NHS
Cheshire and Merseyside

Budesonide orodispersible tablets (Jorveza®) for induction and maintenance of remission in eosinophilic oesophagitis in adults

The Cheshire and Merseyside Area Prescribing Group recommends the prescribing of budesonide orodispersible tablets (Jorveza®), with specialist initiation, for induction and maintenance of remission in eosinophilic oesophagitis in adults

AMBER patient retained by specialist

Budesonide orodispersible tablets (Jorveza®) are licensed for both the induction and maintenance of remission in eosinophilic oesophagitis in adults older than 18 years of age.[1]

Budesonide orodispersible tablets are recommended by NICE as an option for the induction of remission in eosinophilic oesophagitis.[2,3,4] At the time that the NICE technology appraisal was started budesonide orodispersible tablets were only licensed for induction of remission and no recommendations were made for use in the maintenance treatment.

The use of budesonide orodispersible tablets for maintenance of remission in eosinophilic oesophagitis is in accordance with the product licence[1] and national guideline recommendations.[5] It is indicated for patients who have completed a successful 12-week induction course with budesonide orodispersible tablets and for whom ongoing maintenance treatment is considered by the specialist to be clinically appropriate.

Budesonide orodispersible tablets **at a total dose of 1mg daily (0.5mg twice a day) for maintenance of remission** are considered appropriate for prescribing in primary care following specialist initiation. Patients taking budesonide orodispersible tablets will remain under the care of the specialist team.

The prescribing of orodispersible budesonide tablets for the induction of remission is the responsibility of the specialist.

If ongoing maintenance treatment is indicated the specialist will continue to prescribe this and undertake a review after 12 months.

If maintenance with orodispersible budesonide tablets, at a total dose of 1mg daily, is to be continued beyond 12 months then prescribing will be transferred to the patient's GP with annual review by the specialist. If maintenance with orodispersible budesonide tablets at a total dose of greater than 1mg daily is to be continued beyond 12 months then prescribing will be retained by the specialist.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

Budesonide orodispersible tablets (Jorveza®) for induction and maintenance of remission in eosinophilic oesophagitis in adults

Effectiveness

Budesonide is a glucocorticosteroid, its anti-inflammatory action is via binding to the glucocorticoid receptor. It inhibits pro-inflammatory signal molecules in the oesophageal epithelium, which results in a significant reduction of the oesophageal eosinophilic inflammatory infiltrate. Optimal exposure of the oesophageal mucosa to budesonide is key to ensuring efficacy.[1]

Induction of Remission

A double-blind, multicentre, placebo-controlled study (BUL-1/EEA) compared induction treatment with budesonide orodispersible tablet (ODT) with placebo in 88 people with active eosinophilic oesophagitis whose condition was refractory to proton pump inhibitors. Induction treatment with budesonide ODT was given for 6 weeks and if the condition did not go into remission it was extended for another 6 weeks. The primary outcome was clinico-histological remission. The primary outcome was seen in 57.6% of patients (34 out of 59) who had budesonide ODT, and none of the 29 patients on placebo ($p<0.0001$). Similarly, histological remission was seen in 93.2% of patients (55 out of 59) who had budesonide ODT, and none of the patients on placebo ($p<0.0001$).[2]

Maintenance of Remission

A phase-3 double blind randomised placebo-controlled trial (BUL-2/EER) included adults with EoE in clinic-pathological remission. It compared maintenance treatment with either 0.5 mg twice a day or 1mg twice a day orodispersible budesonide with placebo over 48 weeks. At week 48 the primary endpoint was demonstrated in 73.5% (0.5mg twice a day) and 75% (1mg twice a day) patients in the treatment arms compared with 4.4% in the placebo arm. The double-blind period was followed by optional 96-week open-label treatment with either 0.5 mg twice a day or 1 mg budesonide twice a day. More than 80% of the patients maintained clinical remission (defined as weekly Eosinophilic Esophagitis Activity Index-Pro ≤ 20) over the 96-week period, while only 2/166 patients (1.2%) experienced a food impaction. In addition, 40/49 patients (81.6%) maintained deep histological remission (0 eosinophils/mm^2 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 the total period of up to 3 years no loss of efficacy was observed.[6]

Safety

Contraindications

Hypersensitivity to the active substance or to any of the excipients.[1]

Cautions

See SmPC for complete list of cautions.[1]

- Infections - suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. 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.[1]
- 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.[1]

Interactions

- *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.[1]
- *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.[1]
- *Cardiac glycosides*
  The action of glycosides can be potentiated by potassium deficiency which is a potential and known adverse reaction of glucocorticoids.[1]
- *Diuretics*

Concomitant use of glucocorticoids may result in enhanced potassium excretion and aggravated hypokalaemia.[1]

Side effects

See SmPC for complete list of known adverse effects.[1]

- Fungal infections in the mouth, pharynx and the oesophagus were the most frequently observed adverse effects in clinical studies.[1]
- 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. These adverse reactions depend on the duration of treatment, concomitant and previous glucocorticosteroid treatment and the individual sensitivity .[1]
- Angioedema has been reported, mostly as part of allergic reactions which included rash and itching. If signs of angioedema are observed, the treatment should be stopped.[1]
- 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.[1]

Cost[7]

Induction of Remission

Orodispersible budesonide tablets (Jorveza®) 1 mg twice daily for 6 weeks - cost per patient per course (ex VAT)- £301.56

Treatment may be extended to up to 12 weeks if required - cost per patient per course (ex VAT)- £603.12

At the time of NICE TA 708 publication (2021) NICE did not expect this guidance to have a significant impact on resources; that is, the resource impact of implementing the recommendations in England will be less than £9,000 per 100,000 population. This is because the overall incremental cost of treatment is low and eosinophilic oesophagitis is a rare condition affecting around 13,000 people in England.

Maintenance of Remission

Orodispersible budesonide tablets (Jorveza®) 0.5mg twice a day - cost per patient per year (ex VAT) - £2613.40

Orodispersible budesonide tablets (Jorveza®) 1mg twice a day - cost per patient per year (ex VAT) - £2619.88

Cost per annum of £5226.80 - £5239.76 per 100,000 population (two patients per 100,000 in Cheshire & Merseyside).

Patient factors

- 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 and should therefore be monitored for the occurrence of such effects.[1]
- 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.[1]
- 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.[1]
- Pregnancy and breast feeding - administration during pregnancy should be avoided unless there are compelling reasons for treatment. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of foetal development. The relevance of this to man has not been established.[1]

Prescribing information[1]

Induction of Remission

Budesonide 1mg twice daily. The usual duration of induction treatment is 6 weeks. For patients who are not appropriately responding during the 6 weeks, the treatment can be extended to up to 12 weeks.

Maintenance of Remission

Budesonide 1mg daily, as a dose of 0.5mg twice daily, or 1mg at night-time, A higher maintenance dose of budesonide 1mg twice daily is recommended for patients with a long-standing disease history and/or high extent of oesophageal inflammation in their acute disease state. The higher dose of budesonide 1mg twice daily for maintenance treatment would be at the discretion of the specialist and dependent upon individual clinical requirements.

Implementation notes

Prescribing Responsibility

The prescribing of orodispersible budesonide tablets for the induction of remission of EoE, is the responsibility of the specialist.[3,4] Patients who are treated with orodispersible budesonide tablets for induction of remission (6 or 12 week course) will be reviewed by a specialist to determine the need for ongoing maintenance treatment. If ongoing maintenance treatment is indicated, the specialist will continue to prescribe this and undertake a review after 12 months. As part of the review the specialist may re-challenge or recommend a move to a food-elimination diet.

If these measures are ineffective and it is decided that maintenance with orodispersible budesonide tablets is to be continued indefinitely, at a **total daily dose of 1mg**, then at 12 months prescribing will be transferred to the patient's GP with annual review by the specialist. The annual review will include a decision about whether treatment is to continue or stop. Communication from the specialist to the GP should contain clear information about dose and frequency. Patients will remain under the care of the specialist and the GP should contact the specialist if there are any concerns about adverse effects or a loss of efficacy.

If orodispersible budesonide tablets is to be continued indefinitely at a **total daily dose of more than 1mg**, then prescribing will be retained by the specialist.

Method of administration

Patients should be counselled by the specialist on how to administer orodispersible budesonide tablets. The details below are included in the product patient information leaflet.[9]

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 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 orodispersible budesonide tablets. The orodispersible tablet should not be chewed or swallowed undissolved.[1]

Risk of systemic side effects

The British Society for Gastroenterology makes the following recommendation in its Consensus Guidelines on Eosinophilic Oesophagitis: Systemic side effects of topical steroids have not been documented during the long- term treatment of patients with eosinophilic oesophagitis; continued monitoring of bone mineral density and adrenal suppression is recommended in children and adolescents. This recommendation is supported by safety data from a 48 week follow-up study of 136 patients treated with budesonide orodispersible tablets,[5] a 96 week follow up study of 166 patients[9] and experience of 230,000 treatment cycles (1mg twice a day) with no changes in the spectrum of potential systemic side effects.[10]

Patients receiving orodispersible budesonide tablets will be provided with a blue steroid card and an emergency steroid card by the specialist centre. The necessity for sick day rule advice will be considered on a case-by-case basis taking into consideration any other steroid treatments the patient may be prescribed.[11] Blue steroid cards, emergency steroid cards and any required sick day rule advice will be provided by the specialist centre.

Steroid treatment should be initiated and reviewed in accordance with the National Patient Safety Alert (2020) .[12] If any further steroid medication is prescribed, it is the responsibility of the initiating prescriber of that treatment to consider whether sick day rule advice is required, taking into consideration any other steroid treatments the patient may be prescribed, including orodispersible budesonide.

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