REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

# HEALTH TECHNOLOGY ASSESSMENT

**Alofisel**

**suspension for injection 5 million cells/ml – 6 ml x 4**

darvadstrocel

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| **Therapeutic indication(s)** | 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. |
| **Start/end date of procedure** | 28.05.2019 – 15.07.2020 |
| **Final decision** | Rejects inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases, paid by the NHIF, and in Annex 2 of the PDL for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the value of the rendered medical services. |

**Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Alofisel**

## Health problem

Crohn's disease (CD) is a chronic idiopathic granulomatous transmural inflammatory disease of the entire gastrointestinal tract. In CD there is a tendency for erosions, ulcers, penetrations, abscesses and fistulas to occur. The disease is characterized by segmental involvement and intermittent activity, leading to fibrosis and obturation.

CD can affect any part of the gastrointestinal tract. Patients with CD usually complain of chronic or nocturnal diarrhea and abdominal pain, weight loss, fever, and rectal bleeding. In addition, CD is often associated with extraintestinal manifestations, such as joint pain, mouth ulcers, lymphadenomegaly, and skin lesions (erythema nodosum). The disease progresses with paroxisms, alternating periods of activity and clinical remission. In some patients, persistent subclinical inflammation is observed, leading to strictures, fistulas and abscesses.

Fistula formation is a serious complication of Crohn's disease, leading to increased morbidity and deterioration of the quality of life. Symptoms and complications of perianal fistulas can limit patients' social activity, their ability to engage in sexual intercourse, and lead to obstacles to employment. Mental health problems are also important, with patients reporting mental health problems, including anxiety, depression, and suicidal thoughts during the course of disease.

Current therapeutic strategies are associated with poorly sustained level of disease eradication and high recurrence rates. Patients with complex perianal fistulas would undergo a median of six surgical procedures, and these patients are subjected to repeated operations that have an increased risk of sphincter muscle damage leading to fecal incontinence. In case of failure of repeated surgical interventions, proctectomy is considered in 12-38% of patients. The goal of treatment is to achieve a lasting clinical response, endoscopic remission (mucosal healing), and to interrupt the natural progressive development of the disease. The choice of treatment often depends on the anatomical distribution and activity of the disease.

Alofisel is indicated for the treatment of complex perianal fistulas in adult patients with inactive/mild Crohn's luminal disease when fistulas have shown an inadequate response to at least one conventional or biological treatment. Alofisel is injected directly into the walls of the fistula (the fistula and the cells come into contact with pro-inflammatory cytokines). Its immunoregulatory activity reduces inflammation, which can allow the tissues around the fistula to be treated like a normal wound.

## Efficacy data

The primary endpoint for health outcome assessment is the achievement of clinical remission after 24 weeks, defined as the closure of all treated external fistula openings that had been draining at the initial visit. The end result is confirmed by the so-called clinical assessment - lack of drainage (secretion) during physical examination.

One clinical trial was identified - a double-blind, placebo-controlled, randomized, multicenter phase 3 study - ADMIRE - CD - in a patient population over 18 years of age.
DVS is effective in achieving combined remission after 24 and 52 weeks (ITT population). A significantly higher percentage of patients in the DVS group compared to placebo achieved the primary endpoint - combined remission after 24 (49.5% vs 34.3%) and after 52 weeks (54.2% vs 37.1%). The obtained results are similar in the ITT, mITT and PP populations and in additionally performed sensitivity analyses. Fewer patients with combined remission after 24 weeks of DVS compared with placebo had a relapse after 52 weeks (25% vs 44.1%). The mean time to achieve clinical remission was shorter with DVS compared with placebo (6.7 vs 14.6 weeks). After 6 weeks, more DVS patients were in clinical remission compared to the control group (51.4% vs 34.3%), these differences persisted at all visits and after 52 weeks reached 17% (57.0% vs 40,0%). In the studied populations, significantly more patients in the DVS group compared to the control group achieved a clinical response after 24 weeks (68.9% vs 55.4%) and after 52 weeks (66.0%; vs 55.4%). The improvement in the score for inactive perianal disease PDAI in the DVS group compared to placebo was significantly greater after 6, 12 and 18 weeks, but not after 24 and 52 weeks. The mean overall PDAI score after 24 weeks in patients with DVS is close to the threshold for inactive perianal disease (PDAI < 4), when patients do not require medical or surgical treatment.

## Safety data

The observed safety profiles in the DVS group and the placebo group are similar. There were no deaths during the study, the most common serious TEAEs were anal abscess/fistula, and the most commonly reported TEAEs were proctalgia, anal abscess, and nasopharyngitis. In 17% of patients with DVS, compared with 29% in the control (placebo) group, treatment-related TEAE occurred, among which anal abscess and proctalgia were the most common.

## Data on comparators

Currently recommended treatments for perianal fistulizing CD include drainage and immunosuppressive therapy. Antibiotics and thiopurines are considered adjunctive therapy and anti-TNF is considered the gold standard.

Existing pharmacological treatments for complex perianal fistulas are antibiotic therapy, immunomodulators, and anti-tumor necrosis factor (TNF) alpha (TNFα). These are subject to the following restrictions:

- limited efficacy in inducing fistula healing;
- relapses occur after discontinuation of treatment in the majority of patients;
- the profile of the side effects of these therapies.

## Pharmacoeconomic indicators

**Published health technology assessments performed by governmental institutions, intended for the health care systems of other countries**

Health technology assessments were performed by government institutions in the United Kingdom (NICE), France (HAS), and Germany (IQWIG).

**Applied analysis**

Pharmacoeconomic cost-benefit and cost-utility analyses with an outcome measure quality adjusted life years (QALY) have been employed. In the cost-benefit analysis, the benefits have been calculated as avoided costs for 5-year treatment of fistulas with surgical interventions, specialist examinations and hospitalizations, clinical trials, biological therapy, and costs for treatment of biological product-related ADR. As comparators, medicinal products currently used in therapeutic practice, as well as surgical procedures and patient monitoring have been used. The analysis is from the point of view of the paying institution NHIF, for a time horizon of 5 years with a discount of 3.5%.

The cost-benefit analysis performed for the population of patients with Crohn's fistulizing disease shows that the costs of using darvadstrocel outweigh the benefits reported as avoided costs. The results of the cost-benefit analysis show that darvadstrocel use leads to gained quality adjusted years of life and to increased costs for the health care system.

**Costs for the assessed health technology**

Cost of single dose administration and cost of disease therapy with other medicinal products have been presented.

Direct medication and ADR management costs and costs for patients follow-up have been included.

**Budget impact analysis**

The budget impact analysis has been prepared from the point of view of the National Health Insurance Fund with the time horizon 5 years. The size of the target patient population

refractory to previous therapy, eligible for receiving Alofisel, was two for the first year, increasing by one each year. Sensitivity analysis was performed with the variables being the number of patients on drug alternatives and cost of alternatives, with the most sensitive data being the ones related to the change in the cost of Alofisel.
The inclusion of the medicinal product Alofisel in the PDL is associated with an increase in the NHIF budget without taking into account risk-sharing agreements and patient access schemes.

## Conclusion

Alofisel is effective in achieving combined remission in patients with perianal Crohn's fistulizing disease, not responding to treatment after 24 and 52 weeks with a single dose of the medicine. It is used as a third-line therapy, after failure of treatment with conventional and biological therapy and the effect of therapy should be monitored due to lack of data on therapeutic effectiveness and unfavorable cost-benefit ratio.