מאי 2019

רופא/ה, רוקח/ת נכבד/ה,

Alofisel® ; אלופיסל®

חברת טקדה מבקשת מתכבדת להודיעכם כי העלון לרופא של התכשיר שבנדון, התעדכן במאי 2019.
העדכונים המהותיים ביותר מופיעים במכתב זה, אך קיימים עדכונים נוספים.
למידע נוסף יש לעיין בעלון לרופא המעודכן אשר נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות.
כמו-כן, וניתן לקבלו מודפס על ידי פניה לבעל הרישום, טקדה ישראל בע"מ בטלפון 03-3733140.

נוסח ההתוויה כפי שאושרה ע"י משרד הבריאות:

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).

צורת מינון:

Suspension for injection

הרכב וחוזק:

Darvadstrocel 5,000,000 cells/ML

בברכה,

חן פרידליס
רוקחת ממונה

IL/CX6/0519/0017

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העדכונים העיקריים בעלון לרופא הינם (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה):

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

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Posology

A single dose of Alofisel consists of 120 million cells ~~distributed~~ supplied 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 t~~The efficacy or safety of repeat administration of Alofisel has not been established.

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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

For ~~intralesional use~~ 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 ~~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 whether ~~that~~ 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:* ~~Firstly, if setons are in place, they must be removed. Conditioning of the fistula tracts comprises the following steps~~:

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a) If setons are in place, they must be removed.
b) Identify the location of the internal openings. For this, ~~it is recommended~~ to 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 ~~to close them~~.

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 suspension 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 ~~the~~ external openings). ~~As commonly done for intra tissue injections, just~~ After ~~injecting~~ 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 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 in small deposits 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.

4.4 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~~ 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%) ~~use of~~ (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 ~~this~~ these may compromise the ~~cells~~ viability of the cells and, therefore, may affect the effectiveness of the treatment.
Alofisel is indicated only for ~~intralesional~~ injection ~~only~~ in the fistula tract tissue as described in section 4.2. 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.
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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%) (e.g. hydrogen peroxide, methylene blue, iodine solutions or hypertonic glucose solutions) (see section 4.2 and section 4.4) through the fistula tracts ~~Dyes~~ and use of local anaesthesia is not recommended due to the unknown effect ~~of local anasthetics~~ on the injected cells (see section 4.4).

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6.4 Special precautions for storage

Store between 15ºC and 25ºC.
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 or otherwise sterilise.

6.6 Special precautions for disposal and other handling

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 suspension is obtained, avoiding bubble formation. For further information on the use of Alofisel see section 4.2.
Any unused product or waste material should be disposed of in accordance with local requirements.

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