



Cost-effectiveness of darvadstrocel (Alofisel®) for treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal Crohn's disease, when fistulae have shown an inadequate response to at least one conventional or biologic therapy.

Darvadstrocel should be used only after conditioning of the fistulas.

The NCPE has issued a recommendation regarding the cost-effectiveness of darvadstrocel (Alofisel®). Following assessment of the Applicant's submission, the NCPE recommends that darvadstrocel (Alofisel®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Takeda) economic dossier on the cost effectiveness of darvadstrocel (Alofisel®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In January 2019, Takeda submitted a dossier which investigated the cost-effectiveness of darvadstrocel for the treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal Crohn's Disease, when fistulae have shown an inadequate response to at least one conventional or biologic therapy. Darvadstrocel should be only used after conditioning of the fistulas. Darvadstrocel received marketing authorisation from the EMA in March 2018. Takeda are seeking reimbursement in the hospital setting.

Darvadstrocel is an advanced therapy medicinal product. It is the first stem cell treatment to be licensed for the treatment of patients with Crohn's disease and complex perianal fistulas. Darvadstrocel is a suspension of expanded human adipose derived stem cells of allogenic origin. These stem cells have the potential to regulate the function of immune cells including B lymphocytes, T lymphocytes, NK cells, monocyte derived dendritic cells and neutrophils resulting in local immunosuppression. This local immunosuppression may allow the tissues around the fistula tract to heal. The cell suspension containing 120 million cells (4 vials) is given as a single administration. The content of two vials (60 million cells) is injected into the fistula walls along the length of the fistula tract and two vials (60 million cells) injected around the internal opening during an examination under anaesthesia (EUA). The full content of the 4 vials must be administered for the treatment of up to two internal openings and up to three external openings. This means that with a dose of 120 million cells it is possible to treat up to three fistula tracts that open to the perianal area.

1. Comparative effectiveness of darvadstrocel

Evidence from the Phase III ADMIRE-CD study forms the main pivotal evidence supporting product registration. The ADMIRE-CD study was a company sponsored, randomised double blind placebo controlled multicentre trial designed to assess the efficacy and safety of a single treatment course of darvadstrocel in 212 patients (54.7% male, 92.5% Caucasian) with non-active/mildly active luminal Crohn's disease (Panes et al 2016; Panes et al 2018). Patients were refractory to treatment with at least one of the following: antibiotics (ciprofloxacin or metronidazole with no response after one month); immunomodulators (azathioprine, 6-mercaptopurine or methotrexate with no response after three months) or anti-

tumour necrosis factor (TNF) treatments (no response either 12 weeks after the start of induction treatment or loss of response after 12 weeks of maintenance). Eligible patients underwent a fistula preparation visit which included examination under anaesthesia (EUA), drainage, curettage and seton placement, if clinically indicated. Patients were randomised equally to receive darvadstrocel 120 million cells or placebo administered by intralesional injection, divided between the internal and external opening of the fistulas. Randomisation was stratified by concomitant treatment at baseline (anti-TNF, immunosuppressant, both or neither). The use of any established immunosuppressant or anti-TNF treatment was maintained at stable doses during the study period. The use of corticosteroids at screening was reduced and stopped within four weeks. Following administration of study medicine, patients could receive antibiotics for up to four weeks. During the study, patients with flares of luminal Crohn's disease were treated with a course of corticosteroids (prednisolone 40mg or equivalent, reduced over 12 weeks). The primary outcome of the trial was remission after 24 weeks, with clinical and MRI confirmation of fistula healing.

The results from the ADMIRE-CD study showed that there was a statistically significant difference between the numbers of patients in combined remission in the intervention and standard of care arms. In the primary intention-to-treat (ITT) population (n=212), the combined remission in the intervention arm was 49.5% and in the placebo arm was 34.5% (difference 15.0%, 97.5% CI: 0.5, 31.2; $p=0.021$). The EMA commented that the difference of 15% appeared to be modest but clinically meaningful given that other treatment options for fistulas have failed.

Patients were also clinically assessed at weeks 36 and 52. At week 52 the beneficial effect of darvadstrocel was maintained in the ITT population with 54.2% of patients achieving combined remission compared with 37.1% in the placebo arm (difference 17.1%, 97.5% CI: NR; $p=0.012$). Similar results were observed in the modified-ITT (mITT) population (56.3% vs 38.6%; 95% CI: 4.2, 31.2; $p=0.01$).

Key secondary endpoints were clinical remission (closure of all external openings that were draining at baseline despite gentle finger pressure compression) and clinical response (closure of $\geq 50\%$ of external openings) at week 24. The primary outcome result was

supported by the key secondary and other secondary endpoints although differences in secondary endpoints were not statistically significant. Health Related Quality of life was measured in the ADMIRE-CD trial using the inflammatory bowel disease questionnaire (IBDQ), with no statistically significant differences shown between darvadstrocel and placebo.

Although the primary outcome of ADMIRE-CD was combined remission (assessed both clinically and by MRI), the Applicant also did a post-hoc analysis of an alternative outcome. This was suggested by clinical opinion sought by the Applicant from St. Mark's Hospital (UK) who indicated that the clinical outcome of most relevance to patients with Crohn's disease with perianal fistulae should include a component of pain and discharge in addition to clinical remission (i.e. clinical and patient-centric [CPC] remission). This was defined as the closure of all external openings that were draining at baseline on clinical assessment with no draining on gentle finger compression and the absence of pain or discharge assessed as a score of 0 for pain and discharge on the perianal disease activity index (PDAI). The time to CPC remission, and time to relapse after CPC remission, were therefore considered to be indicators of the clinical effectiveness of darvadstrocel compared with placebo. Results were broadly in line with the primary efficacy outcome. The RG consider however that there are certain aspects of the trial that may limit its generalisability to clinical practice in Ireland, for example conditioning of the fistula both two weeks before and immediately prior to study medication being administered; the experience of the surgeon. Also, patients who had been receiving immunosuppressants and/or anti-TNFs at baseline could continue to receive stable doses during the study period. It is not clear how optimising the use of concomitant treatment would affect the generalisability of the study results to clinical practice.

2. Safety of darvadstrocel

The primary safety data to support the targeted indication for darvadstrocel came from the pivotal Phase III ADMIRE-CD study in 212 patients. The safety analyses for licensing included data up to the week 52 visit.

At week 24, the most commonly reported adverse events in the darvadstrocel and standard of care groups respectively were: proctalgia (13% and 11%), anal abscess (12% and 13%), nasopharyngitis (9.7% and 4.9%), diarrhoea (6.8% and 2.9%), abdominal pain (3.9% and 5.9%) and new fistula (2.9% and 5.9%). Treatment related adverse events reported in the respective groups were: anal abscess (5.8% versus 8.8%), proctalgia (4.9% versus 8.8%), procedural pain (1.0% versus 2.0%), fistula discharge (1.0% versus 2.0%).

The incidence of anal abscess was similar in both treatment groups at week 24 (12% and 13% respectively). However when patients were followed to week 52, there were more cases of anal abscess in the darvadstrocel than standard of care group (19% versus 14%). Anal abscess was reported as a serious adverse event in 14% of darvadstrocel and 7.8% of patients on placebo up to week 52. These cases mainly occurred in the initially treated fistula and were considered to reflect a lack of efficacy in some patients rather than a safety issue.

3. Cost effectiveness of darvadstrocel

The Applicant presented a cost utility analysis comparing darvadstrocel with control treatment (surgical EUA with or without prior seton placement plus curettage) in adult patients with complex perianal fistula and non-active/mildly active Crohn's disease. Key clinical data used in the model were taken from the ADMIRE-CD study. The key clinical data used in the economic model were based on the post-hoc CPC remission outcome at week 52. Health related quality of life data (IBDQ) were collected in the ADMIRE-CD study but were not used in the model, and were instead obtained through a separate vignette study. Although this is not a major driver in the model, the use of a different source of utility data does lead to uncertainty. A time horizon of 60 years was applied. The long term benefit of darvadstrocel was highly uncertain and the model was highly sensitive to the choice of (i) outcome measure from the pivotal trial (i.e. the primary vs secondary vs post hoc derived outcome) and (ii) the parametric curve for the long term extrapolation of relapse rate. There was a high level of uncertainty with the clinical effectiveness evidence and as a result it was difficult to decide the most plausible estimate of cost effectiveness. The results of the

economic analysis may be less robust because of the use of a post-hoc outcome measure that was not included in the original study design.

A discount rate of 5% was used for the base case and 4% was included in a sensitivity analysis.

In the Applicant's base case analysis, darvadstrocel was associated with an additional 0.898 QALYs for an additional cost of €53,544, when compared with control treatment. This resulted in a (deterministic) incremental cost per QALY of €59,646 per QALY.

The probabilistic analysis resulted in darvadstrocel being associated with an additional 0.87 QALYs for an additional cost of €53,668, when compared with control treatment, resulting in a probabilistic ICER of €61,757 per QALY. Scenario analyses highlighted the impact of changes to key parameters on the ICER; for example, when the definition of remission was changed to 'combined remission', i.e. the primary outcome measure in the ADMIRE-CD trial, the ICER increased to €109,058 per QALY. Also, when an alternative parametric modelling approach was used for the relapse curve (i.e. log normal) the ICER increased to €248,548 per QALY.

In the Applicant's probabilistic sensitivity analysis, the probability of cost effectiveness for darvadstrocel compared with control treatment at €45,000 per QALY was 19%. The probability of cost effectiveness at €20,000 per QALY was 0%.

4. Budget impact of darvadstrocel

The price to wholesaler of darvadstrocel is €60,000 excluding VAT. The cost per patient per year to the HSE (incorporating VAT and mandatory 5.5% rebate) is €70,500 assuming patients receive one course of treatment. The Applicant predicts that the number of patients eligible for treatment with darvadstrocel will increase annually, starting with 4 patients in year 1 and rising to 31 patients by year 5. However, the Review Group estimate that the figures could be closer to 6 patients in year 1 and 47 by year 5. The Applicant estimates the 5-year cumulative net-budget impact to be approximately €5.1 million; the NCPE estimate a figure of €7.8 million.

5. Patient submissions

No patient submissions were received during the course of this appraisal.

6. Conclusion

Data on clinical effectiveness of darvadstrocel show only modest benefit over and above placebo. The long term benefit of darvadstrocel was highly uncertain and the model was highly sensitive to the choice of (i) outcome measure from the pivotal trial and (ii) the parametric curve for the long term extrapolation of relapse rate. The economic analysis was therefore weakened by the modest clinical data, which made it difficult to decide the most plausible estimate of cost effectiveness.

Following NCPE assessment of the Applicant's submission, cost effectiveness of darvadstrocel (Alofisel®) for the treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal Crohn's disease, when fistulae have shown an inadequate response to at least one conventional or biologic therapy has not been demonstrated, and therefore is not recommended for reimbursement.