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Dr Falk

Jorveza pivotal studies

Induction

Efficacy of budesonide orodispersible tablets as induction therapy for eosinophilic oesophagitis in a randomised placebo-controlled trial[1]

Maintenance

Budesonide orodispersible tablets maintain remission in a randomised, placebo-controlled trial of patients with eosinophilic oesophagitis[2]

Open-label extension

Over a period of up to 3 years, budesonide orodispersible tablets were highly effective in preventing clinical, endoscopic and histological relapse[3]

0.5 mg & 1 mg now available

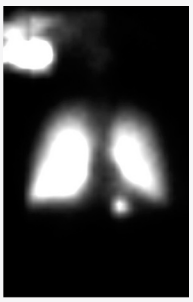
BUDESONIDE
Jorveza®
ORODISPERSIBLE TABLETS

Prescribing information can be found on the back cover

Induction study

Eosinophilic oesophagitis (EoE), a chronic disorder in which eosinophils infiltrate the oesophageal epithelium, has emerged as one of the major causes of dysphagia and food impaction in adults.[4]

As with other allergic diseases, oesophageal inflammation and eosinophilia in EoE are relatively responsive to the administration of corticosteroids.[5] Off-label budesonide formulations are not, however, optimised for oesophageal delivery.[6] Unwanted lung deposition may occur, and drug concentrations in the oesophagus are widely variable.[6,7]



Nebulised swallowed budesonide[6]

Oral viscous budesonide[6]

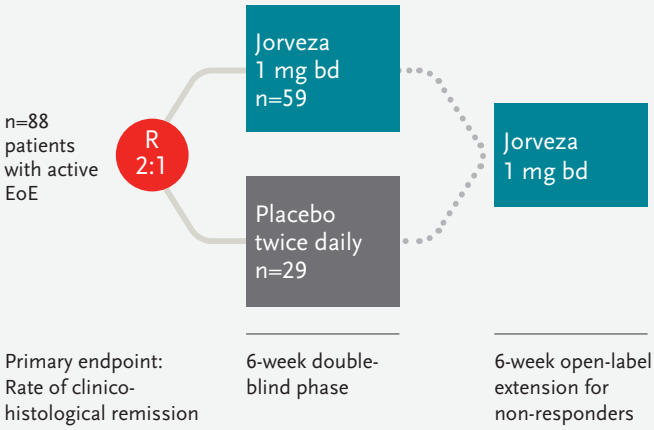
Reprinted from Gastroenterology, vol. 143, issue 2, Evan S. Dellon *et al*, Viscous Topical Is More Effective Than Nebulized Steroid Therapy for Patients With Eosinophilic Esophagitis, 321-324, © 2012 with permission from Elsevier.

Study aim

To assess the efficacy, safety and tolerability of the orodispersible budesonide tablet, Jorveza, for the induction of clinical and pathological remission in adult patients with active EoE.[1]

Study design

European, multi-centre, phase III, randomised, double-blind, placebo-controlled study[1]



In line with accepted thinking, a combined clinico-pathological primary endpoint was chosen:[1]

- clinico-histological remission, defined as a peak of <5 eosinophils/high power field (eos/hpf), and;
- resolution of symptoms, defined as a severity of ≤2 points on 10-point numerical rating scale (NRS) for dysphagia and pain during swallowing on each day in the week prior to week 6

Baseline characteristics

Patients were required to have active symptoms and histological EoE. Largely male (83%), patients were representative of a typical adult EoE population. The average delay in diagnosis from the first onset of symptoms was 4.3 years. Over half had received prior treatment with a topical steroid (unlicensed).[1]

Baseline characteristics[1]		Jorveza n=59	Placebo n=29
Male		81%	86%
Age (mean, years)		37	37
Time since diagnosis (mean, months)		49	58
Time since first symptoms (mean, months)		134	139
Symptom history	Dysphagia	98%	100%
	Odynophagia	59%	48%
	Food impaction	95%	90%
History of allergic disease		80%	79%
Previous oesophageal dilation		15%	17%
Previous dietary therapy	Elemental	0%	0%
	Elimination – allergy tested	7%	14%
	Elimination – undirected	41%	35%
Previous topical steroid treatment*		63%	59%
Previous PPI trial		100%	100%
Concomitant use of PPIs		12%	10%

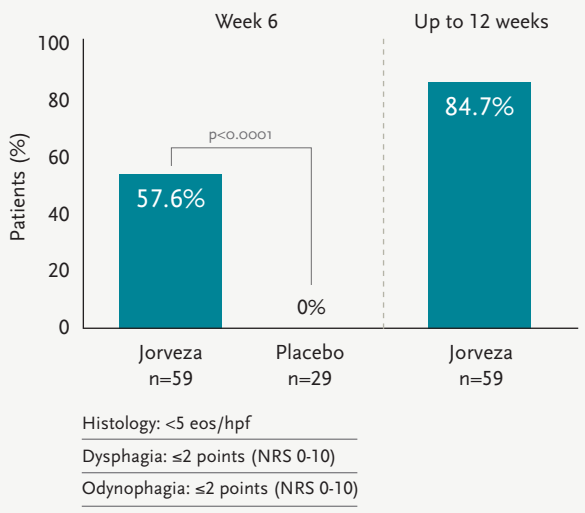
* Topical fluticasone or topical budesonide in the form of swallowed asthma spray, swallowed nasal drops or swallowed powder

PPI: proton pump inhibitor

Results

Jorveza was highly effective at inducing remission in EoE.[1]

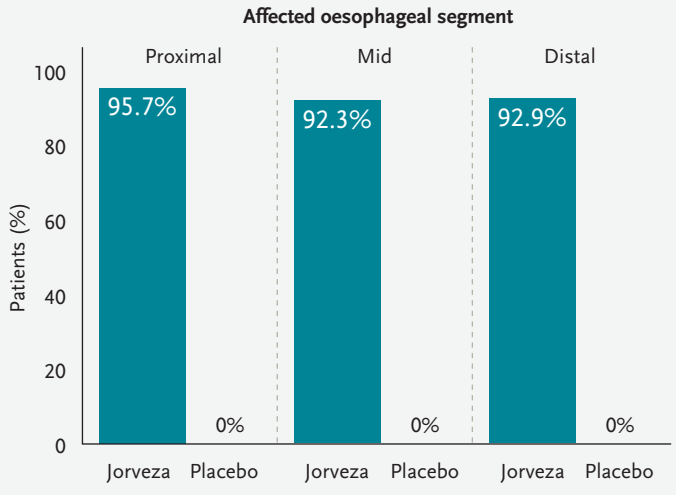
Clinico-histologic remission with Jorveza at week 6[1]



Prolongation of therapy to 12 weeks is beneficial to bring more patients into clinico-histologic remission[1]

Histological remission was observed in over 90% of Jorveza patients.[1] Jorveza was equally effective and superior to placebo for inducing histological remission in all parts of the oesophagus, suggesting it provides optimal targeting of the whole oesophagus.[1]

Histological remission at week 6 by location of inflammation at baseline[1]

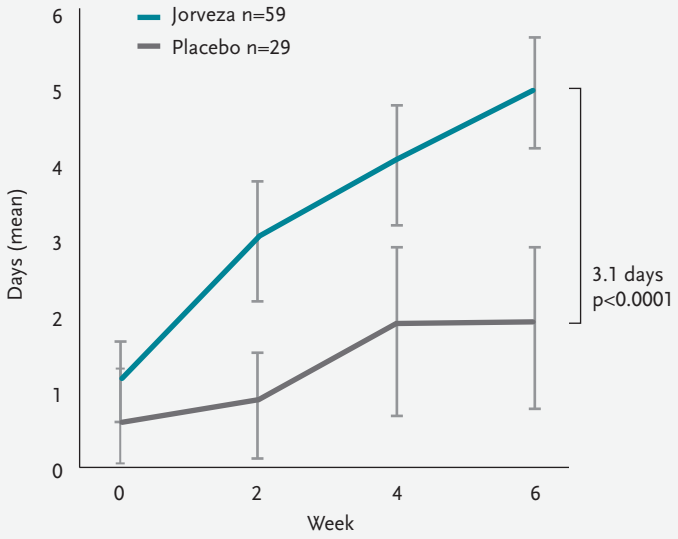


As well as the expected improvement in inflammatory signs, Jorveza improved the Endoscopic Reference Score (EREFS) fibrotic subscore.[1]

Symptoms can be unpleasant, socially embarrassing and restricting – they can also cause a sense of panic.[8] At baseline, most patients had symptoms most days of the week, indicating a high unmet need in these patients.[1]

Jorveza led to a quick onset of symptom resolution.[1]

Number of days with no or only minimal dysphagia[1]



Both social function and disease-related worry were significantly improved with Jorveza vs placebo.[1]

Jorveza was well tolerated.[1]

5% of Jorveza patients presented with symptoms and histologically confirmed fungal infection; in all cases, symptoms were mild.[1]

Bolus impaction requiring an emergency endoscopy for retraction was observed in one patient in the placebo group.[1] Neither serious adverse events nor clinically relevant changes in the morning serum cortisol levels were observed in any treatment group.[1]

In an earlier study, 76 patients with active EoE who had taken both orodispersible tablets and a viscous suspension were asked which was their preferred budesonide formulation in a double-blind, double-dummy, randomised, placebo-controlled, multi-centre trial.[9]

80% of patients preferred Jorveza over a viscous budesonide suspension.[9]

Conclusion

Treatment with Jorveza was highly superior to placebo for induction of clinico-pathological remission in EoE. Histological remission was induced in nearly all patients treated with Jorveza independently of the localisation, extent, or severity of oesophageal inflammation, thus indicating that the orodispersible tablet formulation offers optimal oesophageal targeting.

Maintenance study

It has become increasingly clear that most, if not all, patients with EoE will need maintenance therapy to control inflammation.[10]

Natural history studies have clearly documented that the disease persists without treatment, and progression of significant fibrostenoses has been reported in most patients with over a decade of untreated EoE.[11]

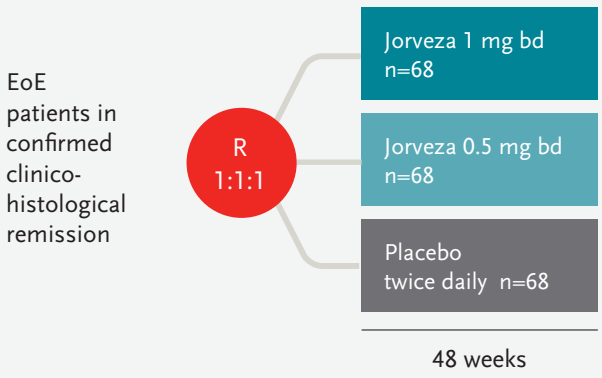
While there is an apparent treatment need, confirmatory maintenance trials with swallowed topical corticosteroids are scarce.[2]

Study aim

To evaluate the efficacy and safety of the orodispersible budesonide tablet, Jorveza, for the maintenance of remission in adult patients with EoE.[2]

Study design

European, multi-centre, phase III, randomised, double-blind, placebo-controlled, 48-week study[2]



As EoE is defined as a clinico-histologic syndrome in which clinical manifestations and pathologic data should not be interpreted in isolation, a combined primary efficacy outcome was used in this trial.[2]

The primary outcome was remission at week 48, with:[2]

- no clinical relapse (dysphagia or odynophagia with severity ≥4 points on at least 1 day during the previous week)
- no histological relapse (peak of ≥48 eos/mm^2 hpf corresponding to ≥15 eos/hpf
- no food impaction requiring endoscopic intervention
- no need for dilation
- no premature withdrawal for any reasons

Baseline characteristics

Eligible patients were either in confirmed clinico-histological remission at baseline, after either:[2]

- achieving the goals of the Jorveza pivotal induction therapy study
- or by receiving open-label induction with Jorveza 1 mg twice daily for 6 weeks

Patients from both entry routes showed similar demographic and disease specific characteristics.[2]

Disease activity at baseline of maintenance treatment[2]

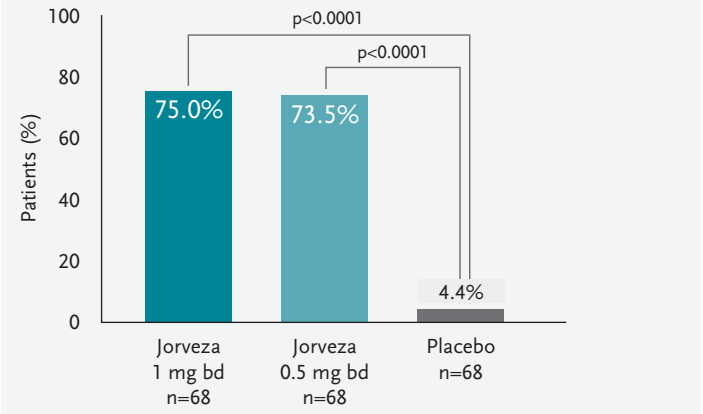
	Jorveza 1 mg bd n=68	Jorveza 0.5 mg bd n=68	Placebo twice daily n=68
Daily dysphagia (NRS 0-10, mean)	1	1	1
Daily odynophagia (NRS 0-10, mean)	1	1	0
Total weekly EEsAI-PRO (0-100, mean)	16	16	16
Patient's Global Assessment of EoE activity (0-10, mean)	1	1	1
Total modified EREFS (0-9, mean)	1	1	1
Endoscopic "no signs of EoE"	66%	74%	63%
Peak eos/mm^2 hpf (mean)	0	0	1

EEsAI-PRO: Eosinophilic Esophagitis Activity Index - Patient Reported Outcome

Results

Jorveza was highly effective at maintaining remission in EoE.[2]

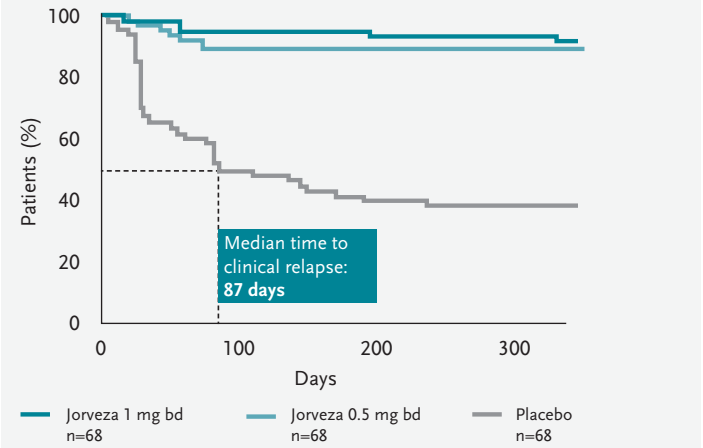
Patients in clinico-histological remission at week 48



Remission rates in patients with extended inflammation (all 3 segments affected at baseline of induction therapy) were higher for Jorveza 1 mg than 0.5 mg (80% vs 68% vs 3% for placebo).[2]

While half of placebo patients had clinically relapsed within 3 months, over 90% of Jorveza patients were still in clinical remission at week 48.[2]

Time to clinical relapse[2]



All secondary efficacy outcomes confirmed superiority of Jorveza over placebo.[2]

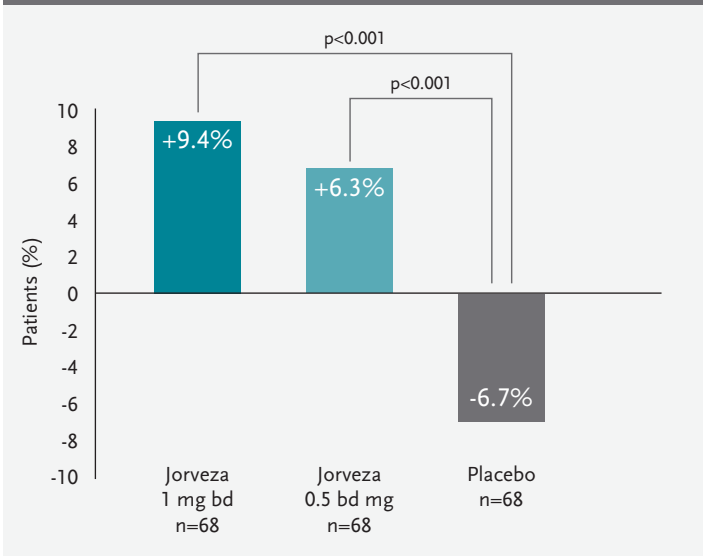
	Jorveza 1 mg bd	Jorveza 0.5 mg bd	Placebo
Deep histological remission (0 eos/mm² hpf)	**79.4%***	**76.5%***	**1.5%**
Deep endoscopic remission (no signs of EoE)	**73.5%***	**67.5%***	**7.4%**
Clinical remission (EEsAI-PRO ≤20)	**73.5%***	**72.1%***	**20.6%**

*p<0.001 vs placebo

Jorveza can reduce the emotional and social toll of EoE long-term.[2]

Eosinophilic Oesophagitis Quality of Life Scale for Adults (EoE-QoL-A) significantly improved in all domains with Jorveza 0.5 mg and 1.0 mg twice daily, but deteriorated with placebo.[2]

Change from baseline in EoE-QoL-A 30 score at week 48[2]



Bearing in mind that all patients started with an already very good QoL, the relative improvement and deterioration under Jorveza and placebo respectively are clinically relevant.

Jorveza was well tolerated.[2]

The frequency of adverse events was similar in the Jorveza and placebo groups.[2]

Food impaction requiring endoscopic intervention occurred in two patients receiving placebo, but in no Jorveza patient. Morning serum levels of cortisol were in the normal range at baseline and did not significantly change during treatment.

Local fungal infections with Candida occurred at a higher frequency with Jorveza.[2] The rate of confirmed and symptomatic oesophageal candidiasis was 5.9% and 1.5% for Jorveza 0.5 mg and 1 mg twice daily respectively. It was easy to treat and almost never interfered with the daily life activities of patients. Clinically manifested candidiasis did not increase throughout the study period.

Conclusion

The trial confirmed firstly that EoE requires therapeutic long-term management, and secondly that Jorveza is an effective maintenance therapy for adult patients with EoE who achieved disease remission with the same compound.[2]

Open-label extension

Owing to its chronic nature, treatment of eosinophilic oesophagitis should be seen as a long-term strategy for most patients.[12]

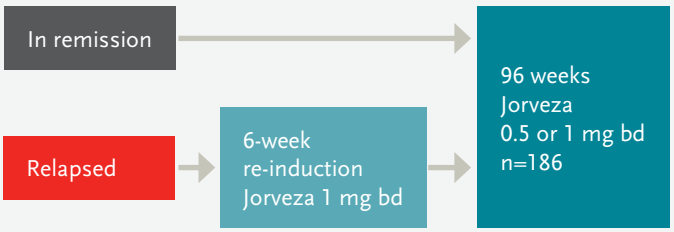
Historically, swallowed topical corticosteroids have been effective in the long-term treatment of EoE. However, remission rates have generally been lower than those observed after induction therapy.[12] With the exception of the Jorveza maintenance trial, no study in adults has, for example, maintained histological remission in more than half of its patients.[12] There is, therefore, an unmet need for long-term histologic, endoscopic, and symptomatic disease control.[13]

Study aim

To examine rates of sustained remission and long-term safety beyond one year of Jorveza treatment.[3]

Study design

96-week, open-label extension for patients (placebo and Jorveza completing the double-blind, 48-week study[3]



Outcome measures[3]

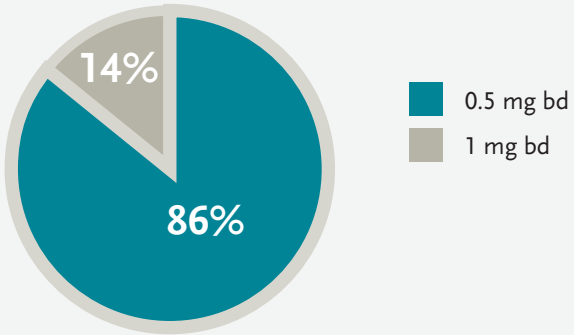
- Eosinophilic Esophagitis Activity Index-Patient Reported Outcome (EEsAI-PRO)
- Dysphagia (numerical rating scale)
- Odynophagia (numerical rating scale)
- Patients' Global Assessment (PatGA)
- Patients' global satisfaction
- Endoscopic Reference Score (EREFS)
- Histological remission (peak eos: <5/hpf)
- Deep histological remission (peak eos in all biopsies: 0/hpf)
- Adverse events

Baseline characteristics

Disease activity at baseline of maintenance treatment[2]

	Jorveza 0.5 or 1 mg bd[3]
Male gender (%)	85%
Age (mean, years)	36.9
Weekly dysphagia NRS (0-10, mean)	0
Weekly odynophagia NRS (0-10, mean)	0
PatGA of EoE activity (0-10, mean)	1
Weekly EEsAI-PRO (0-100, mean)	9
Weekly EEsAI-PRO ≤20 (%)	78%
Total modified EREFS (0-9, mean)	1
EREFS – inflammatory subscore (0-4, mean)	0
EREFS – fibrotic subscore (0-4, mean)	0

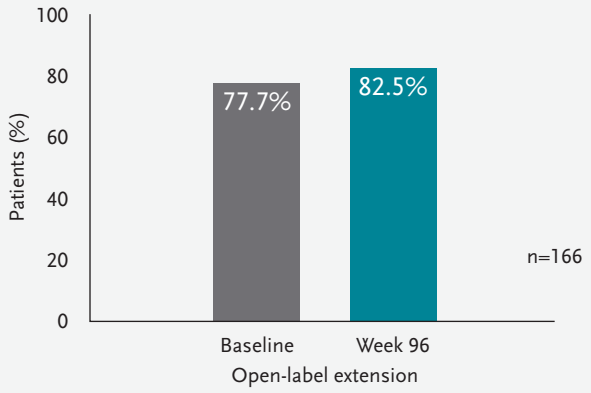
86% of patients were treated with the lower dose of Jorveza 0.5 mg bd[3]



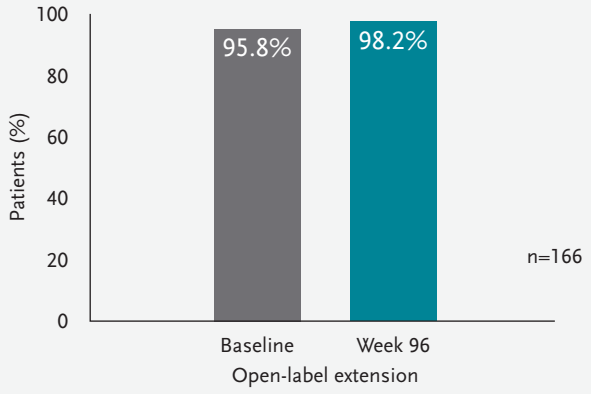
Results

Over a period of up to three years, no loss of efficacy was observed with Jorveza.[3]

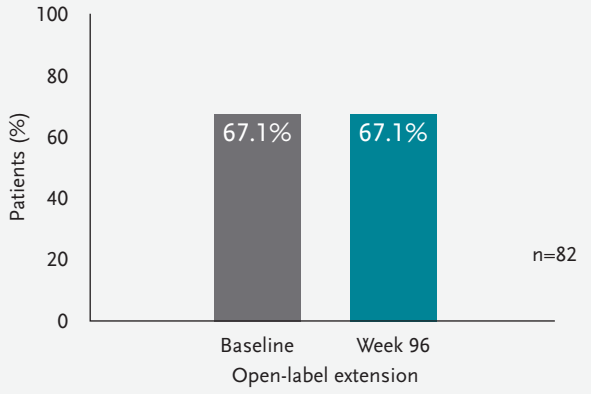
Patients in clinical remission with Jorveza 0.5 mg bd[3,14]



PatGA of EoE activity ≤2 with Jorveza 0.5 mg bd[3,14]



Total modified EREFS of 0 with Jorveza 0.5 mg bd[3,14]



78.8% of patients had achieved deep histological remission at week 96.[3]

Patients' global satisfaction at end of treatment[3]	
Extremely satisfied	**77.7%**
Satisfied	**19.9%**
Neither satisfied nor dissatisfied	**0.6%**
Missing	**1.8%**

Over a period of up to three years, no increase in side effects was observed with Jorveza.[3]

Treatment emergent adverse events led to withdrawal in 5 patients (2.7%).[3]

Long-term treatment with Jorveza did not increase the rate of local candidiasis; cases were generally mild in intensity and did not impact upon the treatment effect.[3]

No clinically relevant changes in serum morning cortisol levels were observed from the open-label extension baseline to the end of treatment.[3]

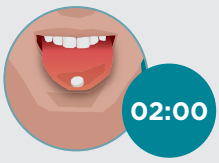
Conclusion

Jorveza was highly effective in preventing clinical, endoscopic and histological relapse in adult EoE patients over a period of up to 3 years, with no increase in side effects observed.[3]

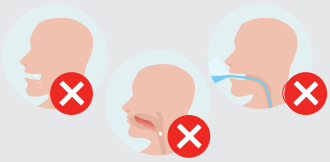
Taking Jorveza for optimal effect

Jorveza is placed on the tip of the tongue, then gently pressed against the roof of the mouth while it dissolves.

It should take about 2 minutes for the Jorveza tablet to dissolve completely.



Jorveza should not be chewed, or swallowed undissolved, or taken with liquid.



It's very important that patients give Jorveza time to work. So, at the very least, they should leave 30 minutes before eating, drinking, cleaning teeth or chewing gum.

It may help if patients take Jorveza after they have had breakfast and brushed their teeth in the morning and very last thing at night, just as they go to bed. That way Jorveza will stay in contact with the oesophagus for as long as possible.

See an animation on how to take Jorveza here

Recommended dosing

Induction	Maintenance
1 mg bd	0.5 or 1 mg bd

Prescribing Information (refer to full SmPC before prescribing).

Presentations: Jorveza 1mg and 0.5mg orodispersible tablets containing 1mg or 0.5mg of budesonide. **Indications:** treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age). **Dosage:** Induction of remission: one 1mg tablet taken twice daily (morning and evening) after a meal and immediately after removal of the tablet from the blister pack. Usual duration of induction treatment is 6 weeks. Extend up to 12 weeks for non-responding patients. Maintenance of remission: 0.5mg twice daily or 1mg twice daily depending on clinical need. A maintenance dose of 1mg twice daily is recommended for patients with long-standing disease history and/or high extent of esophageal inflammation in the acute disease state. Duration of maintenance treatment - to be determined by the treating physician. Administration: tablet is placed on tip of tongue and pressed to top of mouth then swallowed slowly without liquid or food and without chewing or swallowing undisintegrated. May take 2 to 20 minutes to disintegrate and swallow completely. Wait at least 30 minutes before eating, drinking or performing oral hygiene. **Contra-indications:** hypersensitivity to budesonide or any ingredient of the tablets. **Warnings/precautions:** infections - Suppression of inflammatory response and immune function increases susceptibility to infections and their severity which can be atypical or masked. Oral, oropharyngeal and esophageal candida infections occur at high frequency. Treat symptoms with topical or systemic anti-fungals. Jorveza treatment can continue. Chickenpox, herpes zoster and measles - can be more serious in patients treated with glucorticosteroids. Check vaccination status. Avoid exposure. Vaccines - avoid co-administration of live vaccines and glucocorticosteroids. The antibody response to other vaccines may be diminished. Special populations - monitor patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataract, family history of glaucoma. Systemic effects of glucocorticosteroids may occur, depending on duration of treatment, concomitant and previous glucocorticosteroid treatment and individual sensitivity. Patients with reduced liver function - an increased systemic availability of budesonide may be expected, with increased risk of adverse reactions. Patients with hepatic impairment should not be treated. Not recommended for use in patients with severe renal impairment. Angioedema - treatment should be stopped if signs of angioedema are observed. Visual disturbance - patients with blurred vision or other visual disturbances should be considered for referral to an ophthalmologist. Causes may include cataract, glaucoma or central serous chorioretinopathy resulting from corticosteroid use. 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. Serological testing - adrenal function may be suppressed by budesonide so an ACTH stimulation test for diagnosing pituitary insufficiency might show false (low) results. Sodium - contains 52 mg of sodium per daily dose. **Interactions:** CYP3A4 inhibitors - concomitant treatment with ketoconazole or other potent CYP3A inhibitors including grapefruit juice should be avoided to reduce the risk of systemic side effects unless the benefit outweighs the risk. Such treatment should be monitored. Oestrogens, oral contraceptives - may elevate plasma concentrations and enhance effects of glucocorticosteroids. Concomitant intake of low dose combination oral contraceptives has not shown this effect. Cardiac glycosides - action of glycoside can be potentiated by potassium deficiency - a potential and known adverse reaction of glucocorticoids. Saluretics - potassium excretion can be enhanced and hypolalaemia aggravated. Use in pregnancy should be avoided unless there are compelling reasons for therapy. Breast-feeding - budesonide is excreted in human milk. The benefit of breast feeding for the child and the benefit of therapy for the woman should be assessed. Fertility - there are no data on the effect of budesonide on human fertility. **Undesirable effects:** fungal infections in the mouth, pharynx and the oesophagus were the most frequently observed adverse reactions in clinical studies. Long term treatment did not increase the rate. Adverse reactions and frequencies: Very common: esophageal candidiasis, oral and/or oropharyngeal candidiasis, Common: sleep disorder, headache, dysgeusia, dry eyes, gastroesophageal reflux disease, nausea, oral paraesthesia, dyspepsia, upper abdominal pain, dry mouth, glossodynia, tongue disorder, oral herpes, fatigue, blood cortisol decreased. Uncommon: nasopharyngitis, pharyngitis, angioedema, , anxiety, agitation, dizziness, , hypertension, cough, dry throat, oropharyngeal pain, abdominal pain, abdominal distension, , dysphagia, erosive gastritis, gastric ulcer, lip edema, gingival pain, rash, urticaria, sensation of foreign body, osteocalcin decreased, weight increased. . Other (class) effects with unknown frequency that may occur: increased risk of infection, Cushing's syndrome, adrenal suppression, growth retardation in children, hypokalaemia, hyperglycaemia, depression, irritability, euphoria, psychomotor hyperactivity, aggression, pseudotumor cerebri including papilloedema in adolescents, glaucoma, cataract (including subcapsular cataract), blurred vision, central serous chorioretinopathy (CSCR), increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy), duodenal ulcers, pancreatitis, constipation, allergic exanthema, petechiae, delayed wound healing, contact dermatitis, ecchymosis, muscle and joint pain, muscle weakness and twitching, osteoporosis, osteonecrosis, malaise. **Legal category**: POM. **Cost**: 1mg - pack of 90 - £323; 0.5mg - pack of 60 - £214.80. Not currently available in Ireland. **Product licence holder**: Dr. Falk Pharma GmbH. **Product licence number**: IE/NI: 1mg: EU/1/17/1254/004, 0.5mg: EU/1/17/1254/008. GB: 1mg: PLGB08637/0030; 0.5mg: PLGB08637/0032. **Date of preparation**: February 2023.

Further information is available on request

Adverse events should be reported. In the UK visit www.mhra.gov.uk/yellowcard. In Ireland: https://www.hpra.ie/homepage/about-us/report-an-issue/human-adverse-reaction-form. Adverse events should also be reported to Dr Falk Pharma UK Ltd on pv@drfalkpharma.co.uk or 0044 (0)1628 536600.

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UK--2300074

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If you would like more information about EoE, please email your interest to eoe@drfalkpharma.co.uk

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