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

HEALTH TECHNOLOGY ASSESSMENT

TREMFYA

100 mg solution for injection x 1 pre-filled pen

Guselkumab

Therapeutic indications	Treatment of moderate to severe plaque psoriasis in adults suitable for systemic therapy
Start - end of the procedure	17.04.2019 – 27.09.2019
Final decision	Final decision is positive for an inclusion in: - Annex 1 of the Positive Drug List (PLL) for home treatment of diseases paid for by the National Health Insurance Fund (NHIF) - Annex 2 of the PDL for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act

Summary of the report on the clinical and pharmacoeconomic evaluation of the health technology of the medicinal product Tremfya

Health problem

Psoriasis is a relatively common, chronic recurrent disease affecting the skin and joints, often associated with other endocrine and vascular diseases. In about 90% of cases, the disease is chronic, significantly affecting the quality of life of patients. Depending on its severity, psoriasis can be a significant health problem, both in terms of physical activity and disability of patients, and due to their psychological stigma.
The diagnosis of the disease is made clinically, by the presence of typical skin lesions located on the predilection sites (scalp, elbows, knees, trunk), the presence of clinical symptoms (Auspitz, Voronov, Köbner's phenomenon, etc.). The examination also reports the presence of nail changes and joint involvement. Dermatoscopic examination of psoriatic plaques gives a typical morphological picture. Paraclinical studies represent a constellation of inflammatory disease.
The diagnosis of psoriasis is verified by histological examination.
Tremfya (guselkumab) is indicated for the treatment of moderate-to-severe psoriasis vulgaris: affected body surface area (BSA) > 10; Psoriasis Area Severity Index (PASI) > 10 and Dermatology Life Quality Index (DLQI) > 10.

Epidemiological data

The prevalence of psoriasis is approximately 1 to 5% of the population in different parts of the world. Worldwide, psoriasis affects 0.09% of Tanzanians to 11.4% of Norwegians. For the countries of the Balkan Peninsula, disease statistics about prevalence are available for Croatia - 1.2% of the population.
Treatment of psoriasis is carried out with local, systemic and phototherapy according to international and national therapeutic guidelines and consensus. Depending on the severity of the disease, the size of the affected area and the presence of joint involvement, the various therapeutic agents are applied in numerous combinations. In all variants of psoriasis, emollients are an integral part of topical therapy. In mild forms of psoriasis vulgaris, topical treatment with keratolytics, topical steroids, vitamin D3 analogues, calcineurin inhibitors, dithranol, topical retinoids and tars is performed. Phototherapy (broad-spectrum BB-UVB, narrow-spectrum NB-UVB, PUVA and Re PUVA) can be used for disseminated skin lesions. Systemic therapy with methotrexate, retinoids, cyclosporine is indicated for the treatment of severe psoriasis in patients in whom other therapy is inappropriate or current treatment has no effect or has exhausted its effect.
Several groups of biological products have been registered in the European Therapeutic Guidelines and the Pharmacotherapeutic Guidelines for Skin and Sexually Transmitted Diseases: tumor necrosis factor alpha (TNFα) antagonists (infliximab, adalimumab, etanercept), interleukin 12 and 23 antagonists (ustekinumab), interleukin 17 antagonists

(secukinumab), CD2 receptor blockers (alefacept). Biological products are recommended in patients with moderate to severe forms of psoriasis, in which body surface area (BSA), Psoriasis Area and Severity Index (PASI) and dermatology life quality index (DLQI) is more than 10, and according to the NHIF - BSA> 10, PASI> 10 in persons under 18 years and BSA > 20, PASI> 20 in patients over 18 years of age in which it is impossible to conduct phototherapy and standard systemic treatment due to concomitant severe disease or life-threatening, as well as patients who have developed serious adverse effects from standard systemic therapy or have exhausted its effect.

Tremfya (Guselkumab) is indicated for the treatment of clinically and histologically verified, moderate to severe psoriasis vulgaris (ICD code L40.0) in patients in whom:

- ✓ BSA, PASI is more than 20 in patients over 18 years;
- ✓ There is resistance to standard systemic treatment for at least 6 months and optimal phototherapy in terms of doses and duration;
- ✓ There are contraindications for standard systemic treatment and phototherapy due to concomitant severe or life-threatening disease;
- ✓ Develop intolerance / hypersensitivity to systemic treatment with other drugs.

Efficacy data

In order to evaluate the therapeutic efficacy and safety profile of the new health technology, the following clinical trials have been described: VOYAGE 1, VOYAGE 2 and NAVIGATE. The presented clinical trials are double-blind, randomized, multicenter clinical trials.

In the VOYAGE 1 study, patients randomized to guselkumab received 100 mg at weeks 0 and 4 and then every 8 weeks to week 48, while those randomized to adalimumab received 80 mg at week 0 and 40 mg at week 1, followed by 40 mg every other week up to week 48.

In VOYAGE 2, patients randomized to guselkumab treatment at week 0 who achieved a PASI> 90 reduction at week 28 of VOYAGE 1 continued guselkumab treatment every 8 weeks or received placebo, while the adalimumab group who didn't have PASI> 90, started receiving guselkumab at weeks 28 and 32 and every 8 weeks thereafter.

In both VOYAGE 1 and 2 studies, patients randomized to placebo received guselkumab 100 mg at weeks 16, 20 and every 8 weeks thereafter. The NAVIGATE study looked at the efficacy of guselkumab in patients with plaque psoriasis with an inadequate response to ustekinumab (Investigator's Global Assessment IGA ≥ 2) at week 16. Initially, all patients received ustekinumab (45 mg or 90 mg) at weeks 0 and 4 in an open-label study. Subsequently, at week 16, patients with an IGA score ≥ 2 were randomized to either continue ustekinumab treatment or to start guselkumab treatment at weeks 16, 20, and every 8 weeks thereafter.

Guselkumab showed a rapid onset of efficacy with a statistically significant higher percent of improvement in PASI in comparison to placebo at week 2.

Clinical outcomes for plaque psoriasis in adults treated with guselkumab and objectified by reduction of PASI> 75, PASI> 90, and PASI> 100 were statistically significantly better (p <0.001) than those obtained in the placebo and adalimumab-treated groups according to data from clinical trials VOYAGE 1 and 2.
With the same baseline disease severity data selected in the NAVIGATE study, patients in the guselkumab group achieved a statistically significant improvement of the disease at week 28 (p <0.001) as measured by the Investigator Global Assessment Index, as well as an improvement in quality of life as measured by Dermatology Life Quality Index (DLQI) at week 52 (p <0.002) compared to the ustekinumab group.
Health-related quality of life (HRQoL) in psoriasis patients treated in the guselkumab group at week 16 of the VOYAGE 1 and 2 studies, objectified with the Dermatology Life Quality Index questionnaire, was statistically significantly better than in the placebo and adalimumab groups (p <0.001).

Safety data

Guselkumab may increase the risk of infection and therefore should not be used in patients with clinically significant active infection until resolution. Patients treated with Tremfya should be consulted if symptoms of acute or chronic infection occur.
Before starting treatment, patients should be tested for tuberculosis infection and monitored for signs and symptoms of active tuberculosis after starting treatment.
The most common ADRs include herpes simplex infections, dermatophytosis, headache, diarrhea, urticaria, arthralgia, and gastroenteritis.

Data for comparative alternatives

Treatment with Tremfya, guselkumab 100 mg, solution for injection is an alternative to systemic therapy with methotrexate, retinoids, cyclosporine, as well as the biological products infliximab, adalimumab, etanercept, ustekinumab, and secukinumab, in patients with psoriasis vulgaris, in whom the effect is exhausted or have developed serious adverse effects from previous systemic treatment or phototherapy.

Pharmacoeconomic indicators

Published assessments of health technology performed by state institutions for the purposes of another national health care system

Evaluations of the health technology performed for other national health systems developed by NICE (UK), SMC (Scotland), GBA and IQWiG (Germany), HAS (France) and TLV (Sweden) have been published. Everyone recommends guselkumab for the treatment of

patients with plaque psoriasis when they are suitable for standard therapy, when patients do not respond to standard therapy or standard therapy is not suitable for them.

Applied analysis

A pharmacoeconomic cost-benefit analysis was applied, which was performed on the basis of the data from the VOYAGE 1 and 2 studies. The perspective of the applied cost-benefit analysis is that of the paying institution NHIF. The time horizon is 1 year and no discounting has been performed. As alternatives for comparison are selected all biological medicinal products for the treatment of plaque psoriasis in Bulgaria, which are included in the PDL and are paid by the NHIF - adalimumab, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab. The modeling of the costs and results was carried out within 1 year and a Markov model was applied, which includes 3 lines of biological therapy before the transition to the best supportive care. For each line of therapy there are 2 time periods - induction and maintenance period.
The results of the applied analytical method are presented as a cost per 1 QALY for each alternative and the incremental cost-benefit ratio is calculated. Compared to the alternative with the highest QALY (ixekizumab), the applicant health technology is dominant as it has a lower cost and a higher QALY.
Subgroup analysis is not applicable.

Costs for the assessed health technology

The direct costs of treatment with the medicinal products (of the applicant health technology and of the comparators) and the costs of treatment of adverse drug reactions are included. The value of a therapeutic course is calculated on the basis of data on the administration of drugs from the respective SmPCs, and the evaluation of ADR is based on epidemiological data on the frequency of ADR.

Budget impact analysis

The analysis of the budget impact reflects the point of view of the paying public institution. The time horizon is 5 years. The target population was selected based on the spread of the disease in Bulgaria - about 17% of patients are with psoriasis, assessment of patients suitable for the new health technology based on NHIF data on the number of patients treated with biologic therapy, and assessment of the presumed market share, it is projected to grow. It is predicted that the number of patients who will be treated with the assessed health technology will be 110 in the first year and their number will increase to 570 in the fifth year. A Tornado-type susceptibility analysis was performed to assess the effect of uncertain data on the number of patients and the value of drug therapy. The analysis shows that the change in

the price for the 5-year period under consideration will have the greatest influence on the budget. Savings are expected as the inclusion of Tremfya in PDL will lead to a reduction in the budget for the treatment of patients with moderate to severe psoriasis with biologics, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The results of the clinical and pharmacoeconomic evaluation of the Tremfya health technology (INN guselkumab) show that there is a statistically significant superiority of the new health technology over placebo and active comparators. The safety profile is manageable and in accordance with the mechanism of action of the medicinal product.
The conducted pharmacoeconomic analysis shows that guselkumab therapy is cost-effective for the healthcare system in Bulgaria.
The analysis of the budget impact on the expected number of patients and on the assumption of market distribution shows that the inclusion of Tremfya in PDL will lead to savings of the NHIF.