Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2115

darvadstrocel 30 million cells/6mL suspension for injection (Alofisel®)

Takeda UK Ltd

7 December 2018 *(Issued June 2019)*

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

ADVICE: following a full submission assessed under the orphan medicine process

darvadstrocel (Alofisel®) is not recommended for use within NHSScotland.

Indication under review: For the treatment of complex perianal fistulas in adult patients with non-active / mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy.

In a randomised, double-blind, phase III study, the rate of combined remission at week 24 was significantly higher with darvadstrocel than placebo in patients with Crohn's disease and complex perianal fistulas.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of complex perianal fistulas in adult patients with non-active / mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Darvadstrocel should be used after conditioning of fistula.[1]

Dosing Information

Darvadstrocel should only be administered by specialist physicians experienced in the diagnosis and treatment of conditions for which it is indicated.

A single dose of darvadstrocel consists of 120 million cells distributed in four vials. Each vial contains 30 million cells in 6mL of suspension. The full content of the four 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.

Darvadstrocel is for intralesional use in a surgical environment under anaesthesia (general or regional). In line with standards for the management of complex perianal fistulas, characterisation of the patient's fistula is needed prior to treatment. This comprises in-depth knowledge of their anatomy (number of existing fistulas and openings), topography (extent and relationship with the sphincters and other pelvic muscles) and potential associated complications (such as abscesses). Before scheduling darvadstrocel administration, the surgeon must ensure that no abscesses are present and that local mucosal disease is mild or inactive. In case of an abscess, incision and drainage are needed, and setons should be placed, if appropriate, in accordance with routine surgical procedures.

Prior to the administration of darvadstrocel, if setons are in place, they must be removed and the fistula tracts should be conditioned as follows:

- identify the location of the internal openings. For this, it is recommended to inject sodium chloride 9mg/mL (0.9%) solution through the external openings until it gets through the internal openings.
- perform a vigorous curettage of all fistula tracts, with special emphasis in the internal openings areas, using a metallic curette.
- suture the internal openings to close them.

Two vials of darvadstrocel should be used for the internal openings and the remaining two for the external openings as detailed in the summary of product characteristics (SPC).

There is currently limited experience with the efficacy or safety of repeat administration of darvadstrocel.[1]

Date of licensing

23 March 2018

Product availability date

April 2019

Darvadstrocel has been designated an orphan medicine for the treatment of anal fistula by the European Medicines Agency (EMA) and meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Darvadstrocel is an allogeneic somatic cell therapy medicinal product that contains expanded adipose stem cells (eASC) which exhibit immunomodulatory and anti-inflammatory effects at inflammation sites. Anal fistulas are characterised by local inflammation that is exacerbated by bacterial infections and faecal contamination and in inflamed areas, there is infiltration of activated lymphocytes and local release of inflammatory cytokines. These inflammatory cytokines, particularly interferon-γ released by activated lymphocytes, activate eASC. Once activated, eASC impair proliferation of activated lymphocytes and reduce the release of pro-inflammatory cytokines. This immunoregulatory activity reduces inflammation, which may allow the tissues around the fistula tract to heal.[1, 2]

The evidence to support the use of darvadstrocel comes from the pivotal, randomised, double-blind, placebo-controlled, phase III study (ADMIRE-CD). This enrolled 212 adult patients with non-active or mildly active luminal Crohn's disease for ≥six months (with a Crohn's Disease Activity Index [CDAI] of ≤220; scores range from 0 to 600, with higher scores indicating more severe disease) who had complex perianal fistulas (defined as at least one of: high inter-sphincteric; high trans-sphincteric; extra-sphincteric or supra-sphincteric origin; ≥two external openings or associated collections). Fistulas had a maximum of two internal and three external openings, assessed clinically and by MRI, and had been draining for ≥six weeks before study entry. 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).[2, 3]

The primary outcome was combined remission at week 24 defined as:

- the closure on clinical assessment (despite gentle finger compression) of all external openings that were draining at baseline and
- the absence of collections >2cm of the treated perianal fistulas in at least two of three dimensions confirmed by centrally reviewed MRI images.[2, 3]

To maintain the double-blind design, clinical assessments were performed by an investigator masked to study treatment, and MRI scans were assessed by a central laboratory masked to study treatment. A combined remission at week 24 was achieved by 50% (53/107) of patients in the darvadstrocel group and 34% (36/105) of patients in the placebo group: difference of 15% (97.5% confidence interval [CI]: 0.2 to 30), p=0.024.

There were two key secondary outcomes, clinical remission and clinical response, which were not significantly different between darvadstrocel and placebo at week 24. Clinical remission was defined as closure of all external openings that were draining at baseline despite gentle finger pressure compression. Clinical response was defined as closure ≥50% of external openings, ie one opening closed if the number of openings at baseline were one or two and two openings closed if there were three openings at baseline.[3] Other secondary outcomes included time to clinical remission, time to clinical response and relapse (defined in patients with clinical remission at any previous visit as reopening of any of the treated external openings with active drainage as clinically assessed or development of a >2cm perianal collection of the treated perianal fistulas confirmed by central MRI assessment). Details of the primary and main secondary outcomes to week 24 are presented in table 1.

Table 1: Primary and secondary outcomes in the ITT population of the ADMIRE-CD study[2, 3]

Outcomes	**Darvadstrocel**	**Placebo**	**Difference (95% CI)**
Combined remission (primary outcome) at 24 weeks	50% (53/107)	34% (36/105)	15% (97.5% CI: 0.2 to 30), p=0.024
Clinical remission at 24 weeks	53% (57/107)	41% (43/105)	12% (-1.0 to 26), p=0.064
Clinical response at 24 weeks	66% (71/107)	53% (56/105)	13% (-0.1 to 26), p=0.054
Time to clinical remission by 24 weeks, median	6.7 weeks	14.6 weeks	HR 0.57 (0.41 to 0.79)

Time to clinical response by 24 weeks, median	6.3 weeks	11.7 weeks	HR 0.59 (0.43 to 0.81)
Relapse of clinical remission by week 24	38% (30/79)	50% (28/56)	12% (-29 to 4.9)

ITT=intention to treat; CI=confidence interval, HR=hazard ratio.

In the modified ITT population, changes in the Perianal Disease Activity Index (PDAI) score (range from 0 to 20, with higher scores indicating more severe disease) from baseline scores of 6.7 and 6.5 were -2.3 versus -1.3, respectively to week 24, difference -0.8 [95% CI: -1.8 to 0.2]). There were no significant differences between the treatment groups in the change from baseline to week 24 in the CDAI score which assesses the severity of Crohn's disease or the Van Assche Score, an MRI-based score of perianal Crohn's disease severity. Quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ) which includes domains applicable to luminal Crohn's disease (range from 32 to 224, with higher scores indicating better quality of life). There were small increases from baseline to week 24 in the darvadstrocel group (3.8 [SD 26]) and the placebo group (4.0 [SD 26]) and no significant difference between the treatment groups.[2, 3]

Sixty-two percent of patients in the ITT population completed follow-up to week 52 and results suggest that the treatment effect was maintained. Currently available data to week 104 are limited.[2, 4]

The company performed post hoc analysis to assess clinical and patient-centric (CPC) remission which the company suggested was more relevant to clinicians. 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 PDAI. Results reported at week 52 in the ITT population found that CPC remission was achieved by 55% (59/107) of darvadstrocel patients and 41% (43/105) of placebo patients. At follow-up, CPC relapse had occurred in 51% (30/59) of darvadstrocel patients and 60% (28/47) of placebo patients. The median time to CPC relapse was estimated as 48.7 weeks in the darvadstrocel patients and 12.9 weeks in the placebo patients.[5, 6]

Summary of evidence on comparative safety

In the ADMIRE-CD study, safety was analysed in the safety population, defined as all patients who received study treatment. An adverse event was reported in 66% (68/103) of darvadstrocel-treated patients and 65% (66/102) of placebo-treated patients at week 24 and by 77% (79/103) and 73% (74/102) of patients respectively at week 52. Adverse events were considered related to study treatment in 17% of darvadstrocel-treated patients and 29% in placebo-treated patients at week 24 and in 20% and 26% of patients respectively at week 52. Serious treatment related adverse events were reported in 4.9% (5/103) of darvadstrocel-treated patients and 6.9% (7/102) of placebo-treated patients at week 24.[7] Adverse events led to discontinuation in 4.9% and 5.9%

of darvadstrocel- and placebo-treated patients respectively at week 24 and in 8.7% and 8.8% respectively at week 52.[2, 3]

At week 24, the most commonly reported adverse events in the darvadstrocel and placebo 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%).[2, 3]

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 placebo group (19% versus 14%). Anal abscess was reported as a serious adverse event in 14% of darvadstrocel and 7.8% of placebo patients 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.[2]

The study did not find a meaningful risk due to the presence of donor specific antibodies but data from a greater number of patients are required.[2]

Summary of clinical effectiveness issues

Fistulas are a common complication of Crohn's disease and perianal fistulas, which connect the anorectum with the perianal area, are a particular complication for patients with disease affecting the distal bowel. Perianal fistulas may develop in 20 to 30% of patients with Crohn's disease and recurrences have been observed in about 30% of cases. They are characterised by local inflammation which is exacerbated by bacterial infection and faecal contamination. Complex fistulas typically affect more of the anal sphincter, have multiple openings, are associated with abscesses or affect adjacent structures. They are more difficult to treat than simple fistulas and options depend on the position of the fistula and the number of channels. An initial EUA helps to determine the most appropriate treatment. The medical management of complex perianal fistulas includes antibiotics, immunosuppressants and biologics. Surgery is often required and aims to drain and heal the fistula while avoiding damage to the sphincter muscle which could subsequently affect bowel control. The Seton technique is frequently used and involves a seton, or thread, passed through the fistula to hold it open to drain. The success of this procedure will be dependent on appropriate placement and experience of the surgeon.

Darvadstrocel contains eASC which exhibit immunomodulatory and anti-inflammatory effects at inflammation sites. It is the first stem cell treatment to be licensed for the treatment of patients with Crohn's disease and complex perianal fistulas. Clinical experts consulted by SMC considered this to be an area of unmet need due to current suboptimal treatment options for the management of fistulating Crohn's disease. Darvadstrocel has been granted European Medicines

Agency (EMA) orphan designation for the treatment of anal fistulas and meets SMC orphan criteria.[1, 2, 8]

There are no validated outcomes for assessing perianal fistulas. In the ADMIRE-CD study, the primary outcome of combined remission comprised clinically and MRI assessed remission and the difference between darvadstrocel and placebo at week 24 was statistically significant. The EMA commented that the difference of 15% appeared to be modest but considered it to be clinically meaningful given that other treatment options for fistulas have failed. The key secondary outcomes of clinical remission and clinical response, although supportive, did not reach statistical significance at week 24. There was a higher than expected combined remission rate in the placebo group in the study (34% compared with an estimated a rate of 25%). There were also substantial responses for placebo in the key secondary outcomes of clinical remission and response at week 24. This may have been due to prior conditioning of the fistulas and to the continued use of baseline immunosuppressants and/or anti-TNFs. However, these factors would have also increased outcomes in the darvadstrocel group. There were no statistically significant differences between darvadstrocel and placebo for health-related quality of life measures, although the IBDQ may not be sensitive to changes related to perianal fistulas and patients had scores indicating good quality of life at baseline.[2, 3]

The effect of treatment appears to be maintained after 52 weeks of follow-up but the overall drop-out rate of 38% to week 52 of the study may affect the longer-term results. There are currently limited data to week 104 and the longer term benefit of treatment is unclear.[2, 4] There is no evidence to show that darvadstrocel reduces infections, helps maintain faecal continence or reduces the numbers of patients requiring defunctioning surgeries or proctectomies.

The study population was restricted by the inclusion of patients with fistulas which had a maximum of two internal and three external openings, assessed clinically and by MRI; however the licence indication does not restrict based on the numbers of internal/external openings. The study also excluded patients with some types of previous surgery for perianal fistula and patients with more active Crohn's disease.[1, 3] Therefore, the study results may not be generalisable to the treatment of patients in clinical practice with more complex fistulas.

All patients underwent conditioning of the fistula during a fistula preparation visit at least two weeks before study medication was administered. This involved drainage, curettage and seton placements as clinically indicated.[2, 3] The expertise of the surgeon during the conditioning of the fistula and the intralesional injection of study medication may have an effect on the efficacy outcomes. It is not clear if this level of conditioning is more extensive than current clinical practice in Scotland. Patients who had been receiving immunosuppressants and/or anti-TNFs at baseline could continue to receive stable doses during the study period.[3] However it is not clear how optimising the use of concomitant treatment would affect the generalisability of the study results to clinical practice.

The ADMIRE-CD study assessed a single treatment of darvadstrocel and the SPC notes that there is currently limited experience on the efficacy and safety of repeat administration.[1] Darvadstrocel is recommended to be given as a single dose of 120 million cells which can be divided over up to three fistula tracts. Therefore the dose injected into one fistula will be depend on the number of fistulas treated (up to a maximum of three).[1]

The pivotal ADMIRE-CD study compared darvadstrocel with placebo only and the company has suggested that there were no other relevant comparators. However, the licensed indication, for patients with an inadequate response to at least one conventional or biologic therapy, would permit use instead of other second-line therapies. The post hoc analysis, using an outcome of CPC remission, was considered by the company to be more relevant to clinicians. The results for the CPC remission outcome at week 52 are the key clinical data used in the economic analysis. However since the components of this outcome were assessed on a post hoc basis and this outcome was not included in the original study design, the risk of a false positive finding may be inflated and the results may be less robust.

SMC clinical experts considered darvadstrocel to be a therapeutic advancement. Its introduction would provide an additional and novel, less invasive, treatment approach for patients with Crohn's patients and refractory complex perianal fistulas. This is the first stem cell treatment for this condition. There may be implications for the service in preparing patients for and in administering darvadstrocel as well as for training staff in the appropriate preparation and administration of darvadstrocel.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with representation from patient groups and clinical specialists was held to consider the added value of darvadstrocel, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Perianal fistulas are an extremely debilitating complication of Crohn's disease. The symptoms of excruciating pain, discharge and incontinence can have a dramatic negative impact on the physical and mental health and quality of life of patients and their family and carers.
- This painful complication is experienced in addition to Crohn's disease itself and is often diagnosed in younger patients who may subsequently have a lifetime of disease burden.
- This is a difficult condition to treat. Current treatment options are limited and suboptimal, leading to fistula closure in only a minority of patients. There is no standardised treatment.
- Darvadstrocel is an innovative technology which may offer the prospect of long-term healing of perianal fistulas for some patients. This could transform their quality of life and reduce the burden on family members and carers.
- Darvadstrocel appears to be well tolerated and would provide another treatment option before invasive surgery.

Additional Patient and Carer Involvement

We received a patient group submission from Crohn's and Colitis UK, which is a registered charity. Crohn's and Colitis UK has received 5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Crohn's and Colitis UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

A cost-utility analysis was presented comparing darvadstrocel with control treatment (surgical EUA +/- seton placement plus curettage) in adult patients with complex perianal fistulas and non-active / mildly active Crohn's disease. A health care perspective and a 40-year time horizon was selected in the base case of the economic model.

A semi-Markov state transition cohort model, which assumed a single administration of darvadstrocel and a potential lifetime benefit for patients, was used to simulate costs and outcomes with and without darvadstrocel treatment. The model included five main health states: chronic symptomatic fistula, CPC remission, defunctioning surgery, proctectomy and death. Treatment effectiveness was based on the transition probability between chronic fistulae to CPC remission and the reverse transition indicating relapse. The model used a four week cycle length reflective of clinical assessment schedules and lengths of maintenance treatments.

The key clinical data used in the model were taken from the ADMIRE-CD study. In this study, both treatment groups received EUA and conditioning of fistulas which included seton placement if necessary. Important model parameters estimated from the study data were proportions of patients with mild and severe symptoms, time to remission, time to relapse from remission, maintenance treatment mix and probability of adverse events. Observed data on remission and relapse from the study were available up to two years. In order to estimate the probability of achieving remission or relapse over the duration of the time horizon the observed clinical data for both outcomes were extrapolated using the Gompertz function. However, the company also adjusted the Gompertz function to estimate relapse rates beyond two years (i.e. over the long term) by using the average of the rates estimated by the curve from years two and three. Time to remission and relapse were conditional on the treatment mix received in the chronic fistula and remission states respectively (i.e. darvadstrocel or control). Annual probabilities for defunctioning surgery and proctectomy were estimated from cohort studies of patients with fistulating Crohn's disease.

Health-related quality-of-life data (IBDQ) were collected in ADMIRE-CD but the company argued that these measures could not be used to estimate utility values in patients with complex perianal fistula. In addition, utility values for the disease area were not available in the published literature. As a result, utilities for each health state within the model were obtained through a separate

vignette study using samples of the UK general public (base case) and patients with Crohn's disease (scenario analysis).

Applicable costs and health resource use data were identified from retrospective data analysis from a UK hospital, expert opinion and ADMIRE-CD. The model included costs of darvadstrocel and control treatment, administration, maintenance treatments, salvage therapy, routine disease management, adverse events and last resort surgical procedures.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. The base case analysis and selected sensitivity analyses with the PAS for darvadstrocel are presented in table 2 below.

Table 2: **Base case results and selected sensitivity analysis (with PAS for darvadstrocel)**

Scenario	**ICER**
Base case	£20,930
Changing parametric model for outcomes - Gompertz curve for remission and log-normal curve for relapse	£104,552
Changing parametric model for outcomes - Generalized gamma curve for remission and Gompertz curve for relapse	£30,525
Changing parametric model for outcomes - Generalized gamma curve for remission and log-normal curve for relapse	£133,676
Combined scenario – Utility values from patient sample; probabilities for last resort surgery based on St. Marks data; generalized gamma curve for remission; log-normal curve for relapse	£137,290
Combined scenario – Combined remission as outcome; utility values from patient sample	£36,875
Long term relapse rate rates from published study and log-normal curve for short term relapse	£41,251
Relapse hazard ratio (upper CI limit)	£74,250
Remission hazard ratio (lower CI limit)	£33,240
Utility values from vignette study based on patient sample	£22,464
Decrease the time horizon to 20 years	£28,398
Increase long term remission rate for salvage treatment	£34,775
Using alternative outcome definition – Clinical remission	£34,399
Using alternative outcome definition – Combined remission	£34,505
Using St Marks retrospective data set	£21,211

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year, CI = confidence interval. PAS = patient access scheme

The main weaknesses with the analysis are:

- Observed data from the pivotal study are only available up to 2 years and there is substantial uncertainty regarding the long term clinical effectiveness of darvadstrocel. The company used a Gompertz curve to extrapolate the two effectiveness outcomes of time to CPC remission and time to relapse after CPC remission; with a further adjustment to the

Gompertz function for long term relapse as described above. The choice of curve (and the associated long term relapse rate) is a key driver of cost-effectiveness in the model and results are very sensitive to the use of alternative parametric curves. A scenario using the generalized gamma curve for remission and log-normal curve for relapse produced an ICER of £133,676. The extrapolations based on the Gompertz function estimated that of the patients achieving remission with darvadstrocel within the first year, 90% and 81% would maintain remission after 2 and 10 years respectively. This is in comparison to 83% and 69% of control patients who would maintain remission after 2 and 10 years respectively. However, the plausibility of these estimates was considered uncertain given the absence of robust clinical data.

- Quality of life assessments from the ADMIRE-CD study were not used to derive utility values. Although a separate vignette study was conducted to derive utility values there is potential for these values to be underestimations for some health states. Compared to the utility values from the general population sample used in the base case, the mean utilities elicited from the patient sample were higher for CSF, defunctioning and proctectomy states. Even though utility values were not a significant driver of cost-effectiveness in the analysis, the different sources do introduce uncertainty in the model.
- The primary outcome for the economic model (CPC remission) differs from the primary outcome of the ADMIRE-CD study (combined remission). Further, the study was not powered to detect changes in CPC remission and relapse and hence, these were analysed *post hoc*. The company provided sensitivity analysis which used combined remission as the primary outcome (see table above). The use of CPC remission in clinical practice along with its relevance to clinicians and patients is unclear.
- The economic analysis is restricted to the patient population specified in the ADMIRE-CD study and does not extend to the most severe patients experiencing complex multiple fistulae. The lack of observed long-term data also contributes to uncertainty in estimates of other parameters in the model such as the probabilities for last-resort surgeries and relative treatment effectiveness of salvage therapy compared to control.

The Committee also considered the benefits of darvadstrocel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as darvadstrocel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifier, the Committee was unable to accept darvadstrocel for use in NHS Scotland.

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

Additional information: guidelines and protocols

Currently, there are no specific Scottish or British guidelines for the management of complex perianal fistulae in patients with Crohn's disease.

The European Crohn's and Colitis Organisation (ECCO) published "3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations".[9] Following the diagnosis of fistulising perianal Crohn's disease, ECCO recommends first line treatment with infliximab or adalimumab, following adequate surgical drainage if indicated. Imaging before surgical drainage is recommended. For complex fistulae, EUA is mandatory for surgical drainage of sepsis. Also, abscess drainage and loose seton placement should be performed.[9] Additionally, to improve short-term outcomes, ECCO recommends to combine biologic therapies (including certolizumab) with ciprofloxacin. It is also noted that to enhance the effect of biologic therapies, a combination of biologic therapies with thiopurines may be considered. Lastly, the recommended therapies for continuing treatment for perianal fistula includes: pharmaceutical treatment (thiopurines and/or biologics), seton drainage, or combined pharmaceutical treatment with seton drainage.[9]

The National Institute for Health and Care Excellence (NICE) published in 2017 a briefing describing the use of video-assisted anal fistulae treatment (VAAFT). Although this is not a guideline, this briefing addresses the current NHS pathway for patients with perianal fistulae, which involves diagnosis and operation (the use of biologics is not mentioned).[10] Following the diagnosis of anal fistulae, fistulostomy is the most common surgical procedure. This involves cutting open the whole length of the fistula, from the internal opening to the external opening, before the surgeon cleans out the contents and flattens it out. This leaves an open wound which must be cleaned and dressed while healing; after 1 to 2 months, the fistula will heal into a flat scar. Other procedures carried out include: Seton placement, ligation of inter sphincteric fistula tract (LIFT), mucosal advancement flap and VAAFT, which is a technique that allows the surgeon to see inside the anal fistula tract and locate the internal opening using an endoscope light. VAAFT is designed to only affect the fistula tract, preserving sphincter muscle function and faecal continence. [10]

These documents predate the availability of darvadstrocel.

Additional information: comparators

There are no relevant medicine comparators.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
darvadstrocel	**120 million cells by intralesional injection**	**£54,000**

Costs for darvadstrocel from the company submission. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 449 patients eligible for treatment with darvadstrocel in year 1, rising to 466 patients in year 5 to which confidential uptake rates were applied.

Without PAS
The gross impact on the medicines budget was estimated to be £1.5m in year 1 rising to £8.3m in year 5. As no medicines were assumed to be displaced, the net medicines budget impact is the same as the gross.

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

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This assessment is based on data submitted by the applicant company up to and including 12 October 2018.

**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.