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1. NAME OF THE MEDICINAL PRODUCT

Alofisel®

5 million cells/mL suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Alofisel contains darvadstrocel which is an expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells - eASC).

2.2 Qualitative and quantitative composition

Each vial contains a suspension of 30 million cells (eASC) in 6 mL solution, corresponding to a concentration of 5 million cells/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

White to yellowish homogenous suspension containing a sediment, which is readily dispersed on shaking.

Patient information brochure

The marketing of Alofisel is subject to a risk management plan (RMP) including a 'Patient information brochure'. The 'Patient information brochure', emphasizes important safety information that the patient should be aware of before and during treatment.

Please explain to the patient the need to review the brochure before starting treatment.

Prescriber guide

This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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, see section 4.2.

4.2 Posology and method of administration

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

Posology

A single dose of Alofisel 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 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. There is currently limited experience with the efficacy or safety of repeat administration of Alofisel.

Special populations

Elderly

Data on the use of darvadstrocel in the elderly population are limited, however, given the cell-based nature of darvadstrocel and its local administration route it is not expected that the benefit-risk profile of darvadstrocel in elderly patients will differ from that observed in non-elderly patients. Therefore, no dose adjustment is required in elderly patients.

Hepatic or renal impairment

Data on the use of darvadstrocel in patients with hepatic or renal impairment are not available, however, given the cell-based nature of darvadstrocel and its local administration route it is not expected that the benefit-risk profile of darvadstrocel in hepatically or renally impaired patients will differ from that observed in non-hepatically or non-renally impaired patients. Therefore, no dose adjustment is required in hepatically or renally impaired patients.

Paediatric population

The safety and efficacy of darvadstrocel in children aged 0 to 17 years have not yet been established. No data are available.

Method of administration

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 fistulas is needed prior to treatment. This comprises an 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 Alofisel 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 Alofisel, the fistula tracts should be conditioned as follows:

Firstly, if setons are in place, they must be removed. Conditioning of the fistula tracts comprises the following steps:

- a) Identify the location of the internal openings. For this, it is recommended to inject a sodium chloride 9 mg/mL (0.9%) solution through the external openings until it gets out through the internal openings. The injection of any other substance through the fistula tracts, such as hydrogen peroxide, methylene blue, iodine solutions or hypertonic glucose solutions is not allowed, as these agents compromise the viability of the cells to be injected.
- b) Perform a vigorous curettage of all fistula tracts, with special emphasis in the internal openings areas, using a metallic curette.
- c) Suture the internal openings to close them.

After conditioning of the fistula tracts, Alofisel should be administered according to the following two steps:

1. Preparation
 - a) Re-suspend the cells by gently tapping the bottom of the vials until a homogeneous suspension is obtained, avoiding bubble formation. Each vial should be used immediately after re-suspension to prevent the cells from re-sedimenting.

- b) Remove the cap from the vial, turn the vial upside down, and gently aspirate the whole content using a syringe with a conventional needle no thinner than 22G.
- c) Replace the needle with a longer needle, also no thinner than 22G, in order to reach the intended sites of injection. A needle for spinal anaesthesia measuring around 90 mm in length is required.
- d) Repeat steps (a), (b) and (c) for each of the vials in turn after the cells from one vial have been injected.

2. Injection

Two of the vials should be used for the internal openings and the remaining two for the external openings. As commonly done for intra-tissue injections, just after injecting the needle tip into each intended injection site, perform a slight aspiration to avoid intravascular administration.

- a) Injection around the internal openings of the fistulas tracts: insert the needle through the anus and proceed as follows:
 - If there is a single internal opening, inject the content of each of the two vials (one after the other) in small deposits into the tissue surrounding the single internal opening.
 - If there are two internal openings, inject the content of the first of two vials in small deposits into the tissue around one internal opening. Then inject the content of the second vial into the tissue around the second internal opening and make small deposits of the cell suspension.
- b) Injection along the walls of the fistula tracts: insert the needle through the external openings and, from within the fistulas lumen:
 - If there is a single external opening, inject separately the content of each of the remaining two vials superficially into the tissue walls along the length of the fistula tracts, making small deposits of the cell suspension.
 - If there are two or three external openings, inject the content of the remaining two vials equally between the associated tracts.

The procedure for injection along the walls of the fistula tracts should be performed based on prior knowledge of the anatomy and topology of the fistula tracts, as determined during the fistulas characterisation. Ensure cells are not injected into the lumen of the fistula tracts to avoid leakage of cells.

Softly massage the area around the external openings for 20–30 seconds and cover the external openings with a sterile bandage.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to bovine serum.

4.4 Special warnings and precautions for use

Alofisel may contain trace amounts of benzylpenicillin and streptomycin. This should be considered in patients with known acute hypersensitivity (history of anaphylactic reactions) to these classes of compounds.

Local anaesthesia is not recommended due to the unknown effect of local anaesthetics on the injected cells.

The use of hydrogen peroxide, methylene blue, iodine solutions or hypertonic glucose solutions through the fistula tracts is not allowed before, during, or after the injection of Alofisel as this may compromise cells viability and, therefore, may affect the effectiveness of the treatment.

Alofisel is indicated for intralesional injection only. Alofisel must not be administered using a needle thinner than 22G. Thinner gauge needles can cause cell disruption during injection, and may compromise cell viability and therefore may affect efficacy of treatment.

As Alofisel is a living stem cell therapy it cannot be sterilised, and therefore could contain potentially infected biological material although the risk is considered to be low and controlled in the manufacturing. Patients should be followed up for potential signs of infection after administration.

Conditioning reactions

Conditioning of fistulas has been associated with proctalgia and procedural pain (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed.

In vitro interaction studies have shown that the cell viability and immunomodulatory function of Alofisel is not affected by the presence of clinically-relevant concentrations of conventional therapies for Crohn's disease (infliximab, methotrexate and azathioprine).

Dyes and local anaesthesia is not recommended due to the unknown effect of local anaesthetics on the injected cells (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of darvadstrocel in pregnant women.

Animal studies are not available with respect to reproductive toxicity (see section 5.3).

Darvadstrocel is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

As a precautionary measure, darvadstrocel is not recommended for administration during breast-feeding.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

Darvadstrocel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common treatment-emergent adverse events were anal abscess (Alofisel: 19.4% patients; control group: 13.7% patients), proctalgia (Alofisel: 14.6% patients; control group: 11.8% patients) and anal fistula (Alofisel: 10.7% patients; control group: 7.8% patients).

Tabulated list of adverse reactions

The following listing of adverse reactions is based on the clinical trial experience and is displayed by system organ class. The frequency of adverse reactions is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from available data).

Table 1. Adverse reactions

System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Common	Anal abscess
Gastrointestinal disorders	Common	Proctalgia*
	Common	Anal fistula
Injuring, poisoning and procedural complications	Common	Procedural pain*

*Conditioning reactions occurring up to seven days after the fistula cleaning for treatment administration.

Description of selected adverse reactions

Anal abscess

Up to Week 52, 20 (19.4%) and 14 (13.7%) patients developed 21 and 19 anal abscess adverse events in the Alofisel and control groups, respectively, of which 4 and 5 adverse events in respective groups (3.9% patients in both groups) were of severe intensity. Up to Week 104, 15 (14.6%) and 8 (7.8%) patients developed 15 and 9 serious adverse events of anal abscess in the Alofisel and control groups, respectively.

Proctalgia

Up to Week 52, 15 (14.6%) and 12 (11.8%) patients developed 20 and 17 proctalgia adverse events in the Alofisel and control groups, respectively, none of these events being serious in any group up to Week 104. There were no patients in Alofisel group with events of proctalgia of severe intensity and 3.9% patients with 4 events in the control group.

Anal fistula

Up to Week 52, 11 (10.7%) and 8 (7.8%) patients developed 12 and 8 anal fistula adverse events in the Alofisel and control groups, respectively, none of these being of severe intensity. Up to Week 104, 5 (4.9%) and one (<1.0%) patients developed 5 and 1 anal fistula serious adverse events in the Alofisel and control groups, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {not yet assigned}, ATC code: {not yet assigned}.

Mechanism of action

Darvadstrocel contains expanded adipose stem cells (eASC), which exhibit immunomodulatory and anti-inflammatory effects at inflammation sites.

Anal fistulas typically present as fissures penetrating the intestinal lumen and perianal skin surface, and are characterised by local inflammation that is exacerbated by bacterial infections and faecal contamination. In the inflamed area, there is infiltration of activated lymphocytes and local release of inflammatory cytokines.

Inflammatory cytokines, in particular IFN- γ released by activated immune cells (i.e., 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.

Pharmacodynamic effect

In the ADMIRE-CD study, 36% of the eASC-treated patient population showed anti-donor antibody production at Week 12. Of patients with donor-specific antibodies (DSA) at Week 12, 30% had cleared DSA by Week 52. Lack of *de novo* DSA generation was observed between Week 12 and Week 52. Limited data exist but there does not appear to be a detrimental effect of DSA on efficacy and safety.

Clinical efficacy

The efficacy of Alofisel was assessed in the ADMIRE-CD study. This was a randomised, double blind, parallel group, placebo-controlled, multicentre clinical trial to assess efficacy and safety of Alofisel for the treatment of complex perianal fistulas in Crohn's disease patients.

A total of 212 patients were randomised, and 205 patients received a local intralesional injection of either Alofisel 120 million cells or placebo in a 1:1 design. Patients were to have had draining complex perianal fistulas with an inadequate response to at least one of the following treatments: antibiotics, immunosuppressants or anti-TNFs. Concomitant use of stable doses of immunosuppressants (18% of patients) or anti-TNFs (33%) or both (28%) was allowed during the study.

The primary endpoint was the combined remission at Week 24 after study treatment, defined as clinical closure of all treated fistulas (absence of draining despite gentle finger compression) and absence of collection (>2 cm) confirmed by blinded central MRI. The key secondary endpoints were defined as clinical remission (clinical closure of all treated fistula) and response (clinical closure of at least 50% of all treated fistulas) at Week 24. In addition a long term follow-up was conducted up to Week 52.

	Alofisel group (Alofisel+standard of care*) N= 103	Control group (Placebo+standard of care*) N= 102	P value
Combined remission at Week 24 (% patients)	52	35	0.019
Combined remission at Week 52 (% patients)	56	38	0.009

* It might include abscess drainage, seton placement/removal, curettage, suture of internal openings and medical treatments

Results of the key secondary endpoints show that the proportion of patients with clinical remission at Week 24 was 55 % in the Alofisel group and 42 % in the control group (p=0.052) and the corresponding figures for response were 69% and 55% (p=0.039).

The proportion of patients with clinical remission at Week 52 was 59 % in the Alofisel group and 41 % in the control group (p=0.012) and corresponding figures for response were 66% and 55% (p=0.114). In a limited number of patients followed up to Week 104, clinical remission at Week 104 was 56% in the Alofisel group and 40% in the control group.

In Alofisel group, the number of patients who had combined remission at Week 24 and subsequently developed anal abscess/anal fistula by Week 52 was 2.9% (3/103), whereas the number of patients without combined remission at Week 24 who subsequently developed anal abscess/anal fistula by Week 52 was 9.7% (10/103).

In control group, the number of patients who had combined remission at Week 24 who developed anal abscess/anal fistula by Week 52 was 4.9% (5/102), whereas the number of patients without combined remission at Week 24 who developed anal abscess/anal fistula by Week 52 was 2.9% (3/102).

There is currently limited experience with the efficacy or safety of repeat administration of Alofisel.

5.2 Pharmacokinetic properties

The product is intended for intralesional injection.

The nature and intended clinical use of darvadstrocel are such that conventional studies of pharmacokinetics (absorption, distribution, metabolism and elimination) are not applicable.

A number of biodistribution studies in preclinical models were conducted with the objective of evaluating the persistence of eASC at the site of injection and their potential migration into other tissues or organ systems. After perianal and intrarectal injection of human eASC in athymic rats, cells were present in the rectum and jejunum at the site of injection for at least 14 days and were

undetectable after 3 months. eASC were not present in any of the tissues analysed after 3 months or 6 months.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Reproductive and developmental toxicity studies have not been performed for darvadstrocel because preclinical biodistribution studies indicated no migration and integration of eASC into reproductive organs following administration of eASC via different routes.

The effect of *ex vivo* expansion on the genetic stability of cells has been assessed *in vitro* without any indication of carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dulbecco's Modified Eagle's Medium (DMEM).
Human serum albumin 20%.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store between 15°C and 25°C.

Keep the product within the secondary packaging (cardboard box) and inside the shipping container at all times until its administration, to maintain the required temperature.

Preserve the container away from heat and direct light sources and do not refrigerate or freeze.

Do not irradiate.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Alofisel is supplied as one treatment dose contained in 4 Type I glass vials. Each vial contains 6 mL of eASC suspension and is closed with a rubber stopper and a flip-off seal. The vials are placed inside a cardboard box.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Israel Ltd.
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P.O.B 4140
Petach Tikva 4951125

8. MANUFACTURER

TiGenix, S.A.U
C/ Marconi 1, parque tecnologico de madrid,
28760 Tres Cantos
Madrid, Spain

9. MARKETING AUTHORISATION NUMBER