NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Darvadstrocel for treating complex perianal fistulas in Crohn's disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using darvadstrocel in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using darvadstrocel in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 5 September 2018

Second appraisal committee meeting: 18 September 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Darvadstrocel is not recommended, within its marketing authorisation, for previously treated complex perianal fistulas in adults who have non-active/mildly active luminal Crohn's disease.

Why the committee made these recommendations

Darvadstrocel showed only a modest improvement in the proportion of people achieving complete remission compared with placebo in one clinical trial. Reliable follow-up results are only available for up to 1 year, so it is unclear how long the treatment benefit will last. The cost-effectiveness estimates are therefore highly uncertain and the committee was unable to conclude on the most plausible cost-effectiveness estimate. Because of this, darvadstrocel cannot be recommended for routine commissioning for treating complex perianal fistulas in people with Crohn's disease.

2 Information about darvadstrocel

Marketing authorisation	Darvadstrocel (Alofisel, Takeda) is indicated 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'.
Dosage in the marketing authorisation	A single dose of darvadstrocel consists of 120 million cells distributed in 4 vials. Each vial contains 30 million cells in 6 mL of suspension. The full content of the 4 vials must be administered for the treatment of up to 2 internal openings and up to 3 external openings. This means that with a dose of 120 million cells it is possible to treat up to 3 fistula tracts that open to the perianal area. There is currently limited experience with the efficacy or safety of repeat administration of darvadstrocel.
Price	The list price of darvadstrocel is £13,500 per vial. One course of treatment (4 vials) costs £54,000 (company submission). The company has a commercial arrangement (patient access scheme), which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Takeda and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Management of the disease

There are no targeted interventions for complex perianal fistulas in people who have Crohn's disease

3.1 Perianal fistulas are abnormal passages between the lower parts of the gut and the skin near the anus. Complex perianal fistulas have several abnormal passages and openings, or passages that go deep inside the body, or have other complications such as abscesses. In adults with non-active or mildly active luminal Crohn's disease, perianal fistulas are

managed with medical therapies including antibiotics, immunosuppressants and biological therapy. If the fistula and any associated abscesses do not heal, surgery is needed. Using general anaesthesia, the abscesses are drained and a seton (piece of thread) is passed through the fistula. This keeps the fistula open so that it can drain. The clinical experts explained that setons are not usually curative, but aim to reduce the risk of abscess formation. Long-term remission rates are relatively low (about 10%). The success rate of seton placement also depends on the surgeon's experience in treating complex perianal fistulas with multiple tracts. Because setons are not usually curative and remission rates are low, people may need to have defunctioning surgery (a temporary diversion of the bowel to allow healing of the perianal fistula) or a proctectomy (permanent removal of part of the bowel to bypass the perianal fistula).

New treatment option

Perianal fistulas are chronic and debilitating, and a new treatment option would be welcome

3.2 The patient experts explained that perianal fistulas are highly debilitating, have a big impact on the person's everyday life and greatly reduce their quality of life. People can experience excruciating pain and are limited in their everyday activities. The availability of systemic biological treatments, has improved people's quality of life, however these treatments can have serious side effects and do not specifically treat the perianal fistula. Darvadstrocel is injected directly into the perianal fistula. It is the first stem-cell treatment that is specifically developed to promote healing of fistulas caused by Crohn's disease and, if successful, would be a life-changing intervention. The committee understood that patients and clinicians would welcome a new treatment option that is targeted to heal

the perianal fistula rather than to reduce complications such as abscesses.

The method of administration of darvadstrocel

Using darvadstrocel needs training of the multidisciplinary team and careful planning and scheduling of treatment

3.3 Darvadstrocel is a suspension of allogeneic expanded human adipose-derived stem cells. Administration requires re-suspension of the cells, which need to be used within 48 hours. Because of its short shelf life, careful planning and scheduling is necessary to avoid procedures being cancelled and darvadstrocel being wasted. The clinical experts explained that the pharmacist and surgeon would need training in its preparation and administration. They also emphasised that patients should be seen by a multidisciplinary team who are experienced in treating complex perianal fistulas. Not all fistulas would be considered suitable for this treatment (see section 3.4). The committee noted that darvadstrocel requires an additional procedure compared with current management. Standard examination under anaesthesia, with conditioning of the fistula is done first, then an additional procedure is done 2 weeks later to administer darvadstrocel. The clinical experts explained that the outcome of the intervention is highly dependent on the appropriate conditioning of the fistula and optimal placement of the darvadstrocel injection. They suggested that it should only be used in specialist centres where a multidisciplinary team is available, who could gain appropriate experience in the use of this technology. However the clinical experts did not consider this to be a barrier to implementation of darvadstrocel in the NHS. The committee concluded that because darvadstrocel is the first stem-cell treatment in this disease area, and noting the requirements and logistics of administration of darvadstrocel, it would only be used in specialist centres following additional training.

Clinical evidence

Darvadstrocel would only be appropriate for a specific group of people with complex perianal fistulas, in line with the eligibility criteria of ADMIRE-CD

3.4 The clinical evidence comes from the ADMIRE-CD randomised controlled trial. This included adults with Crohn's disease who had a complex perianal fistula with up to 2 internal openings and up to 3 external openings, which had not responded to treatment with antibiotics, immune-modulators, TNF-alpha inhibitors, or a combination of these treatments. The clinical experts explained that the trial excluded people with the most severe and the least severe fistulas (that is, people with multiple complex fistulas, and those with 1 fistula with 1 single tract). The clinical experts noted that the benefit for people with multiple fistulas would be limited because of the restrictions around the volume of darvadstrocel that can be used for a single administration. Therefore in NHS practice it would only be used in the population specified in ADMIRE-CD. The committee noted that people with proctitis were excluded from the clinical trial, because this condition makes perianal fistula healing unlikely. The clinical experts agreed that these patients are unlikely to benefit from darvadstrocel. The committee concluded that if darvadstrocel were recommended, it should only be used in a population identical to the population in ADMIRE-CD.

The evidence on the natural history of the disease and outcome of current practice in the UK is limited

3.5 ADMIRE-CD was a multicentre trial but it did not include patients from the UK. To show that the data are generalisable to people in the UK, the company presented the results of a retrospective cohort study from St Mark's Hospital in London. This was a retrospective cohort study that collected data from January 2008 until July 2017, about people with complex perianal fistulas that would have met the eligibility criteria of

ADMIRE-CD. It was used to externally validate the results from ADMIRE-CD and calculate the transition to the proctectomy state. The ERG also used the data for adjusting the probabilities of moving to the proctectomy and defunctioning surgery health states in the model (see section 3.15). The committee noted that people in the St Mark's study were more likely to be male and had a different medication history; in particular, a higher percentage had had biological treatments than in ADMIRE-CD. It heard from the clinical experts that, because the study reported previous and current treatment together, the data is of limited usefulness and would not help the committee to decide who would be eligible for darvadstrocel in the NHS. It also noted that the St Mark's study did not report on the outcome of treatments, so it provides no evidence about the success rates of current NHS practice. The clinical experts explained that evidence on the natural history of Crohn's disease with perianal fistulas is limited. The committee considered the St Mark's study useful for understanding the patient population in the NHS, but concluded that it does not contribute significantly to predicting the clinical effectiveness of darvadstrocel in UK clinical practice.

Clinical-effectiveness data for darvadstrocel is from only 1 trial with a relatively short time-frame

3.6 ADMIRE-CD compared darvadstrocel with placebo (saline solution injection). The primary outcome of the trial is remission after 24 weeks, with clinical and MRI confirmation of fistula healing. Results from longer-term follow-up are also available (at 52 weeks and 104 weeks). The company and the ERG stated that the results are only reliable up to 52 weeks, because of a protocol change at that time, and the longer-term results are highly uncertain. The committee would have liked to have seen longer follow-up given that darvadstrocel, after a single use, is expected to have lifelong benefit.

Using clinical and patient-centric assessment of remission is appropriate

3.7 Although the primary outcome of ADMIRE-CD was 'combined remission' (that is, assessed both clinically and by MRI), the company also did a post-hoc analysis of an alternative outcome. This had been suggested by clinicians who advised that, in addition to medically and clinically assessed remission, the outcome should include a component of patient-assessed pain and discharge (that is, clinical and patient-centric [CPC] remission). The time to CPC remission, and time to relapse after CPC remission, were considered to be indicators of the clinical effectiveness of darvadstrocel compared with placebo. The committee noted that the trial was not powered to detect changes in CPC remission and relapse. However it heard from the ERG and the clinical experts that this outcome would be the most relevant to clinicians and patients. The committee concluded that using CPC remission and relapse is appropriate, but remained concerned that these outcomes were defined post hoc and that the trial was not powered to detect changes in these outcomes.

ADMIRE-CD shows a statistically significant but numerically modest benefit of darvadstrocel compared with placebo

3.8 ADMIRE-CD shows a statistically significant difference in combined remission for darvadstrocel compared with placebo at week 24 (49.5% and 34.3%, respectively; difference 15.2%, p=0.024). This statistically significant difference was maintained at week 52 (54.2% compared with 37.1%, respectively; difference 17.1%, p=0.012). The committee also considered the results of the post-hoc analysis which shows that CPC remission is statistically significantly higher for darvadstrocel than placebo (55.1% compared with 41.0%, respectively, p=0.014). It noted that only around 14.1% more patients experienced CPC remission with darvadstrocel, compared with placebo. While the committee understood the benefit to patients of achieving complete remission, it considered that

this additional remission rate is disappointingly modest. It also noted that the data are only reliable up to 52 weeks (see section 3.6). The committee concluded that ADMIRE-CD shows a benefit of darvadstrocel compared with placebo but this is not large, and there are uncertainties about how long the benefit will be maintained.

There is an ongoing clinical trial, which will provide further results on the clinical effectiveness of darvadstrocel

3.9 The committee noted that an ongoing clinical trial (ADMIRE-CD II, NCT03279081) is expected to provide further evidence on the clinical effectiveness of darvadstrocel for a complex perianal fistula in people who have Crohn's disease. The study is planning to recruit more people (n=326) than were included in ADMIRE-CD (n=212). The committee considered that the results of the 2 studies together will form a more robust evidence base. It also noted that the European Medicines Agency considers that further information on efficacy is necessary, and that the marketing authorisation is subject to the submission of the results of ADMIRE-CD II.

Generalisability of ADMIRE-CD data to UK clinical practice

The treatment effects/results observed in the placebo group of ADMIRE-CD do not reflect UK clinical practice

3.10 The clinical and patient experts explained that standard care for complex perianal fistulas in people with Crohn’s disease is surgical intervention and seton placement, which allows free drainage to prevent deep abscess formation. As the ADMIRE-CD trial did not include patients from the UK, it is unclear to what extent the outcomes seen in the placebo group of the trial reflect the outcome of clinical practice in the UK. In ADMIRE-CD the interventions given in the placebo arm resulted in a much higher rate of remission than would be expected with standard care in the UK. The

reasons for this are unclear, it may be a placebo effect or it may reflect differences between the trial setting and real life clinical practice. The clinical experts indicated that careful conditioning of the fistula and thorough abscess drainage and curettage is key to successful treatment and that perhaps more experienced surgeons were involved in the trial, which may have increased the remission rate with placebo. They explained that there is variability in the level of service across the NHS. The committee reiterated its previous conclusion that darvadstrocel would only be suitable for administration in specialist centres (see section 3.3). It concluded that there was uncertainty in the generalisability of the placebo arm of the ADMIRE-CD trial to UK clinical practice, and therefore it is uncertain whether the benefit shown for darvadstrocel in the trial would translate to the same benefit over and above standard care in the NHS.

ADMIRE-CD did not collect patient-reported health-related quality of life data

3.11 ADMIRE-CD collected disease severity scores as secondary outcomes (Perianal Disease Activity Index and Van Assche Score). The clinical experts explained that although the Perianal Disease Activity Index is a patient-reported outcome measure, it does not capture health-related quality of life. The committee noted that the reference case in section 5.3.1 of NICE's guide to the methods of technology appraisal (2013) specifies that health-related quality of life data should be obtained from patients using the EQ-5D questionnaire. The committee concluded that it would have welcomed the collection of health-related quality of life outcomes in the trial, particularly using EQ-5D.

The company's economic model

The company's model structure is appropriate and suitable for decision making

3.12 The company presented a semi-Markov state transition cohort model, which assumed a single administration of darvadstrocel (the committee noted no evidence had been presented by the company for repeated treatments with darvadstrocel), and a lifetime benefit for patients. It used a 40-year time horizon and a 4-week cycle length. The committee agreed with the structure of the model and considered it suitable for decision making.

Discounting future costs and benefits

A reference case discount rate of 3.5% should be used for both benefits and costs

3.13 The company deviated from the reference case in its base-case analysis, using a 1.5% discount rate for future benefits and a 3.5% discount rate for costs, because it considered that section 6.2.19 of NICE's guide to the methods of technology appraisal applies. This states that in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near-full health, and when this is sustained over a very long period, a non-reference-case discount rate of 1.5% for costs and benefits may be considered. The ERG suggested that evidence is lacking that darvadstrocel restores quality of life to full or near-full health for a prolonged period (at least 30 years, as defined by section 6.2.19 of NICE's guide to the methods of technology appraisal). The committee agreed that it has not been shown that darvadstrocel restores a patient's quality of life to full or nearly-full health (partly because it does not treat the underlying condition, Crohn's disease). It also noted the lack of evidence on the long-term benefits of darvadstrocel. Furthermore the

committee noted that NICE's guide to the methods of technology appraisal does not support using different discount rates for costs and benefits. The committee concluded that a reference case discount rate of 3.5% should be used for both costs and benefits in the economic model.

Time horizon of the model

Using a 60-year time horizon in the economic model is in line with the NICE reference case

3.14 The company's model used a 40-year time horizon. The committee heard from the ERG that at 40 years only 31.7% of patients will have died, so the time horizon might be too short to capture differences in costs and benefits for darvadstrocel compared with standard care. The ERG explored the impact of using a 60-year time horizon. The committee noted this had a minimal impact on the incremental cost-effectiveness ratio (ICER) and concluded that time horizon was not a driver of cost-effectiveness.

Base-case cost-effectiveness estimates

3.15 The company presented a base-case cost-effectiveness estimate of £21,685 per quality-adjusted life year (QALY) gained (incremental costs £21,811; incremental QALYs 1.01), using the following assumptions: the reference case discount rate of 3.5% for both costs and QALYs; a 40-year time horizon; and applying the patient access scheme for the treatment costs of darvadstrocel. The committee noted that the ERG's preferred base-case analysis produced an ICER of £23,176 (incremental costs £23,978; incremental QALYs 1.01), using the following corrections and assumptions:

- correcting for programming errors in the model

- adjusting the probabilities of moving to the proctectomy and defunctioning surgery health states in the model, based on the available evidence from St Mark's study
- amending the long-term remission rates for subsequent therapies in the standard-care group, based on the time-to-event functions of subsequent therapies and the methods used in the darvadstrocel group
- using a 60-year time horizon.

The committee considered the ERG's corrections and assumptions to be appropriate.

Modelling the long-term benefits of darvadstrocel

The long-term benefits of darvadstrocel are highly uncertain, and the model is highly sensitive to the choice of parametric curve for long term extrapolation

3.16 To model the long-term clinical effectiveness of darvadstrocel, the company used a Gompertz curve to extrapolate both time to CPC remission and time to relapse after CPC remission. The ERG explained that the choice of curve is a key driver of the model and that the cost-effectiveness results are very sensitive to the extrapolation method used, particularly the time to relapse. The ERG presented a scenario analysis, similar to that presented by the company, but including the ERG's preferred base-case assumptions and using the second-best options; the generalised gamma curve for extrapolating time to CPC remission, and the log-normal curve for time to relapse following CPC remission. This results in a substantially higher ICER (£143,131 per QALY gained) compared with the company's base case (see section 3.15). The committee discussed the clinical plausibility of the different curves with the clinical experts, particularly the choice of curve for time to relapse following CPC remission. The clinical experts explained that without more

evidence on the natural history of the disease, it is difficult to predict the relapse rate after the time horizon of the trial. However the experts highlighted that if the fistula is healed and remission is maintained until 2 years, and there is no underlying risk for future recurrence, recurrence rates are likely to be very low after this time (around 10 to 20%), but it is not eliminated. They also explained that relapse tends to occur soon after treatment, rather than later. The company stated that its model assumes 40% of people have the probability of remaining relapse free, with a low ongoing risk of relapse, after remission has been maintained with darvadstrocel for 2 years. Based on the evidence that was presented and discussed at the meeting, the committee concluded that the risk of relapse over time (hence the method of extrapolation from the trial to the long term) is a key driver of the model and that it was unable to select the most appropriate method for modelling the long-term effectiveness of darvadstrocel. It expressed concern that no reliable data on the number of people in remission at 2 years is available, and that the choice of curves has a large effect on the ICER (with a difference of more than £100,000 per QALY gained between the best and second-best fitting curves). It concluded that only better data on long-term outcomes from the ongoing trial, or more robust information on the natural history of the disease, would make it possible to decide which is the most plausible ICER.

There is limited evidence available on health-related quality of life for Crohn's disease with complex perianal fistula

3.17 ADMIRE-CD did not include a direct health-related quality of life measurement, and there are no published utility values for this disease area. To calculate the health-related quality of life benefits of darvadstrocel, the company did a vignette study to derive utility values for each health state in the model. The committee noted that this is not in line with the NICE reference case. The ERG's clinical experts considered that

the utility value following successful defunctioning (0.567) or proctectomy surgery (0.564) may be underestimated in the company's base case, as well as the utility value for the 'mild chronic symptomatic fistulae' health state (0.578). In a conservative scenario analysis, the ERG explored the impact of using the same utility value (0.865) for remission, for a mild chronic symptomatic fistula and for successful defunctioning and successful proctectomy surgery. The resulting ICER is £63,721 per QALY gained. The committee discussed this scenario with the patient and clinical experts at the meeting, who explained that a patient's quality of life after defunctioning surgery is expected to be substantially lower than the quality of life of a patient in remission. The committee considered that the utilities in some heath states might be too low, and that correctly derived utility values for these 3 health states could result in higher ICERs. However, it concluded that the ERG's suggested scenario is extreme and not plausible, but found that it was informative in that it showed the impact that the utility values had on the cost-effectiveness results.

Most plausible cost-effectiveness estimate

The most plausible cost-effectiveness estimate is uncertain, and darvadstrocel is unlikely to be a cost-effective use of NHS resources

3.18 The key factors affecting the ICER are the parametric curve chosen for extrapolating the time to CPC remission and particularly time to relapse following CPC remission and to a smaller extent, the utility values for a mild chronic symptomatic fistula and for successful defunctioning and successful proctectomy surgery. Using a generalised gamma curve to extrapolate time to CPC remission, and log-normal to extrapolate time to CPC relapse, results in an ICER of £143,131 per QALY gained. The committee noted that this ICER is considerably higher than the company's base case and, given the reasonable fit of the curves, it could be correct. The very large difference in the ICERs, depending on the curves chosen,

emphasises how sensitive the cost-effectiveness estimate is to the duration of remission. The lack of long-term evidence from the trial and limited evidence on the natural history of the disease, particularly on long-term relapse rates after successful treatment, make it very difficult to decide the most plausible estimate of cost effectiveness. Therefore the committee was unable to conclude on the most plausible cost-effectiveness estimate.

Other factors

3.19 No equality issues were identified during the appraisal and discussed by committee.

3.20 The company stated that darvadstrocel is innovative and the first licensed allogenic stem-cell treatment in the UK for this disease. The clinical experts explained that this is the first targeted treatment option for complex perianal fistulas in Crohn's disease, and that it represents a step-change in the management of the disease. The committee considered these factors to be important and concluded that darvadstrocel is potentially innovative in the short term, but its long-term benefit is uncertain.

Conclusion

3.21 The committee reiterated its view that darvadstrocel shows only modest clinical-effectiveness gain compared with placebo. Data on clinical effectiveness is only available for up to 1 year, so the duration of benefit is uncertain. The committee concluded that the clinical benefit to patients in the NHS is not known. The cost-effectiveness estimates are also highly uncertain reflecting uncertainty about how long treatment benefit will last and the most appropriate extrapolation method for time to CPC remission and particularly time to relapse following CPC remission. Taking all the uncertainties into account, the committee concluded that darvadstrocel

was not a clinically and cost-effective use of NHS resources and could not be recommended for routine commissioning.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive when the results of the ongoing ADMIRE-CD II trial become available (see section 3.8). NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Jane Adam
Chair, appraisal committee
July 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Boglarka Mikudina
Technical Lead

Joanna Richardson
Technical Adviser

Thomas Feist
Project Manager

ISBN: [to be added at publication]