AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence summary report for a limited assessment

Budesonide (Jorveza®) 0.5 mg and 1 mg orodispersible tablets

Indication
Maintaining remission of eosinophilic oesophagitis in adults.

Company
Dr Falk Pharma UK Ltd

Background
Jorveza® is an orodispersible budesonide tablet (from here, orodispersible budesonide) which was licensed for inducing remission of eosinophilic oesophagitis (EoE) in adults in January 2018. In June 2020, the license was extended to include maintenance of EoE remission in adults (SmPC).

In 2020, AWMSG issued a statement of advice for orodispersible budesonide, indicating that its use within NHS Wales to maintain remission of EoE in adults could not be endorsed due to the company not providing a submission. AWTTC subsequently received requests from two health boards to review this statement of advice. Clinical experts from Cardiff and Value University Health Board (CAVUHB) submitted a medicines request form to AWTTC. The AWMSG Scrutiny Panel concluded that a limited assessment would be appropriate, and the company has now provided a submission.

EoE is a chronic inflammatory condition of the oesophagus which is increasing in prevalence (British Society of Gastroenterology [BSG] and British Society of Paediatric Gastroenterology, Hepatology and Nutrition [BSPGHAN] joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults, 2022). EoE is diagnosed in patients with relevant oesophageal symptoms (e.g. dysphagia and/or food bolus obstruction) and a peak eosinophil count of ≥ 15 eosinophils (a type of white blood cell) per 0.3 mm^2 on oesophageal biopsy (BSG/BSPGHAN guidelines). In 2021, the estimated prevalence and annual incidence rates in England and Wales are 12.8 and 2.07 per 100,000 population, respectively (NICE Technology Appraisal 708 committee papers). However, evidence suggests that the prevalence of EoE is increasing globally (Hahn et al., 2023).

Guidance and recommendations
The BSG/BSPGHAN guidelines recommend dietary or pharmacological interventions to induce remission of EoE in adults. Pharmacological therapies include proton pump inhibitors (PPI) and topical corticosteroids, including orodispersible budesonide. Although other topical, swallowed corticosteroid formulations (such as inhaled corticosteroids and oral viscous budesonide, also referred to as budesonide slurry) are referenced in the BSG/BSPGHAN guidelines, orodispersible budesonide tablets are recommended to induce remission of EoE in adults because of its licensed status (there are no alternative UK-licensed oral treatment options available). Given the high risk of relapse following withdrawal of topical corticosteroids, the

BSG/BSPGHAN guidelines also recommend orodispersible budesonide for maintenance of remission of EoE in adults, in preference to other formulations.

In 2021, NICE recommended orodispersible budesonide for inducing remission of EoE in adults. When the appraisal started, orodispersible budesonide was only licensed for inducing EoE remission. Therefore, NICE did not make recommendations for maintenance treatment. NICE have guidance awaiting development for orodispersible budesonide for maintaining remission of EoE in people aged 2 years and over. Although the publication date has yet to be confirmed, [commercial in confidence text removed].

Orodispersible budesonide is accepted for restricted use in NHS Scotland for the induction of EoE remission in adults; restricted to patients unsuccessfully treated with PPIs. The case presented to the Scottish Medicines Consortium (SMC) was for induction of remission. SMC do not plan to assess the licence extension for maintenance treatment.

Orodispersible budesonide is not commissioned for maintenance treatment of EoE by NHS England. However, the submitting company advises AWTTC that some regions (Integrated Care Boards) have made orodispersible budesonide available for maintaining remission of EoE, including NHS Cheshire and Merseyside, and NHS North East and North Cumbria.

In Wales, orodispersible budesonide for maintaining remission of EoE in adults is associated with a non-formulary status in all health boards except for Swansea Bay University Health Board (SBUHB). SBUHB's formulary states that the treatment can be offered to patients that experience relapses following multiple induction courses. However, intelligence gathered by AWTTC reveals that clinicians in all health boards across NHS Wales prescribe orodispersible budesonide as maintenance treatment of EoE in adults to varying extents, despite its non-formulary status and AWMSG's statement of advice.

Supply arrangements differ between health boards. In some areas, the medicine is prescribed mainly via WP10(HP) prescriptions, while in others prescribing takes place mainly via GPs. In two health boards, requests for maintenance treatment with orodispersible budesonide need to be made via Individual Patient Funding Requests.

Technology

For maintaining EoE remission, the licensed dose of orodispersible budesonide is 0.5 mg or 1 mg twice daily, with the higher dose recommended for patients with long standing disease history and/or a high extent of oesophageal inflammation in their acute disease state (SmPC). According to clinicians, there is emerging data to support the use of orodispersible budesonide 1 mg once daily for maintaining remission of EoE. As the scope of this assessment is the licensed posology, only the licensed doses are considered in this report, except for the Budget Impact section.

The duration of maintenance therapy is determined by the physician (SmPC). According to a clinical expert, long-term maintenance with orodispersible budesonide would be the preferred treatment for patients who are inducted successfully, unless patient preference or side effects warranted a change in treatment.

Currently, orodispersible budesonide is not licensed for any other indications beyond EoE treatment in adults.

Marketing authorisation date: January 2018.
Date of licence extension: June 2020.

Criteria for limited assessment

The AWMSG Scrutiny Panel reviewed the request for the assessment of orodispersible budesonide and considered it was suitable for a limited assessment via the Licensed One Wales Medicines Assessment Group (LOWMAG). They cited the following reasons for this decision:

- The medicine is recommended for maintaining remission of EoE in BSG/BSPGHAN guidelines.
- Although the budget impact appears high (cost-incurring) from a medicines acquisition perspective, this is likely to be an overestimate as the treatment is already being prescribed to patients across NHS Wales.
- Although NICE health technology appraisal of the treatment is likely, patients in Wales would benefit from interim advice.

As the guideline is a consensus guideline as opposed to a NICE guideline, the AWMSG Scrutiny Panel agreed that the limited assessment should consider the evidence for clinical effectiveness in addition to the budget impact of the treatment.

Comparator(s) and place in pathway

In line with the BSG/BSPGHAN guidelines, the majority of NHS Wales clinicians consulted by AWTTC offer a dietary intervention, or a pharmacological intervention with either off-label PPI therapy or orodispersible budesonide to treat EoE in adults. Dietary interventions involve food exclusion under supervision of an experienced dietician for 8-12 weeks. Clinicians report that dietary interventions are challenging and require access to expert dietitians. Therefore, PPI therapy and orodispersible budesonide are associated with a higher uptake.

Specific prescribing practices in EoE vary between clinicians and across health boards. However, clinicians have reported that orodispersible budesonide is used for both induction and maintenance of EoE remission across NHS Wales with more frequent use in severe cases of EoE. In one health board, approximately 30% and 70% of their patients present with mild inflammation versus severe symptoms, respectively. Approximately 65% of patients with mild inflammation receive induction and maintenance treatment with a PPI, and 27% receive orodispersible budesonide. The remaining patients pursue dietary intervention. Most patients (95%) presenting with severe symptoms such as food bolus obstruction or endoscopically confirmed strictures are prescribed orodispersible budesonide for induction and maintenance treatment.

If orodispersible budesonide was unavailable to maintain remission of EoE, some clinicians have said that no maintenance treatment would be prescribed; re-induction with orodispersible budesonide could be used in relapsing patients. One clinician

noted that they would consider inhaled fluticasone in this scenario. However, it should be noted that these views aren't reflective of current practice, as orodispersible budesonide is currently prescribed by clinicians across NHS Wales for maintaining remission of EoE.

Clinical effectiveness evidence

The following studies provide evidence on the use of orodispersible budesonide for treating EoE. The first study presents data on induction therapy, included to provide context on the treatment's efficacy during induction. The remaining studies evaluate its use in the maintenance setting.

Efficacy of budesonide orodispersible tablets as induction therapy for eosinophilic esophagitis in a randomised placebo-controlled trial (BUL-1 study)
Lucendo, et al. (2019)

In this double-blind, placebo-controlled study, 88 people with active EoE were randomised to receive orodispersible budesonide at a dose of 1 mg twice daily (n=59) or placebo treatment (n=29) for 6 weeks. All patients were refractory to PPI treatment at standard doses. Clinico-histologic remission was achieved in 57.6% and 0% of patients in the treatment and placebo groups respectively ($p<0.0001$). Histological remission was achieved in 93.2% and 0% of patients in the treatment and placebo groups, respectively ($p<0.0001$).

Budesonide orodispersible tablets maintain remission in a randomised, placebo-controlled trial of patients with eosinophilic esophagitis (BUL-2 study)
Straumann et al. (2020)

In this phase 3, double-blind randomised placebo-controlled trial, EoE patients (n=204 adults) in clinical and histologic remission were randomly assigned to receive orodispersible budesonide 0.5mg twice daily (n=68), 1 mg twice daily (n=68), or placebo twice daily (n=68) for up to 48 weeks. The use of other topical corticosteroids, systemic glucocorticoids, immunosuppressants, biologic drugs, or onset of dietary restrictions was not permitted. Concomitant treatment with PPIs at stable dosages was permitted throughout the trial.

The primary outcome was remission at week 48, that is, the rate of patients who did not fulfil any of the following criteria: clinical relapse, histological relapse, food impaction requiring endoscopic intervention, the need of an endoscopic dilation, or premature withdrawal for any reason.

At 48 weeks, 73.5% of patients receiving orodispersible budesonide at a dose of 0.5 mg twice daily, and 75% receiving a dose of 1 mg twice daily were in persistent remission compared with 4.4% of patients in the placebo group ($p<0.001$ for both comparisons of orodispersible budesonide versus placebo). The median time to relapse in the placebo group was 87 days; 50% of patients in the placebo group relapsed within 3 months. Health-related quality of life measured using the EoE-QoL-A questionnaire significantly improved in all domains with orodispersible budesonide treatment but deteriorated with placebo.

Efficacy and safety of budesonide orodispersible tablets for eosinophilic esophagitis up to 3 years: An open-label extension study
Biedermann et al. (2025)

A total of 186 patients from the 48-week BUL-2 study participated in a 96-week open-label extension (OLE) study and received orodispersible budesonide at a dose of either 0.5 mg twice daily or 1 mg twice daily. The high rates of clinical remission reported in the BUL-2 study were maintained. At 96 weeks, 81.9% of patients were in clinical remission (EoE Symptom Activity Index score of ≤20) versus 77.7% at OLE baseline, and 80.1% patients were in histological remission (peak eosinophils per high power field <5) versus 91.8% at OLE baseline. Mean EoE-QoL-A scores improved from 3.3 at OLE baseline to 3.5 at week 96.

Safety
In the clinical studies assessing orodispersible budesonide for maintaining remission of EoE, localised candidiasis was the most frequently reported adverse event. This aligns with the SmPC for orodispersible budesonide, which lists oesophageal candidiasis, oral and/or oropharyngeal candidiasis as a 'very common' adverse event (affecting ≥ 1/10). In the BUL-2 study, clinically manifested candidiasis was suspected in 16.2% and 11.8% of patients in the orodispersible budesonide 0.5 mg group and 1 mg group, respectively. All infections resolved with treatment. Four patients developed low cortisol levels with orodispersible budesonide treatment, without symptoms of adrenal insufficiency.

The most common adverse drug event in the OLE study was localised candidiasis, which was suspected (and resolved with treatment) in 18.3% of patients. Decreased blood cortisol was recorded in 3.2% of patients. However, each case was mild and did not require treatment interruption, and no clinical symptoms of adrenal insufficiency were reported.

Overall, favourable remission rates reported in the BUL-2 and OLE studies suggests that orodispersible budesonide is a clinically effective treatment for maintaining remission of EoE in adults. The adverse events reported by both studies were generally mild and consistent with the known safety profile of orodispersible budesonide, suggesting that it is generally a tolerable treatment for maintaining remission of EoE.

Budget impact

The company estimate for the budget impact (BI) is given in Table 1. The company have used a prevalence of 42.49 per 100,000 and incidence of 4.16 per 100,000 to estimate the number of people with EoE in Wales as 1,186, based on Hahn et al. (2023). The company estimate that all 1,186 patients would be eligible for orodispersible budesonide treatment to maintain remission of EoE, and an annual 3% increase to the size of the eligible patient population, as per Lam et al. (2023). The company have assumed a 10% uptake in Year 1 rising to 40% in Year 5. The comparators were swallowed fluticasone from a Flixotide 50micrograms/dose Evohaler, six-food elimination diet, and no treatment.

Table 1. Company model: budget impact estimate for orodispersible budesonide for maintaining remission of EoE in adults in NHS Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	1,186	1,221	1,257	1,294	1,333
Uptake of ODB maintenance treatment (%)	10%	15%	20%	30%	40%
Number of patients receiving ODB maintenance treatment	119	183	251	388	533
Medicine acquisition costs in a market without ODB maintenance treatment	£214,785	£221,123	£227,643	£234,343	£241,406
Medicine acquisition costs in a market with ODB maintenance treatment	£476,837	£634,093	£800,196	£1,127,240	£1,485,922
Net medicine acquisition costs for ODB maintenance treatment	**£262,052**	**£412,970**	**£572,553**	**£892,897**	**£1,244,516**
ODB; orodispersible budesonide					

The company have used data from a retrospective study by Runge et al. (2017) and the BUL-2 study to estimate that patients receiving orodispersible budesonide for maintenance treatment experience 1.3 fewer food bolus obstructive dilations versus placebo-treated patients per year. Additionally, the company assumed that patients receiving orodispersible budesonide for maintaining remission of EoE need fewer elective endoscopic biopsies. Using NHS England HRG codes, the company estimates that reduced interventions in budesonide-treated patients versus patients treated with comparator therapies would lead to cost savings of £287,884 in Year 1 (119 patients) and £1,249,263 in Year 5 (533 patients).

Critique of company BI model

- AWTTC agree that orodispersible budesonide is a cost-incurring treatment option for this indication.
- Clinician engagement indicates that, in the absence of orodispersible budesonide to maintain remission of EoE, treatment options in NHS Wales would include both swallowed fluticasone from an inhaler, or no maintenance treatment (with re-induction(s) with orodispersible budesonide where required). The medicine acquisition cost of re-induction with orodispersible budesonide has not been considered in the company's BI model. The annual medicine acquisition costs of fluticasone therapy (at the dose used in the company's BI) and re-induction with budesonide are comparable (see Appendix 2 for details).
- The company did not assign a cost for the management of adverse events associated with orodispersible budesonide and the fluticasone comparator. While management of adverse events (e.g. oral thrush) is expected to incur some cost, these costs are likely to be comparable between the two treatments. The company did not apply monitoring costs in their BI model.

- Feedback from clinicians support the company's assumption that maintenance treatment with orodispersible budesonide would reduce the requirement for dilatations and endoscopies, thereby reducing secondary and tertiary care resource costs. One clinical expert estimated that, locally, emergency food bolus obstruction dilations are required in an estimated 10% of patients in non-remission and 0% of patients in remission. However, the company's estimated cost savings are subject to uncertainty as they're derived from the extrapolation of trial data. In the absence of data relating specifically to NHS Wales, the company's estimated cost savings are difficult to validate.
- AWTTC considers the number of eligible patients in the company's model to be overestimated. The BI model assumes that all prevalent patients are eligible for maintenance treatment with orodispersible budesonide. However, clinician feedback indicates that not all prevalent patients are inducted with orodispersible budesonide, with some patients pursuing PPI therapy or dietary interventions. Consequently, the number of patients eligible for maintenance treatment with orodispersible budesonide in NHS Wales is likely to be smaller than the total prevalent population.
- Most clinicians that AWTTC consulted do not anticipate a positive recommendation to significantly affect prescribing practice in this area. Therefore, the current trend in prescribing is expected to continue if orodispersible budesonide is recommended for maintaining remission of EoE. Although there could be a small increase in prescribing as a result of a positive recommendation, AWTTC do not believe the company's estimated annual increase in uptake to be representative of prescribing practice in NHS Wales in the event of a positive recommendation.

Taking into account the critique points raised above, AWTTC used linear extrapolation of Welsh prescribing data for the past 4 years (2021-2025) to estimate the BI. It was assumed that 75% of prescribed orodispersible budesonide is used for maintenance treatment based on clinician estimates. The displaced comparator was assumed to be annual re-induction with orodispersible budesonide (one course per year). The estimated net medicine acquisition costs (excluding VAT) were £183,087 in Year 1 (85 patients) rising to £257,680 in Year 5 (119 patients). The BI does not consider any costs outside of medicine acquisition.

In practice, some NHS Wales clinicians prescribe orodispersible budesonide at the licensed doses for maintenance treatment, whereas others prescribe an off-label dose of 1 mg once daily for maintaining remission of EoE in adults. Although AWTTC do not endorse the off-label use of orodispersible budesonide, AWTTC have also estimated the BI by considering the off-label dose to reflect real-world prescribing. In this scenario, the estimated net medicine acquisition costs (excluding VAT) were £145,090 in Year 1 (169) rising to £203,852 in Year 5 (238 patients). The BI only considers medicine acquisition costs. For further information on the costs and patient uptake used to inform AWTTC's BI estimates, please refer to Appendices 1 and 2.

Engagement with clinicians in all seven health boards revealed that orodispersible budesonide is currently prescribed for maintaining remission of EoE in adults. Therefore, if orodispersible budesonide were recommended for this indication in NHS Wales, the actual budget impact is be expected to be low.

Impact on health and social care services

Maintenance treatment of EoE with orodispersible budesonide is anticipated to reduce the amount of clinic time for secondary care clinicians, the requirements for elective oesophagogastro duodenoscopy (OGD), and the number of emergency admissions for the management of food bolus obstruction.

Patient factors

Clinicians anticipate that maintenance treatment with orodispersible budesonide will improve the quality of care provided to patients, and their quality of life. Clinicians report that orodispersible budesonide to be helpful to prevent longer term complications of stricture, repeated OGD for dysphagia, admissions and procedures for food bolus obstruction, and repeated GP visits with symptoms.

The BSG/BSPGHAN guidelines state that anxiety and depression in EoE affects patients due to persistent symptoms and social restrictions, which is alleviated by effective therapy. A patient organisation submission received from the EOS Network further highlights the impact of poorly managed EoE, which include social, physical and financial implications to the patient, and their family/carers. The EOS Network noted that EoE can be isolating for patients, as many will withdraw from social activities to maintain their dietary restrictions.

Equality and health impact assessment

AWTTC have completed an Equality and Health Impact Assessment. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that orodispersible budesonide will have a potential negative impact on people based on the protected characteristics of the Equality Act 2010.

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Appendix 1: Medicine acquisition costs used to inform budget impact (BI) critique and the development of AWTTC's BI

Orodispersible budesonide maintenance regimens	Pack size	Cost per pack	Cost per tablet	Cost of one year of treatment
Orodispersible budesonide 0.5 mg tablets twice daily	60 x 0.5 mg tablets	£214.80	£3.58	£2,613
Orodispersible budesonide 1 mg tablets twice daily	90 x 1 mg tablets	£323.00	£3.59	£2,621
Average medicine acquisition cost of one year of budesonide maintenance treatment (licensed doses)				**£2,617**
Orodispersible budesonide 1 mg tablets once daily	90 x 1 mg tablets	£323.00	£3.59	£1,310
Medicine acquisition cost of one year of budesonide maintenance treatment (off-label dose)				**£1,310**
Orodispersible budesonide induction regimens	**Pack size**	**Cost per pack**	**Cost per tablet**	**Cost of one induction course**
Orodispersible budesonide 1 mg tablets twice daily for 6 weeks (minimum duration)	90 x 1 mg tablets	£323.00	£3.59	£302
Orodispersible budesonide 1 mg tablets twice daily for 12 weeks (maximum duration)	90 x 1 mg tablets	£323.00	£3.59	£603
Average cost of one course of budesonide induction treatment				**£452**
Fluticasone maintenance treatment	**Pack size**	**Cost per pack**	**Number of packs required for one year* of treatment**	**Cost of one year of treatment**
Flixotide® 50microgram/dose Evohaler, 1,100 micrograms (22 doses) per day	120 inhalations of 50 micrograms	£6.53	67	£438
All costs exclude VAT. All medicine acquisition costs reflect NHS indicative prices.				

Appendix 2: Estimated acqusition costs, patient uptake, and net medicine acquistions costs of orodispersible budesonide maintenance treatment

Two budget impact scenarios are depicted, one is informed by the licensed doses of orodispersible budesonide (Table 1) and the second is informed by the off-label dose that is prescribed by some clinicians across NHS Wales (Table 2). Estimated acquisition costs of maintenance treatment were calculated via linear extrapolation of NHS Wales prescribing data between April 2021 and March 2025, All costs exclude VAT. The comparator treatment is annual re-induction with orodispersible budesonide.

Table 1. AWTTC budget impact model – based on licensed doses.

Year	Estimated acquisition cost of maintenance treatment	Estimated patient uptake	Estimated net medicine acquisition cost
Year 1 (2026/27)	£221,536	85	£183,087
Year 2 (2027/28)	£244,029	93	£201,961
Year 3 (2028/29)	£266,522	102	£220,384
Year 4 (2029/30)	£289,015	110	£239,258
Year 5 (2030/31)	£311,509	119	£257,680
Estimated patient uptake was calculated by dividing the estimated annual acquisition cost of maintenance treatment with the average cost of one year of maintenance treatment using the licensed doses (0.5 mg twice daily and 1 mg twice day).			

Table 2. AWTTC budget impact model – based on off-label dose.

Year	Estimated acquisition cost of maintenance treatment	Estimated patient uptake	Estimated net medicine acquisition cost
Year 1 (2026/27)	£221,536	169	£145,090
Year 2 (2027/28)	£244,029	186	£159,894
Year 3 (2028/29)	£266,522	203	£174,697
Year 4 (2029/30)	£289,015	221	£189,048
Year 5 (2030/31)	£311,509	238	£203,852
Estimated patient uptake was calculated by dividing the estimated annual acquisition cost of maintenance treatment with the average cost of one year of maintenance treatment using the off-label dose (1 mg once daily).			