Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2158

budesonide 1mg orodispersible tablets (Jorveza®)

Dr Falk Pharma UK Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

budesonide (Jorveza®) is accepted for restricted use within NHSScotland.

Indication under review: Treatment of eosinophilic oesophagitis (EoE) in adults (older than 18 years of age).

SMC restriction: For patients unsuccessfully treated with proton pump inhibitors.

One randomised, double-blind phase III study, demonstrated superiority of budesonide over placebo in inducing clinico-histologic remission in adult patients with EoE, refractory to treatment with a proton pump inhibitor.

The case presented to SMC was for induction of remission. The marketing authorisation for budesonide (Jorveza®) has subsequently been extended to include maintenance of remission. SMC does not plan to assess this licence extension.

Chairman
Scottish Medicines Consortium

Indication

Treatment of eosinophilic oesophagitis (EoE) in adults (older than 18 years of age).[1]

Dosing Information

Induction of remission

The recommended daily dose is 2mg budesonide as one 1mg tablet in the morning and one 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.

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 dissolve. This will usually take about two minutes. The dissolved material should be swallowed with saliva 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 budesonide. The orodispersible tablet should not be chewed or swallowed undissolved. These measures ensure optimal exposure of the oesophageal mucosa to the active substance.

The treatment with this medicinal product should be initiated by a physician experienced in the diagnosis and treatment of eosinophilic oesophagitis. [1]

Product availability date

September 2018.
Budesonide has been designated an orphan medicine for EoE by the European Medicines Agency (EMA).

Summary of evidence on comparative efficacy

Budesonide is a well-known non-halogenated glucocorticosteroid, which acts primarily as an anti-inflammatory via binding to the glucocorticoid receptor. In the treatment of eosinophilic oesophagitis (EoE), budesonide inhibits antigen-stimulated secretion of many pro-inflammatory signal molecules such as thymic stromal lymphopoeitin, interleukin-13 and eotaxin-3 in the oesophageal epithelium, which results in a significant reduction of the oesophageal eosinophilic inflammatory infiltrate.[2]

The submitting company has requested that SMC consider budesonide orodispersible tablet (ODT) when positioned for use for the treatment of patients with a diagnosis of EoE and prior unsuccessful treatment with proton pump inhibitors (PPIs), such as omeprazole or lansoprazole.

The key evidence supporting the efficacy and safety of budesonide ODT comes from BUL-1/EEA, a multi-centre, randomised, double-blind, placebo-controlled, parallel group phase III study. The study recruited patients aged 18 to 75 years with clinico-histologic active EoE, refractory to

treatment with a PPI (at least standard doses for a 4 week period). Patients had to have a severity of ≥4 points on a 0 to 10 numerical rating scale (NRS) for either dysphagia or odynophagia for ≥1 day in the week before randomisation, Patient's Global Assessment (PatGA) of EoE activity ≥4 points on a 0 to 10 NRS and peak eosinophils (eos) ≥65/mm^2 per high power field (hpf) in at least one hpf, as measured in a total of six hpfs derived from six biopsies, two each from the proximal, mid, and distal segments of the oesophagus.[2]

Patients were randomised in 2 to 1 ratio to receive budesonide ODT 1mg twice daily (n=59) or placebo (n=29) for 6 weeks.[2]

The primary outcome was the rate of patients with clinico-histologic remission at the end of treatment (EoT), defined by peak eosinophil count <16 eos/mm^2 hpf at EoT, and resolution of symptoms (no or only minimal problems) defined as a severity of ≤2 points on 0 to 10-point NRS for dysphagia and odynophagia on each day in the week prior to EoT. In addition, any patient in need of endoscopic intervention (for example for food impaction or dilation) or premature study discontinuation was counted as a treatment failure. The primary outcome was assessed for all randomised patients who received at least one dose of study treatment during the double blind phase (intention to treat [ITT] analysis). The primary outcome was achieved in 58% (34/59) of patients receiving budesonide ODT, compared with 0% (0/29) of patients receiving placebo (p<0.001).[2]

Key secondary outcomes are shown in Table 1. A hierarchical statistical testing strategy was applied for the secondary outcomes with no formal testing of outcomes after the first non-significant outcome. The first four (including the two components of the primary outcome) showed significant superiority of budesonide ODT over placebo (p<0.001). Other secondary outcomes are descriptive only.[2]

Table 1: Key secondary endpoints (ITT population)

Key secondary endpoints		Budesonide 1mg twice daily (n=59)	Placebo (n=29)
1. Rate of patients with histological remission at week 6 (LOCF)	% (n)	93% (55/59)	0%* (0/29)
2. Change in the peak eos/mm^2 hpf from baseline to week 6 (LOCF)	Mean (SD)	-225.5 (150.37)	-4.3* (135.64)
3. Rate of patients with resolution of symptoms on each day in the week prior to week 6 (LOCF)	% (n)	59% (35/59)	14%* (4/29)
4. Rate of patients with a total weekly EEsAI-PRO score of ≤20 at week 6 (LOCF)	% (n)	51% (30/59)	6.9%* (2/29)
5. Rate of patients with an improvement from baseline to week 6 (LOCF) in the weekly VDQ score	% (n)	51% (30/59)	38% (11/29)
6. Rate of patients with an improvement from baseline to week 6 (LOCF) in the weekly AMS score	% (n)	12% (7/59)	10% (3/29)

*p<0.001 for budesonide versus placebo; LOCF=last observation carried forward; eos=eosinophils; EEaSI-PRO=eosinophilic oesophagitis activity index patient-reported outcome; VDQ=visual dysphagia question, AMS=avoidance modification and slow eating.

Quality of life (QoL) was assessed using both a modified Short Health Scale (modSHS, range 0 to 100 with lower values indicating better quality of life) and a disease-specific EoE-QoL-A questionnaire. All dimensions of the modSHS and all subscales of the EoE-QoL-A improved from baseline to week 6 with budesonide ODT, the difference was statistically significant for budesonide ODT versus placebo for two of the four modSHS dimensions (social function and disease-related worry), and two of the five EoE-QoL-A sub-scores (eating/diet impact 10-item and 4-item subscales). Overall, the study did not show consistent improvement across all QoL outcomes for budesonide ODT compared with placebo. The EMA concluded that the results do not permit clear conclusions on QoL improvement and noted that this may be due to the observation time being too short.[2]

At the end of the double-blind phase, non-responders (clinical or histological) could enrol in a 6-week open-label treatment phase with budesonide ODT. At the end of this open-label phase, 70% (16/23) of patients originally assigned to the budesonide group and 79% (22/28) of patients originally assigned to placebo achieved clinico-histologic remission. The results indicate that the treatment effect is maintained for up to 12 weeks.[2]

Supportive evidence comes from a randomised, double-blind, placebo-controlled, dose-finding phase II study (BUU-2/EEA) in 76 adults with active EoE. Patients were randomly allocated to 2 weeks of treatment with either budesonide ODT 1mg twice daily (ODT1, n=19), budesonide ODT 2mg twice daily (ODT2, n=19), budesonide oral viscous suspension (OVS) 2×5 mL (0.4mg/mL)/day (OVS, n=19) or placebo (n=19). The two co-primary outcomes were the rate of histological remission (defined as a mean of <16 eos/mm^2 hpf) at week 2 and the change in the mean numbers of eos/mm^2 hpf (eosinophil load) from baseline to week 2. At this time-point, histological remission occurred in 100% (19/19), 95% (18/19) and 95% (18/19) of budesonide ODT1, ODT2 and OVS groups, respectively and in 0% (0/19) of the placebo group (p<0.001). The change in mean numbers of eos/mm^2 hpf were -120, -128, -97 in the budesonide ODT1, ODT2 and OVS groups respectively and -8 in the placebo group (all comparisons yielding to p<0.001 for all comparisons versus placebo). The study failed to determine any difference between the tested doses of budesonide ODT, which appeared equally effective.[2, 3]

The submitting company presented a network meta-analysis (NMA) that included five studies and compared budesonide ODT, budesonide OVS, fluticasone and six-food elimination diet (SFED) for the outcome of histological remission in adult patients with EoE. The submitting company concluded that despite the differences between studies, the NMA demonstrated that budesonide ODT has greater efficacy than the comparators. However, the credible intervals were wide and included one, indicating uncertainty in the results.

Summary of evidence on comparative safety

In the BUL-1/EEA study, during the double-blind phase, treatment-emergent adverse events (TEAE) were reported by 63% (37/59) of patients in the budesonide ODT group and 41% (12/29) in the placebo group and these were considered treatment-related in 39% (23/59) and 3.4% (1/29) respectively. No serious adverse events (AEs) were reported in either group.

The most frequently reported TEAEs of any grade, in the budesonide ODT group (n=59) versus the placebo group (n=29) were: suspected local fungal infection (24% [including candida infection [3.4%], oesophageal candidiasis [17%], oral candidiasis [3.4%] and oropharyngeal candidiasis [5.1%]] versus 0%), pharyngitis (1.7% versus 6.9%), headache (6.8% versus 3.4%), blood cortisol decreased (5.1% versus 0%), GORD (5.1% versus 0%), nasopharyngitis (3.4% for both groups), hypertension (3.4% versus 0%), nausea (3.4% versus 0%), asthma (0% versus 3.4%).[2, 4]

Overall, the EMA concluded that the safety profile of budesonide ODT was acceptable, since the risk of systemic effects was identified as being low.[2]

Summary of clinical effectiveness issues

EoE is a chronic, local immune-mediated oesophageal disease, characterized clinically by symptoms related to oesophageal dysfunction (including solid food dysphagia, food impaction, and non-swallowing associated chest pain) and histologically by eosinophil-predominant inflammation.[5] The disease has a considerable influence on QoL, and a risk of long-term complications such as oesophageal fibrosis, food impaction and oesophageal strictures and subsequent need for oesophageal dilation manoeuvers.[2] Current treatment (off-label) includes PPIs, swallowed topical corticosteroids (fluticasone propionate or budesonide) or elimination dietary therapy (including an empiric six-food group elimination diet [SFED] which involves avoiding the six types of foods most commonly associated with allergy). PPI therapy is established practice and is often used as first-line treatment, with topical corticosteroids or dietary therapy used in patients unresponsive to PPI. Budesonide ODT is the first medicine to be licensed in the UK for the treatment of EoE and it is an EMA designated orphan medicine. Clinical experts consulted by SMC considered that budesonide ODT fills an unmet need for an adequately formulated treatment.

The submitting company has requested that SMC consider budesonide ODT in patients with a diagnosis of EoE and prior unsuccessful treatment with PPIs, such as omeprazole or lansoprazole.[5]

The phase III study (BUL-1/EEA) showed significant superiority of budesonide ODT over placebo in inducing the primary outcome of clinico-histologic remission after 6 weeks of treatment in a population refractory to PPI therapy. An open-label extension study indicated that the treatment effect was maintained up to 12 weeks.[2]

There was no evidence presented on the impact of budesonide ODT treatment on complications such as food impaction, fibrosis or development of stenosis and there was limited evidence of an improvement in quality of life. Subgroup analyses suggested that remission was more difficult to achieve for patients with a longer time since first symptoms and those with a history of any dietary therapy.[2]

The secondary outcomes of improvement in VDQ score and in AMS score were descriptive only. These evaluate food avoidance behaviours and are also part of the total EEsAI-PRO score. The EMA noted that the study may have been too short to address the effects of budesonide ODT treatment on food avoidance behaviours.[2]

Only a small number of patients (8%, n=7) in the study received concomitant therapy with a PPI and budesonide, so the effect of combination treatment is uncertain.

The submitting company conducted an NMA to compare budesonide ODT with budesonide OVS, fluticasone and SFED. Of these, only fluticasone and SFED were included in the economic analysis. The NMA population was broader than the population of the proposed positioning and BUL-1/EEA was the only study that included patients who had failed a previous trial with PPIs. There was a high level of clinical and methodological heterogeneity across studies with regards to study design including in the definition of outcomes, duration of treatment and baseline characteristics. The credible intervals of the calculated odds ratios were extremely wide and are likely to be a result of the limitations of the NMA including the weaknesses in the evidence for the off-label comparators.

Budesonide ODT may have an advantage over currently used treatments in that it may avoid off-label use of fluticasone propionate metered-dose inhaler or an unlicensed preparation of budesonide. It may have an advantage over elimination diet (such as SFED), as it could have less impact on the patient's life style.[5]

Clinical experts consulted by SMC considered that budesonide ODT is a therapeutic advancement as it the first treatment specifically designed for this condition, with evidence showing it is highly effective in improving symptoms without excessive side effects, and constituting an adequate formulation with optimum drug delivery to the oesophageal mucosa. They also considered that the place in therapy of budesonide ODT is for patients with proven diagnosis of EoE after initial treatment with PPI.

Summary of comparative health economic evidence

An economic evaluation was presented evaluating the treatment of budesonide ODT in its licensed indication, with an additional restriction to patients with confirmed EoE, defined by >15 eos/hpf, who have been treated with PPIs prior to diagnosis of EoE. Budesonide ODT was compared with off-label fluticasone (Flixotide® Evohaler®) as a medicinal comparator, with the SFED also included as a non-medicinal comparator.

A seven-state Markov state transition model was used, representing active disease ('EoE active') and remission ('EoE remission') for three lines of treatment, plus an absorbing state of death. Active disease was defined using criteria for histological remission (defined as a mean of <16eos/mm^2 hpf after a cycle of treatment). Patients were assumed to only receive treatment and monitoring for EoE within the 'active' health states. However, it is worth noting that only one line of active treatment was assumed, with patients entering subsequent health states receiving 'no treatment'. A perspective of NHS and social work was taken, a 12-week cycle length used and a 40-year time horizon was applied in the base case.

Clinical data for budesonide ODT were derived from a secondary endpoint of the BUL-1/EEA study (histological remission), and odds-ratios for the comparators obtained from a random-effects NMA, which is described earlier in the DAD. The results of the NMA led to an assumption of varying proportions of patients responding per cycle (budesonide ODT: 94.9%; fluticasone: 68.1%; SFED: 18.5%; 'no treatment': 4.2%). Relapse rates from the remission state were assumed to be independent of treatment received, at 22.0% per cycle. In the absence of utilities for EoE, a published source was used reporting EQ-5D-derived utilities from patients with gastro-oesophageal reflux disease ('active EoE': 0.7) as well as applying population utilities for patients aged 45 – 54 years ('EoE in remission': 0.85). [6,7] Age-related disutility (declining over the time horizon) was not applied.

Medicines acquisition costs were included for budesonide ODT and fluticasone. Costs of AE management were also included. The dose and duration of treatment for budesonide ODT was assumed equivalent to the clinical trial, with a weighted proportion of patients who received 6 weeks (57.6%) versus 12 weeks (42.4%) of treatment; an assumption was used of 12-weeks treatment with fluticasone, and the mid-point of the licensed dose range for asthma was applied (550 micrograms). Costs of gastroenterology outpatient visits, endoscopy plus biopsy, dietician visits (SFED only), and add-on dilation/emergency food bolus removal were applied in the 'active EoE' health state, with an assumption of no costs in the 'EoE remission' health state.

The base case results are shown Table 2. The main driver of additional costs were acquisition costs of budesonide ODT, while cost-savings were predominantly due to the reduced costs of gastroenterology visits, endoscopies and add-on dilation/emergency food bolus removals.

Table 2: Base case results

	Budesonide ODT	**Fluticasone**	**SFED**
Total costs	£27,528	£31,985	£32,850
Total QALYS	16.12	15.30	15.14
ICER	N/A	Dominant*	Dominant*

*Budesonide is estimated to increase health benefits, at a lower total cost, versus the comparator.
ODT=orodispersible tablets; SFED=six food elimination diet; QALYs=quality-adjusted life years; ICER=incremental cost-effectiveness ratio.

A summary of key scenario analyses is presented in Table 3.

Table 3: Key scenario analyses

#	Scenario		ICER vs fluticasone	ICER vs SFED
	Base case assumption	**Scenario assumption**		
1.	No subsequent treatment	Fluticasone after SFED; SFED after budesonide ODT/fluticasone	Dominant	Dominant
2.	Duration of budesonide ODT: 57.6% 6 weeks, 42.4% 12 weeks	Duration of budesonide treatment: 12 weeks	Dominant	Dominant
3.	Random-effects NMA	Random-effects with continuity correction	Dominant	Dominant
4.	Response defined by histological remission alone (94.9%)	Response defined as histological and clinical remission (84.7%)	Dominant	Dominant
5.	No outpatient consultations or endoscopy in remission state	0.46 consultations and 0.23 endoscopies per cycle	Dominant	Dominant
6.	As base case	Combination of scenarios 1 - 5	£6,496	£7,235

SFED= six food elimination diet; ODT= orodispersible tablets; NMA=network meta-analysis

The submission was subject to a number of limitations:

- The estimates of relative effectiveness rely upon an indirect treatment comparison, the results of which are uncertain. However, a probabilistic sensitivity analysis, which reflects variation across the credible intervals, results in consistent estimates to the base case deterministic analysis.
- Feedback from two Scottish clinical experts received by the submitting company suggests that patients may still require ongoing clinical follow-up and endoscopies in the remission health state, despite the company's assumption of no ongoing costs. Application of these costs will result in increased healthcare use and costs versus the company's base case. However, the ICER remains dominant when this alternative assumption is applied (Scenario 5).

- The use of one treatment line may not be representative of clinical practice. An alternative scenario, where patients are assumed to receive SFED or fluticasone depending on their initial treatment, may be more appropriate and would lead to improved estimates of health benefit for the comparators (Scenario 1).
- The rate of clinico-histologic remission at week 12 was lower than histological remission alone (84.7% versus 93.2%), suggesting that the benefits of budesonide may be overstated (Scenario 4).
- Differing assumptions regarding the duration of treatment with budesonide ODT versus fluticasone may bias the results in favour of budesonide. An equal assumption of 12-weeks treatment for both treatments is more appropriate (Scenario 2).

Although the limitations described above result in consistent ICER estimates to the base case, a more conservative combination of these scenarios could be plausible. Although budesonide ODT is no longer dominant relative to the comparators, the ICER remains low for this combined scenario (Scenario 6). The economic case has been sufficiently demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Guts Charity UK and the EOS Network, which are both registered charities.
- Guts Charity UK has received 1.76% pharmaceutical company funding in the past 2 years, including from the submitting company. The EOS Network has not received any pharmaceutical company funding in the past 2 years.
- EoE results in inflammation and narrowing of the oesophagus leading to dysphagia, obstruction, eating difficulties and pain. This condition has an impact emotionally, socially, physically and financially to the patient and their family/carers. Often a sufferer's diet can become extremely restricted whilst trying to discover safe foods. This becomes impossible for some to manage whilst others will withdraw from social activities in order to maintain their restrictions.
- There are currently no treatments licensed for EoE. Some medications are prescribed off-label such as PPIs and corticosteroids. Most patients consulted by the patient groups found PPIs to be ineffective. More patients were satisfied with fluticasone (swallowed puffs from an inhaler) and budesonide (as a viscous slurry) but 25% had difficulties following instructions, as they are different for EoE treatment than standard use (asthma) for these medications.

- Budesonide ODT would provide a simple effective treatment that could dramatically increase the chance of compliance. It could help to reduce the need for: restricted diets and elemental tube feeding, A&E visits due to food bolus obstructions and the need for stretching of the oesophagus due to long term stricture damage.
- Introduction of budesonide ODT would also support a standardised treatment pathway for patients with EoE which could reduce stress and anxiety. A survey conducted by one of the patient groups found it improved symptoms and quality of life for 8 out of the 10 users.
- In summary, budesonide ODT offers faster symptom control and the opportunity to improve the lives of people with EoE.

Additional information: guidelines and protocols

European guidelines, published in 2017, propose evidence-based recommendations for EoE diagnosis, treatment modalities, and patients' follow up. PPIs, topical corticosteroids (fluticasone propionate or budesonide) or elimination dietary therapy (including SFED) might be offered as first line anti-inflammatory therapy. Due to its safety profile, ease of administration and high response rates, PPI therapy is often used as first-line treatment although the choice of therapy should be individually discussed with the patient. Treatment might be potentially changed over time in case of absence of remission, due to treatment side effects or the unwillingness of the patients to continue the medication (topical steroids) or negative impact on quality of life and family resources (dietary intervention). Long-term therapeutic strategy and best maintenance doses for pharmacologic therapies are yet to be defined. Endoscopic dilation should be considered in patients with dysphagia/food impaction unresponsive to anti-inflammatory treatment.[5]

Additional information: comparators

No licensed comparators.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Budesonide ODT 1mg	**1mg twice daily for 6 to 12 weeks**	**301 to 602**

Costs from BNF online on 02 June 2020. Costs calculated for 6-week and 12-week treatment course.

Additional information: budget impact

The submitting company estimated that the population eligible for treatment would be 655 patients each year, to which confidential uptake rates were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

References

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6. Kartman B, Gatz G, Johannesson M. Health state utilities in gastroesophageal reflux disease patients with heartburn: a study in Germany and Sweden. Med Decis Making. 2004;24(1):40-52. Epub 2004/03/10.

7. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. University of York Discussion Paper. 1999;172.

This assessment is based on data submitted by the applicant company up to and including 13 August 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive

access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.