonide.
- The other ingredients are disodium hydrogen citrate, docusate sodium, macrogol (6000), magnesium stearate, mannitol (E 421), anhydrous monosodium citrate, povidone (K25), sodium hydrogen carbonate and sucralose (see also section 2, "Jorveza contains sodium").

#### Jorveza 1 mg orodispersible tablet

- The active substance is budesonide. Each orodispersible tablet contains 1 mg of budesonide.
- The other ingredients are disodium hydrogen citrate, docusate sodium, macrogol (6000), magnesium stearate, mannitol (E 421), anhydrous monosodium citrate, povidone (K25), sodium hydrogen carbonate and sucralose (see also section 2, "Jorveza contains sodium").

### What Jorveza looks like and contents of the pack

#### Jorveza 0.5 mg orodispersible tablet

Jorveza 0.5 mg orodispersible tablets are white, round, biplane. They are debossed with "0.5" on one side. They come in blisters in packs with 20, 60, 90, 100 or 200 orodispersible tablets.

#### Jorveza 1 mg orodispersible tablet

Jorveza 1 mg orodispersible tablets are white, round, biplane. They come in blisters in packs with 20, 30, 60, 90, 100 or 200 orodispersible tablets.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

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**This leaflet was last revised in .**

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