ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alofisel 5×10^6 cells/mL dispersion for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Alofisel (darvadstrocel) is 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 30×10^6 cells (eASC) in 6 mL of dispersion, corresponding to a concentration of 5×10^6 cells/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection (injection).

The dispersion of cells may have settled in the bottom of the vial forming a sediment. After gentle re-suspension, the product is a white to yellowish homogeneous dispersion.

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 only after conditioning of the fistulas (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 darvadstrocel consists of 120×10^6 cells supplied in 4 vials. Each vial contains 30×10^6 cells in 6 mL of dispersion. 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 120×10^6 cells it is possible to treat up to three fistula tracts that open to the perianal area.

The efficacy or safety of repeat administration of Alofisel has not been established.

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 impairment
Data on the use of darvadstrocel in patients with hepatic 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 impaired patients will differ from that observed in non-hepatically impaired patients. Therefore, no dose adjustment is required in hepatically impaired patients.

Renal impairment
Data on the use of darvadstrocel in patients with 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 renally impaired patients will differ from that observed in non-renally impaired patients. Therefore, no dose adjustment is required in renally impaired patients.

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

Method of administration

Perilesional use.

For injection in the fistula tract tissue in a surgical environment under anaesthesia (general or regional (see section 4.4)) as described below.

In line with standards for the management of complex perianal fistulas, characterisation of the patient's fistulas is needed prior to treatment. It is recommended that at least 2 to 3 weeks before the administration day, preparatory surgery is performed comprising exploration (under anaesthesia) of fistula anatomy (number of existing fistulas and openings), topography (extent and relationship with the sphincters and other pelvic muscles), potential associated complications (such as abscesses) and whether local mucosal disease is mild or inactive. Vigorous curettage of all fistula tracts is recommended, with special emphasis in the internal openings area, using a metallic curette. In case of an abscess, incision and drainage are needed, and setons should be placed, if appropriate, in accordance with routine surgical procedures. Before scheduling Alofisel administration, the surgeon must ensure that no abscesses are present.

Immediately prior to the administration of Alofisel, the fistula tracts should be conditioned as follows:

a) If setons are in place, they must be removed.
b) Identify the location of the internal openings. For this, injection of a sodium chloride 9 mg/mL (0.9%) solution through the external openings until it gets out through the internal openings is recommended. 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 (see section 4.4 and section 4.5).
c) Perform a vigorous curettage of all fistula tracts, with special emphasis in the internal openings areas, using a metallic curette.
d) Suture closed the internal openings.

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

1. Preparation
   a) The expiry time: date of Alofisel should be re-confirmed; vials should then be removed from the outer packaging.
   b) Re-suspend the cells by gently tapping the bottom of the vials until a homogeneous dispersion is obtained, avoiding bubble formation. Each vial should be used immediately after re-suspension to prevent the cells from re-sedimenting.
   c) Remove the cap from the vial, gently turn the vial upside down, and gently aspirate the whole content using a syringe with a conventional needle no thinner than 22G (see section 4.4).
   d) Replace the needle with a longer needle, also no thinner than 22G, in order to reach the intended sites of injection. For example, a needle for spinal anaesthesia measuring around 90 mm in length is required.
   e) Repeat steps (b), (c) and (d) 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 injection along the walls of the fistula tracts (via external openings). After inserting the needle tip into each intended injection site, perform a slight aspiration to avoid intravascular administration.
   a) Injection around the internal openings of the fistula 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 in small deposits into the tissue around the second internal opening.
   b) Injection along the walls of the fistula tracts: insert the needle through the external openings and, from within the fistula 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 dispersion.
   - 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 fistula 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, bovine serum or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after the expiry date of the product.

General

Alofisel may contain trace amounts of either gentamicin or benzylpenicillin and streptomycin. This should be considered in patients with known hypersensitivity to these classes of antibiotics.

Local anaesthesia is not recommended due to the unknown effect of local anaesthetics on the injected cells (see section 4.2).

The injection of any substance other than sodium chloride 9 mg/mL (0.9%) solution (e.g. hydrogen peroxide, methylene blue, iodine solutions or hypertonic glucose solutions) (see section 4.2 and section 4.5) through the fistula tracts is not allowed before, during, or after the injection of Alofisel as these may compromise the viability of the cells and, therefore, may affect the effectiveness of the treatment.

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.

Transmission of an infectious agent

As Alofisel is a living stem cell therapy it cannot be sterilised, a risk of transmission of infectious agents exists, although the risk is considered to be low and controlled in the manufacturing process. Healthcare professionals administering darvadstrocel must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Conditioning reactions

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

Blood, organ, tissue and cell donation

Patients treated with Alofisel must not donate blood, organs, tissues and cells for transplantation.

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).

The injection of any substance other than sodium chloride 9 mg/mL (0.9%) solution (e.g. hydrogen peroxide, methylene blue, iodine solutions or hypertonic glucose solutions) (see section 4.2 and section 4.4) through the fistula tracts and use of local anaesthesia is not recommended due to the unknown effect 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

It is unknown whether darvadstrocel is excreted in human milk. A risk to the breast-fed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Alofisel therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

Based on clinical trial and post-marketing data, the most commonly reported adverse drug reactions were anal abscess, proctalgia and anal fistula with the most commonly reported serious adverse drug reactions of anal abscess and anal fistula.

Tabulated list of adverse reactions

The following listing of adverse reactions is based on the clinical trial and post-marketing experience and is displayed by system organ class. The frequency of adverse reactions is defined from clinical trial experience using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 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†

*Also seen in post-marketing experience
†Conditioning reactions occurring up to seven days after the fistula preparation for treatment administration.

Description of selected adverse reactions

The following adverse reactions were identified in the multicentre, pivotal clinical trial ADMIRE-CD.

Anal abscess
Up to week 52, 20 (19.4%) and 14 (13.7%) patients developed 21 and 19 anal abscesses in the Alofisel and control groups, respectively, of which 4 and 5 anal abscesses in respective groups (3.9% patients in both groups) were of severe intensity. Treatment-related anal abscess were reported in 8 (7.8%) and 9 (8.8%) patients in the Alofisel and control groups, respectively. Up to week 104, 15 (14.6%) and 8 (7.8%) patients developed 15 and 9 serious anal abscesses 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 in the Alofisel and control groups, respectively, none of these proctalgia being serious in any group up to week 104. Treatment-related proctalgia were reported in 5 (4.9%) and 8 (7.8%) patients in the Alofisel and

control groups, respectively. There were no patients in Alofisel group with proctalgia of severe intensity and 3.9% patients with 4 proctalgia in the control group.

Anal fistula
Up to week 52, 11 (10.7%) and 8 (7.8%) patients developed 12 and 8 anal fistulas in the Alofisel and control groups, respectively, none of these being of severe intensity. Treatment-related anal fistula were reported in 3 (2.9%) and 3 (2.9%) patients in the Alofisel and control groups, respectively. Up to week 104, 5 (4.9%) and one (< 1.0%) patients developed 5 and 1 serious anal fistulas 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data regarding overdose of Alofisel is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants, ATC code: L04AX08.

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, 63/103 of the eASC-treated patient population were analysed for the presence of donor-specific antibodies (DSA) at baseline and week 12. At week 12, 23/63 (36%) showed anti-donor antibody production. Of patients with DSA at week 12, 7/23 (30%) had cleared DSA by week 52. Lack of *de novo* DSA generation was observed between week 12 and week 52. No association between DSA results and safety or efficacy up to week 52 was seen in the subset tested.

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 injection of either darvadstrocel 120×10^6 cells or placebo in a 1:1 design. Patients 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

* Including 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).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Alofisel in one or more subsets of the paediatric population in the treatment of anal fistula (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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) (containing amino acids, vitamins, salts and carbohydrates).
Human albumin.

6.2 Incompatibilities

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

6.3 Shelf life

72 hours.

6.4 Special precautions for storage

Store between 15 ºC and 25 ºC.

Keep the medicinal product within the outer carton to protect from light and moisture, 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.

Do not refrigerate or freeze.

Do not irradiate or otherwise sterilise.

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

Type I glass vial. Each vial contains 6 mL of eASC dispersion and is closed with a rubber stopper and a flip-off seal. The vials are placed inside a cardboard box.

Pack size: 4 vials.
1 dose consists of 4 vials of 6 mL (in total 24 mL).

6.6 Special precautions for disposal and other handling

Preparation prior to administration

Alofisel must not be filtered or administered using a needle thinner than 22G (see section 4.4).

Immediately before use, Alofisel must be re-suspended by gently tapping the bottom of the vial until a homogeneous dispersion is obtained, avoiding bubble formation. For further information on the use of Alofisel see section 4.2.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Alofisel (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1261/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2018
Date of latest renewal: 10 January 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

TIGENIX, S.A.U.
C/ Marconi, 1, Parque Tecnológico de Madrid, 28760 Tres Cantos, Madrid, Spain

Takeda Ireland Ltd.
Grange Castle Business Park, Nangor Road, Dublin 22, D22 XR57, Ireland

Name and address of the manufacturer responsible for batch release

TIGENIX, S.A.U.
C/ Marconi, 1, Parque Tecnológico de Madrid, 28760 Tres Cantos, Madrid, Spain

Takeda Ireland Ltd.
Grange Castle Business Park, Nangor Road, Dublin 22, D22 XR57, Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Alofisel in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority. The aim of the educational programme is to provide information on how to correctly administer the product in order to minimise the risk of medication errors and to increase awareness about the potential transmission of infectious agents.

The MAH shall ensure that in each Member State where Alofisel is marketed, all healthcare professionals who are expected to handle and administer Alofisel have access to the educational package for health professionals.

- **The educational material for health professionals** should contain:
    - The Summary of Product Characteristics
    - Guide for pharmacists with instructions on the appropriate reception and storage of Alofisel.
    - Guide in form of a video for surgeons and other health professionals involved in the preparation and administration of Alofisel.
    - Guide for surgeons and other health professionals describing the method of administration
    - Guide for health professionals providing information on potential for microbial information and advice on steps to follow in case a positive culture is identified.

- These shall contain the following key elements:
    - Relevant information on the risk of medication errors and the potential for transmission of infectious agents and details on how to minimise these, including reception, storage and administration instructions (i.e. fistula conditioning, preparation and injection).
    - Instructions how to handle medication errors and transmission of infectious agents

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
In order to follow-up on the efficacy of Alofisel, the MAH should submit the results of a Phase III randomised double-blind, placebo-controlled study Cx601-0303 investigating a single administration of Cx601 for the treatment of complex perianal fistulas in Crohn's disease patients.	Final Report to EMA: 1Q/2Q 2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ALOFISEL 5 × 10^6 cells/mL dispersion for injection.
Darvadstrocel.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 30 × 10^6 cells in 6 mL of dispersion.
The medicine contains cells of human origin.

3. LIST OF EXCIPIENTS

Also contains: Dulbecco's Modified Eagle´s Medium (DMEM) and Human albumin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection.
1 dose consists of 4 vials of 6 mL (in total 24 mL)
30 × 10^6 cells/6 mL
4 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Perilesional use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store between 15 ºC and 25 ºC.
Do not refrigerate or freeze.
Keep the medicinal product within the outer carton to protect from light and moisture, and inside the shipping container at all times until its administration, to maintain required temperature.
Do not irradiate or otherwise sterilise.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1261/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ALOFISEL 5×10^6 cells/mL injection.
Darvadstrocel.
Perilesional use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30×10^6 cells/6 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Alofisel 5 × 10^6 cells/mL dispersion for injection
darvadstrocel

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or surgeon.
- If you get any side effects, talk to your surgeon or doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alofisel is and what it is used for

The active ingredient of Alofisel is darvadstrocel which consists of stem cells which are taken from the fat tissue of a healthy adult donor (so-called allogenic stem cells) and then grown in a laboratory. Adult stem cells are a special type of cells found in many adult tissues, whose primary role is the repair of the tissue in which they are found.

Alofisel is a medicine used for the treatment of complex perianal fistulas in adult patients with Crohn´s disease (a disease causing inflammation of the gut) when the other symptoms of the disease are controlled or have a mild intensity. Perianal fistulas are abnormal channels that connect parts of the lower bowel (rectum and anus) and the skin near the anus, so that one or more openings appear near the anus. Perianal fistulas are described as complex if they have multiple channels and openings, if they penetrate deep inside your body or if they are associated with other complications such as collections of pus (infected liquid also called abscesses). Perianal fistulas can cause pain, irritation and discharge of pus through the openings to the skin.

Alofisel is used when the fistulas have not responded sufficiently well to previous treatment. When injected close to the perianal fistulas, Alofisel reduces their inflammation, increasing the likelihood of the fistulas healing.

2. What you need to know before you are given Alofisel

You must not be given Alofisel

- if you are allergic to darvadstrocel, bovine serum or to any of the ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or surgeon before you are given Alofisel.

Alofisel may contain traces of either gentamicin or benzylpenicillin and streptomycin (antibiotics). This should be considered if you are allergic to these antibiotics, as these antibiotics are used in the manufacturing process of this medicine.

Alofisel is a living cell therapy and, therefore, the final product cannot be sterilised. The product is checked at different stages during its manufacture to ensure that it is free of infection. Because the final check takes place just before Alofisel is sent to the hospital, the results of this last check are not known when it is given to you. In the unlikely event that the results detected an infection, your treatment team will be informed who will tell you if you need any laboratory tests of treatment for the infection. If after the procedure you feel ill or have fever, please inform your physician as soon as you can.

Before receiving Alofisel you will undergo the preparation of your fistulas. You may experience pain in the rectum or anus, and pain occurring after fistula preparation.

After you receive Alofisel do not donate blood, organs, tissues or cells for transplants.

Children and adolescents

This medicine should not be given to children and adolescents below 18 years of age. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor/surgeon for advice before you are given this medicine. Treatment with Alofisel is not recommended during pregnancy. Women of childbearing age should use effective contraception during treatment with Alofisel.

The effect of Alofisel on breast-feeding women is not known, and it may harm your breast-fed child. Your doctor will help you decide whether to stop breast-feeding, or whether to stop taking Alofisel, considering the benefit of breast-feeding to the baby and the benefit of Alofisel to the mother.

Driving and using machines

Alofisel is not likely to affect your ability to drive or use tools or machines.

3. How Alofisel is given

Alofisel will always be given to you by a healthcare professional.

You may have had an initial consultation with the Surgeon 2 to 3 weeks prior to Alofisel administration. The following information is related to the day when Alofisel is administered.

Alofisel is injected by a surgeon in the fistula tract tissue.

The recommended dose is 4 vials of 6 mL (120×10^6 cells).

Before treatment with Alofisel, you will be given an anaesthetic.

Once you have been anaesthetised (general or regional anaesthesia), your surgeon will:
- prepare the fistulas with sodium chloride 9 mg/mL (0.9%) solution and remove any scar tissue.
- stitch up the inner openings of the fistulas.
- inject Alofisel. Half of the dose will be injected into the tissue around the inner openings of the fistulas, and half of the dose in the tissue walls along the fistulas.

- massage softly for 20 to 30 seconds the area where the fistula opens on to the skin near your anus.

If you have any further questions on the use of this medicine, ask your doctor or surgeon.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects of Alofisel treatment are related to the preparation of your fistulas. In general, these side effects are quite mild and disappear in the days following the fistula procedure. These side effects may occur up to seven days after the procedure.

Common side effects (may affect up to 1 to 10 patients):
- anal abscess
- anal fistula
- proctalgia (pain in the rectum or anus).
- procedural pain (pain after fistula preparation)

Reporting of side effects

If you get any side effects, talk to your doctor or surgeon. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alofisel

The following information is intended for doctors only.

Do not use this medicine after the expiry date which is stated on the label and the carton.

Store between 15 °C and 25 °C.

Do not refrigerate or freeze.

Keep the medicine inside the cardboard box to protect from light and moisture, and within the shipping container at all times until its administration, to maintain the required temperature.

Alofisel must not be irradiated or otherwise sterilised.

6. Contents of the pack and other information

What Alofisel contains

– The active ingredient is darvadstrocel which consists of human stem cells obtained from the fat tissue of a healthy adult donor that are subsequently grown (expanded) in the laboratory and provided at a concentration of 5×10^6 cells per millilitre in vials which each contain 6 millilitres, i.e. 30×10^6 cells per vial.
– There are two excipients used for storage of the cells: one is a liquid called Dulbecco's Modified Eagle´s Medium containing nutrients for the cells (amino acids, vitamins, salts and carbohydrates), and the other is human albumin, which is a natural protein found in the human body.

What Alofisel looks like and contents of the pack

Alofisel is a dispersion for injection. During shipment, the cells may have settled in the bottom of the vials forming a sediment and will need to be resuspended. After the cells have been resuspended (by gentle manual tapping), Alofisel is a white to yellowish homogenous dispersion.

Alofisel is supplied on an individual patient basis. An individual dose of Alofisel comprises 4 glass vials each containing 6 millilitres of Alofisel contained within a cardboard box.

Marketing Authorisation Holder

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

Manufacturer

TiGenix S.A.U.
C/Marconi 1
Parque Tecnológico de Madrid
28760 Tres Cantos, Madrid
Spain

Takeda Ireland Ltd.
Grange Castle Business Park
Nangor Road, Dublin 22, D22 XR57
Ireland

This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europe.eu.

The following information is intended for healthcare professionals only:

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after the expiry date of the product.

Preparation prior to administration

Alofisel must not be filtered or administered using a needle thinner than 22G.
Immediately before use, Alofisel must be re-suspended by gently tapping the bottom of the vial until a homogeneous dispersion is obtained, avoiding bubble formation.

Administration

Immediately prior to the administration of Alofisel, the fistula tracts should be conditioned as follows:

a) If setons are in place, they must be removed.

b) Identify the location of the internal openings. For this, injection of a sodium chloride 9 mg/mL (0.9%) solution through the external openings until it gets out through the internal openings is recommended. 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 (see section 4.4 and section 4.5).
c) Perform a vigorous curettage of all fistula tracts, with special emphasis in the internal openings areas, using a metallic curette.
d) Suture closed the internal openings.

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

1. Preparation
    a) The expiry time: date of Alofisel should be re-confirmed; vials should then be removed from the outer packaging.
    b) Re-suspend the cells by gently tapping the bottom of the vials until a homogeneous dispersion is obtained, avoiding bubble formation. Each vial should be used immediately after re-suspension to prevent the cells from re-sedimenting.
    c) Remove the cap from the vial, gently turn the vial upside down, and gently aspirate the whole content using a syringe with a conventional needle no thinner than 22G (see section 4.4).
    d) Replace the needle with a longer needle, also no thinner than 22G, in order to reach the intended sites of injection. For example, a needle for spinal anaesthesia measuring around 90 mm in length is required.
    e) Repeat steps (b), (c) and (d) 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 injection along the walls of the fistula tracts (via external openings). After inserting the needle tip into each intended injection site, perform a slight aspiration to avoid intravascular administration.

    a) Injection around the internal openings of the fistula 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 in small deposits into the tissue around the second internal opening.

    b) Injection along the walls of the fistula tracts: insert the needle through the external openings and, from within the fistula 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 dispersion.
    - 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 fistula 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.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Alofisel (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.