EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2018
EMA/92608/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Alofisel (Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue)
Treatment of anal fistula
EU/3/09/667 (EMA/OD/054/09)
Sponsor: TiGenix S.A.U.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue
International Non-Proprietary Name	Darvadstrocel
Orphan indication	Treatment of anal fistula
Pharmaceutical form	Suspension for injection
Route of administration	Intralesional injection
Pharmaco-therapeutic group (ATC Code)	L04
Sponsor's details:	TiGenix S.A.U. Marconi 1, Parque Tecnológico de Madrid Tres Cantos 28760 Madrid Spain
Orphan medicinal product designation procedural history	
Sponsor/applicant	Cellerix S.A.
COMP opinion date	8 July 2009
EC decision date	8 October 2009
EC registration number	EU/3/09/667
Post-designation procedural history	
Sponsor's name change	Name changed from Cellerix S.A. to TiGenix S.A.U - EC letter of 4 February 2003
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	L. Åkerblom, M. Menezes-Ferreira
Applicant	TiGenix S.A.U.
Application submission date	2 March 2016
Procedure start date	24 March 2016
Procedure number	EMA/H/C/004258
Invented name	Alofisel
Therapeutic indication	Alofisel is indicated 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. Alofisel should be used after conditioning of fistula. Further information on Alofisel can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	14 December 2017
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	A. Magrelli / V. Stoyanova
Sponsor's report submission date	13 April 2016, update 10 May 2016
COMP discussion and adoption of list of questions	17-19 January 2017
Oral explanation	5 December 2017

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COMP negative opinion date	20 December 2017
Appeal to the COMP opinion procedural history	
COMP Co-ordinators	E. Malikova / I. Wang
Appeal submission date	9 January 2018
Appeal oral explanation	16 January 2018
Final positive COMP opinion	18 January 2018

2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2009 was based on the following grounds:

- anal fistula (hereinafter referred to as "the condition") was estimated to be affecting approximately 2.3 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating due in particular to incontinence and sepsis aggravated as a result of surgical intervention;
- there is, at present, no satisfactory treatment that has been authorised in the Community for patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Fistulas are abnormal (non-anatomical) connections or passageways between organs or vessels that normally do not connect. The anal fistula is located between the anal canal and the skin surface near the anus. Fistulas can be classified as either "simple" or "complex." A simple fistula is low (superficial or low intersphincteric or low transsphincteric fistula tract), has a single external opening, has no pain or fluctuation to suggest perianal abscess, has no evidence of a rectovaginal fistula, and has no evidence of anorectal stricture.

The approved therapeutic indication "Alofisel is indicated 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. Alofisel should be used after conditioning of fistula' falls within the scope of the designated orphan indication "treatment of anal fistula".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

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Chronically debilitating and/or life-threatening nature

The condition is not life threatening; nevertheless, an appropriate discussion was given by the sponsor demonstrating that the condition remains chronically debilitating at the time of review. The sponsor adequately justified that the condition is chronically debilitating due to pain and itching, local or systemic infection, perianal swelling, fever in case of abscess formation, and drainage of pus, stool or blood from cutaneous fistula openings leading to social, sexual and employment restrictions.

Number of people affected or at risk

The sponsor performed a systematic literature search to identify epidemiological literature for anal fistulas in Crohn's disease, cryptoglandular fistulas, and other potential causes of anal fistula, including anal fistula due to infections, trauma, cancer, radiotherapy and congenital malformations. The literature searches were performed in PubMed, with additional systematic reviews retrieved from PubMed, EMBASE, and Cochrane Databases. In addition the sponsor performed a study by querying a large UK population-based database, The Health Improvement Network (THIN), reporting data on fistulas from all causes.

It is estimated that cryptoglandular fistulas and fistulas in Crohn's disease account for 95 - 98% of all anal fistulas, while fistulas due to, trauma, cancer, radiotherapy and congenital malformations are extremely uncommon. Very limited knowledge about the epidemiology of these types of fistulas exists, and what is available usually comes from case reports or case series. Based on the available sources, the sponsor estimated the prevalence of cancer-related, congenital, traumatic and radiation-induced anal fistulas, to be approximately 0.062 in 10,000 in the EU. Taking into account the limited information available, this estimate appears sufficiently conservative.

Infection-related anal fistulas were reported in the figures of cryptoglandular fistulas, since most of them arise as a result of cryptoglandular infection with resultant perirectal abscess. Cryptoglandular anal fistula has been estimated by the sponsor to have an incidence of 0.86 in 10,000 in the EU, based on a paper from Sainio et al from 1984 that represents the only population-based study currently available. More recently (Ommer A, 2011) the German guidelines for this disease estimate the incidence at 2 in 10,000 per year, based on an article from 2007 (Zanotti et al). However, the article from Zanotti discusses the incidence of anal fistula as a whole and not specifically for cryptoglandular fistulas, and it is based on studies from reference centres from 4 European countries, while no population-based data appear to have been collected in Europe specifically on cryptoglandular fistulas after the study of Sainio et al. It is therefore reasonable to accept that the annual prevalence of cryptoglandular fistulas is likely not above 1 in 10,000.

The prevalence of anal fistula in Crohn's disease was calculated by the sponsor on 27 studies, of which 6 were considered particularly relevant after critical appraisal of more than 300 literature sources. The selected studies included: the SEESG-CD (1999) study, a large survey of gastroenterologists, and a recent paper from Göttgens et al. (2017) with data collected from a population-based Inflammatory Bowel Disease South-Limburg cohort in the Netherlands. In this study the cumulative 5-year perianal fistula rate was 14.1% in the 1991-1998, 10.4% in the 1999-2005, and 10.3% in the 2006-2011. These are cumulative incidence data, i.e. they refer to the number of patients with Crohn's disease who would develop a fistula within 5 years. The number of patients that have the disease at a specific point in time in this period (e.g. annual prevalence or a 2-year period prevalence) may however be lower, since the average duration of disease is shorter than 5 years. The prevalence of Crohn's disease in the EU is extremely variable, from 1.5 to 213 cases per 100,000 persons in different countries, with an average of 71.2 in 100,000 (calculated from Burish et al, 2013, reporting data from the ECCO consortium from 19 studies covering most of the EU), equal to 7.1 in 10,000. Considering the

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cumulative incidence most recent data described by Gottgens et al in the Limburg cohort, that would mean that less than 1 of 10,000 people with Crohn's are affected by anal fistula over a 5-year period.

A recent (2017) query from the sponsor of The Health Improvement Network (THIN), a large UK population-based database, reported an annual prevalence of anal fistula (from all causes) in the UK population of 1.66 in 10,000.

A sensitivity analysis performed by the sponsor based on an estimated average prevalence of anal fistula of 1.69 in 10,000 in the EU resulted in a worst case scenario of 3.47 in 10,000, which was considered by the COMP as a sufficiently conservative estimate of the prevalence of anal fistula in the EU taking into account the variability of the data across member states, and the uncertainty about the potential number of asymptomatic fistulas that are not captured by studies and databases.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The anti-TNFα medicinal product infliximab has a centralized authorization in the European Union. Infliximab is indicated for the treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). Infliximab is a systemic therapy and is recommended for the second line treatment of induction and maintenance of fistula closure in European and in other international guidelines. Antibiotics are also used in case of abscess formation and fistulas that become secondarily infected.

In addition, a number of surgical techniques exist for the treatment of anal fistula. However, different techniques apply to different type of fistulas (e.g. simple vs. complex and etiology) and to different stages. Minimally invasive techniques, such as fibrin glue and fistula plug, have demonstrated inconsistent results and their use is limited. Other approaches, including mucosal advancement flap (MAF), ligation of the inter-sphincteric fistula tract (LIFT), and proctectomy with a permanent stoma, are usually applied to patients who did not respond to pharmacological treatments and, in the case of proctectomy they are reserved to the most severe cases.

Alofisel is intended for the treatment of complex anal fistula. A complex anal fistula is characterised as having an origin above the dentate line, to have multiple external openings or are associated with the presence of perianal abscess, or of a rectovaginal fistulas.. Based on the therapeutic indication received by the CHMP its position in the treatment algorithm of anal fistula in Crohn's is foreseen after patients have failed at least one conventional or biologic therapy. This includes antibiotics, immunosuppressive therapy (conventional therapy) or anti-TNFα treatment (biologic therapy). Minimally invasive surgery, such as setons, is often used at the same time as pharmacological treatment, while more invasive surgical techniques are usually applied at later stage.

Significant benefit

Regarding significant benefit, the sponsor discussed the current management algorithms of complex fistulas, in general and applicable also to Crohn's disease, including pharmacological and surgical management.

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In relation to surgery, a number of different procedures are available for this condition as described above. The heterogeneity of surgical approaches and the lack of conclusive data on the relative efficacy of each technique results in a case by case use of surgery, with surgeons making decisions on a specific technique based on a number of factors including, besides the complexity of the fistula, the degree of preservation of the surrounding tissue. For all these reasons a formal comparison of Alofisel with surgery is not appropriate for the demonstration of significant benefit since surgery will usually be performed in patients who do not respond to pharmacological treatment (including also Alofisel). In addition, Alofisel is administered at the same time as fistula conditioning, i.e. after abscess drainage and application of setons, therefore the effects demonstrated in the Alofisel pivotal trial are on top of these interventions. Furthermore, current guidelines point to a lack of consensus on which surgical technique would be preferable for later stages, and the effectiveness of some of the surgical techniques is controversial. Therefore the COMP was of the opinion that surgery was not to be considered a treatment to which Alofisel had to be compared in the context of the demonstration of significant benefit.

The significant benefit in relation to infliximab was discussed mainly based on the clinical data from the pivotal trial of Alofisel, the ADMIRE-CD study, in which a number of patients were enrolled who had been refractory to previous treatment with infliximab. ADMIRE-CD was a phase III, randomised, double blind, parallel group, placebo controlled, multicentre study spanning over a period of 24 weeks and an extended follow-up period up to 104 weeks. The primary endpoint was combined remission at week 24. Seventy-four out of the 107 patients treated with Alofisel in the study were refractory to treatment with anti-TNFα. This included a significant number of patients treated with infliximab. The clinical data showed that Alofisel treatment offered a 15.9 per cent points difference statistically significant (p= 0.030) improvement in combined remission at 52 weeks in TNFα refractory patients compared to the group of refractory patients treated with placebo, as shown in the table below. The patients refractory to anti-TNFα in the placebo group were 71/105.

Table 3 Percentages of Patients with Combined Remission at Week 52 in the Overall Population and Subpopulation Refractory to Anti-TNF (ITT population) - Pivotal Study Cx601-0302

		Alofisel	Placebo	Difference (95% CI)[b]	P-value[c]
		n/N (%)	n/N (%)		
Combined Remission					
Overall Population	ITT	58/107 (54.2)	39/105 (37.1)	17.1 (3.9, 30.3)	0.012
Refractory anti-TNF	ITT	42/74 (56.8)	29/71 (40.8)	15.9 (-0.2, 32.0)	0.030

a Combined Remission: closure of all treated external openings that were draining at baseline despite gentle finger compression and absence of collections > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment
b Percentage points. Calculated using Wald's stratified asymptotic method.
C For difference in Remission Rate (eASCs - Placebo) the p-value from the Cochran-Mantel-Haenszel test, randomisation strata as stratification variable (use of anti TNF agents or immunosuppressants at randomization)
d LOCF rules applied. Treatment failure is imputed after rescue therapy.
CI=confidence interval; ITT=intent-to-treat; n=number of patients with observation; N=number of patients in analysis population.
Source: CSR-Week 52 Cx601-0302, Table 14.2.2.1.1.1, and Post-hoc Analysis-Table EMA – 2.575

Source: Case Study Report ADMIRE-CD study

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These data were considered relevant for the demonstration of the significant benefit of Alofisel versus anti-TNFα treatment because in previous studies, e.g. the ACCENT II trial of infliximab, no response to infliximab induction treatment was achieved in approximately one third of the patient population and, amongst responders, a fraction lost response over the time. This, and the results presented by the sponsor in terms of response rate, define a medically plausible population and identify a relevant percentage of patients refractory to anti-TNFα who would benefit from treatment with Alofisel. This constitutes a significant benefit for the patients affected by anal fistula.

In relation to relative efficacy, an indirect comparison between the ADMIRE-CD study and ACCENT II, the pivotal trial of infliximab would be very difficult to perform, as the two studies were conducted several years apart, and have different endpoints. In addition the ACCENT II study of infliximab had a very different design, with administration of the product before randomization, at 0, 2, and 6 weeks, and then identification of the responders. Treatment was continued up to 54 weeks. At week 14, those with a response were randomly assigned to receive an infusion of either placebo (placebo maintenance) or 5 mg of infliximab per kilogram (infliximab maintenance) at weeks 14, 22, 30, 38, and 46 and were followed until week 54. The sponsor presented data showing a longer sustained response rate with Alofisel than with infliximab, with the overall patient population and the refractory patient population treated with Alofisel still in remission at 52 weeks, while only 23% of patients treated with infliximab in the ACCENT II trial were still in remission at 54 weeks. The COMP considered this data promising but did not consider the data confirmative enough to base a significant benefit decision upon, due to the differences in the study populations of the ADMIRE-CD and the ACCENT-II study.

Similarly, the potential major contribution to patient care linked to one single administration of Alofisel *vs*. multiple infusions (every 6-8 weeks) of infliximab was considered important, but more long term efficacy data on the two products would be needed for considering this as a robust ground of significant benefit.

The COMP adopted a positive opinion by a majority of 23 members, based on a clinically relevant advantage in the population of patients that do not respond to anti-TNFα treatment. Five COMP members signed a divergent position on the conclusion of the COMP on prevalence and significant benefit. The divergent position is appended to this report.

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4. COMP final position on review of criteria for orphan designation adopted on 18 January 2018

The COMP concluded that:

- the proposed therapeutic indication falls within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of anal fistula (hereinafter referred to as "the condition") is estimated to remain below 5 in 10,000 and was concluded to be less than 3.47 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to pain and itching, recurring local infection and abscess formation, perianal swelling, stool or blood from cutaneous fistula openings leading to social, sexual and employment restrictions and severely compromised quality of life;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Alofisel will be of potential significant benefit to those affected by the orphan condition is confirmed. This is based on clinical data from the phase 3 randomized placebo-controlled clinical trial showing significant clinical efficacy in patients that were refractory to treatment with anti-TNFα medicinal products, currently authorized for the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products recommends that Alofisel, darvadstrocel, EU/3/09/667 for treatment of anal fistula is not removed from the Community Register of Orphan Medicinal Products.

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Appendix 1

Divergent position expressed by some members of the COMP

A divergent opinion was declared by five members. The following was considered as grounds for the divergent opinion:

- Insufficient evidence has been presented to conclude that the prevalence of anal fistula (hereinafter referred to as "the condition") remains below 5 in 10,000 at the time of the review of the designation criteria. The sponsor presented a prevalence calculation that assumed a prevalence of 3.47 in 10,000 persons in the European Union. The sponsor's methodology did not include all possible sources of evidence on the prevalence of anal fistula of all potential aetiologies. In addition, the assumption that a maximum of 14.7% of Crohn's disease patients develop anal fistulas was not sufficiently substantiated, because there is scientific literature suggesting higher figures.
- The significant benefit over existing treatment options is insufficiently substantiated to justify the maintenance of the orphan designation, as per the presented clinical data. The clinical data showed that Alofisel treatment offered a 15.2% improvement in combined remission versus placebo in refractory patients, which is considered of questionable clinical relevance to support significant benefit. In addition the observed improvement in combined remission did not lead to improvements in quality of life of patients as measured by secondary endpoints. The clinical trial design and the overall outcome therefore did not allow the quantifying of the clinically relevant advantage relative to the best standard of care including surgical procedures and authorised anti-TNFα treatment with infliximab. Indirect comparisons of efficacy versus infliximab were attempted but not considered methodologically valid, due to differences in proportion of patients with conditioning. The sponsor therefore failed to establish that Alofisel is of significant benefit to the patients of the orphan condition as defined in the granted therapeutic indication.

Kateřina Kopečková (Czech Republic)

Armando Magrelli (Italy)

Daniel O'Connor (United Kingdom)

Violeta Stoyanova-Beninska (Netherlands)

Kerstin Westermark (European Commission Nominated)

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