Summary of risk management plan for Alofisel (DARVADSTROCEL)

This is a summary of the risk management plan (RMP) for Alofisel. The RMP details important risks of Alofisel, how these risks can be minimised, and how more information will be obtained about Alofisel's risks and uncertainties (missing information).

Alofisel's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Alofisel should be used.
This summary of the RMP for Alofisel should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Alofisel's RMP.

I. The medicine and what it is used for

Alofisel is authorised 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 (see SmPC for the full indication). It contains DARVADSTROCEL as the active substance and it is given INTRALESIONALLY.
Further information about the evaluation of Alofisel's benefits can be found in Alofisel's EPAR, including in its plain-language summary, available on the EMA website under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/alofisel

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Alofisel, together with measures to minimise such risks and the proposed studies for learning more about Alofisel's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Alofisel, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - include PSUR statement only if product has PSUR requirements so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of Alofisel is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Alofisel are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be

regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Alofisel. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Tumorigenicity Ectopic tissue formation Hypersensitivity reactions Transmission of infectious agents Immunogenicity/allo-immunoreactions Development of new anal fistula and/or anal abscess or relapse of treated fistula Medication errors
Missing information	Long-term safety Experience during pregnancy and lactation Experience in the elderly Repeat use

II.B Summary of important potential risks

Important potential risk: Tumorigenicity	
Evidence for linking the risk to the medicine	Evidence from the published scientific literature and clinical development programs.
Risk factors and risk groups	CD patients with persistent inflammation, long-standing disease, extensive disease, young age at diagnosis, family history of colorectal cancer and co-existing primary sclerosing cholangitis.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 5.2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** o ADMIRE-CD II Study o ADMIRE CD II long-term extension study o Retreatment PASS o European multi-database linkage study See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Ectopic tissue formation	
Evidence for linking the risk to the medicine	Evidence from the published scientific literature and clinical development programs.
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 5.2 **Additional risk minimisation measures:**

	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** o ADMIRE-CD II Study o ADMIRE CD II long-term extension study o Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Evidence from the published scientific literature and clinical development programs.
Risk factors and risk groups	Patients with known hypersensitivity to Alofisel or any of its constituents
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 and SmPC section 4.4 Package Leaflet section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** o ADMIRE-CD II Study o Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Transmission of infectious agents	
Evidence for linking the risk to the medicine	Evidence from the published scientific literature and clinical development programs.
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 where it is recommended that patients should be followed-up for potential signs of infection after administering Alofisel. SmPC section 4.8 **Additional risk minimisation measures:** Healthcare Professional Guide
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** o ADMIRE-CD II (Cx601-0303) Study o Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Immunogenicity/allo-immunoreactions	
Evidence for linking the risk to the medicine	Evidence from the published scientific literature and clinical development programs.
Risk factors and risk groups	Patients who develop DSA. However, the number of sensitised Cx601-treated patients was too low to allow for meaningful evaluation of the impact of DSA on the frequency and nature of TEAEs.

Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 SmPC section 5.1 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ○ ADMIRE-CD II (Cx601-0303) Study ○ ADMIRE CD II (Cx601-0303) long-term extension study ○ Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Development of new anal fistula and/or abscess or relapse of treated fistula	
Evidence for linking the risk to the medicine	Evidence from the published scientific literature and clinical development programs.
Risk factors and risk groups	All patients with CD are at risk of developing anal fistula and anal abscess
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 SmPC section 4.8 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** ○ ADMIRE-CD II (Cx601-0303) Study ○ ADMIRE CD II (Cx601-0303) long-term extension study ○ Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Evidence from the published scientific literature and clinical development programs.
Risk factors and risk groups	Risk factors for medication errors could be related to the incorrect administration of the product, to the manipulation of the product, and to the storage of the product. There are no data available about risk groups or risk factors for medication errors with Alofisel.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 SmPC section 4.4 **Additional risk minimisation measures:** Healthcare Professional Guide
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ○ ADMIRE-CD II (Cx601-0303) Study ○ Retreatment PASS See section II.C of this summary for an overview of the

	post-authorisation development plan.
Missing information: Long-term safety	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ○ ADMIRE-CD II (Cx601-0303) Study ○ ADMIRE CD II (Cx601-0303) long-term extension study ○ Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Experience during pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ○ ADMIRE-CD II (Cx601-0303) Study ○ ADMIRE CD II (Cx601-0303) long-term extension study ○ Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Experience in the elderly	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ○ ADMIRE-CD II (Cx601-0303) Study ○ ADMIRE CD II (Cx601-0303) long-term extension study ○ Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Repeat dose	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 **Additional risk minimisation measures:** None

Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** o Retreatment PASS See section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation development plan
II.C.1. Studies which are conditions of the marketing authorisation
The following studies are conditions of the marketing authorisation:

ADMIRE-CD II (Cx601-0303): Phase III Study
Purpose of the study: To evaluate the efficacy and safety of Alofisel compared to placebo for the treatment of complex perianal fistula(s) in patients with Crohn's disease at Week 24 with a follow-up period up to 52 weeks.

II.C.2. Other studies in post-authorisation development plan

ADMIRE-CD II (Cx601-0303) Long Term Extension Study
Purpose of the study: To evaluate the long-term safety and efficacy of darvadstrocel including adverse events of special interest (immunogenicity, tumorigenicity and ectopic tissue formation). The study will also evaluate the long-term effect of darvadstrocel treatment on fistula remission, major fistula-related events (hospitalizations and surgeries).

Retreatment PASS
Purpose of the study: The overall objective of the study is to assess the efficacy and safety of repeat administration of darvadstrocel in patients with Crohn's disease and complex perianal fistula.

European multi-database linkage study: An observational European multi-database linkage study to quantify malignancy rates in Crohn's disease patients with complex perianal fistula patients treated with darvadstrocel.