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

HEALTH TECHNOLOGY ASSESSMENT

SKYRIZI

75 mg solution for injection x 2 pre-filled syringes + 2 alcohol pads

Risankizumab

Therapeutic indications	treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy
Start – end of the procedure	29.05.2019 – 20.12.2019
Final decision	Inclusion: - in Annex 1 for home treatment of diseases paid by the National Health Insurance Fund (NHIF); - in Annex 2 for purchase by medical establishments with state and/ or municipal participation and under Art. 5 of the Medical Establishments Act of the Positive Drug List (PDL)

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

Health problem

Plaque psoriasis (called below psoriasis - PsO) is a serious, chronic, multisystem immune-mediated inflammatory disease characterized by the appearance of red, thick and scaly plaques on the skin. Skin lesions can cover individual areas of the skin, but can also affect the entire body. Chronic plaque psoriasis is the most common form of psoriasis and accounts for approximately 90% of diagnoses. It manifests itself in the form of erythematous plaques affecting the area around the elbows and knees. Other forms of PsO are guttate, pustular, erythrodermic and palmoplantar PsO.

Due to its chronic nature, PsO reduces patients' quality of life (QoL), affecting their physical, emotional and social well-being. Compared to the severity of other chronic diseases, QoL in patients with PsO is more severe, which necessitates long-term disease control. Patients with PsO are at higher risk of developing comorbidities such as cardiovascular disease, diabetes, obesity and metabolic syndrome.

Due to the chronic and persistent nature of moderate to severe PsO, patients need lifelong care after diagnosis. Both the direct costs associated with the treatment of PsO and the indirect costs of disability contribute to the growing economic burden that the treatment of patients with PsO places on health systems.

Principles and criteria for diagnosis

Cutaneous manifestations of PsO are extremely characteristic and the diagnosis is made on the basis of clinical examination and additional tests are rarely required. A skin biopsy that has specific histopathological features can be used to diagnose it. Skin lesions consist of erythrodermic, silvery-white, clearly demarcated plaques. They have an oval or irregular shape, varying in size from one to several centimeters in diameter and are located symmetrically on the extensor surfaces of the limbs (mainly elbows and knees), lower back and scalp. Itching is usually absent, but this is determined mainly by the patient's emotional state.

Determining the severity of the disease is important in determining treatment options.

Epidemiological data

Psoriasis affects 2-4% of the population, with most patients suffering from a mild form of the disease, 25% from a moderate form and approximately 10% from a severe form.

Prevalence

PsO is a chronic systemic disease that affects approximately 125 million people worldwide. According to a 2016 report by the World Health Organization (WHO), the prevalence of PsO varies between 0.09% and 11.43% worldwide and between 1.5% and 5% in the most developed countries. PsO prevalence in Europe varies between 0.6% and 6.5%, and is highest in Northern Europe.

Mortality

In patients with severe PsO, the risk of mortality is 50% higher.

Epidemiological data for Bulgaria

Epidemiological data for Bulgaria are limited based on a study by Rencz and co-authors from 2015, in Bulgaria there are 145,691 patients with psoriasis.

Severity of the disease

The choice of optimal treatment for patients with PsO requires a correct diagnosis and determination of the severity of the disease. Determining the severity of the disease is important in determining treatment options.
The severity of the disease is most often determined by using a Psoriasis Area Severity Index (PASI) scale (index of affected skin area and severity of the disease). Higher PASI values are associated with a higher severity of the disease in terms of erythema, infiltration, desquamation and area of the affected surface (Table 1).

Table 1. PsO severity depending on PASI results

Results PASI	Severity of the disease
PASI <10	Mild form of PsO
PASI: 11-20	Moderately severe PsO
PASI >20	Severe form of PsO

Other criteria for determining the severity of PsO are:

BSA (Body Surface Area) - area of the affected body surface
PGA (Physician's Global Assessment) - general evaluation of the doctor
DLQI (Dermatology Life Quality Index) - dermatological index for quality of life
Two methods are most commonly used to estimate the affected body surface area (BSA) - the 'rule of nines' and the 'rule of the palms' rule.
PGA is a scale for assessing psoriasis by the doctor, which includes the level of erythema, infiltration and desquamation of plaques.
DLQI is assessed through 10 questions covering: symptoms and sensations, daily activities, leisure, work and school, personal relationships and care for the treatment of psoriasis.
In addition to skin problems, PsO is also associated with arthritis called psoriatic arthritis (PsA). The WHO report from 2016 estimated that 34.7% of patients with PsO developed PsA.
PsA, in turn, is associated with a number of concomitant conditions. PsA was associated with gastrointestinal comorbidities. Feelings of stigma, stress, anxiety and depression also appear. There is an increased risk of suicidal tendencies.
Psoriatic plaques can be on any part of the body. Some areas such as nails (10-56%), scalp (48%), and genitals (7%) are more difficult to treat. This adds weight to the disease.

Current treatment of psoriasis

Current methods of PsO treatment include topical drugs, non-biological systemic therapies, phototherapy, and biological therapy. The individual treatment plan of each patient is determined depending on the severity of the disease and the location of the lesions. In most cases, patients with mild to moderate disease are treated with topical agents as first-line treatment. In patients with moderate to severe PsO, systemic, biological and phototherapies are used (Table 2).

Table 2. Treatment regimens depending on the severity of the disease

Severity of the disease	Recommended therapy
Mild form of PsO	Topical corticosteroids Emollients Vitamin D and its analogues: calcipotriol and calcitriol Coal tar Local retinoids: tazarotene Anthralin
Moderate to severe PsO	Phototherapy Systemic therapies: retinoids, methotrexate, cyclosporine, apremilast

	Biological: anti-TNF agents: adalimumab, etanercept, infliximab anti-IL-12/23 molecule: ustekinumab anti-IL-17 molecules: ixekizumab, secukinumab, brodalumab anti-IL-23 molecules: guselkumab, tildrakizumab

Abbreviations used: TNF - tumor necrosis factor; IL – interleukin

Efficacy data

Risankizumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy. To assess the therapeutic efficacy and safety profile of the new health technology, six clinical trials were described, **analyzing the results of the four registration clinical trials and one meta-analysis.**

Clinical trials UltIMMa-1 (NCT02684370) and UltIMMa-2 (NCT02684357) are randomized, phase 3, double-follow-up clinical trials to evaluate the safety and efficacy of Rizankizumab compared to Ustekinumab and placebo.

Results: **UltIMMa-1 (NCT02684370)**

PASI 90 at week 16 - RZB: 75.3%, PBO: 4.9%; *PASI 90 at week 52* - RZB: 81.9%, UST: 44.0%, PBO/RZB: 78.4%; *sPGA 0/1 at week 16*- RZB: 87.8%, PBO: 7.8%; *sPGA 0/1 at week 52*- RZB: 86.2%, UST: 54.0%, PBO/RZB: 90.7%; *sPGA 0 at week 16* - RZB: 36.8%, UST: 14%, PBO: 2.0%; *sPGA 0 at week 52* - RZB: 57.6%, UST: 21.0%, PBO/RZB: 54.6%; *PASI 100 at week 16* - RZB: 35.9%, UST: 12.0%, PBO: 0.0%; *PASI 100 at week 52* - RZB: 56.3%, UST: 21.0%, PBO/RZB: 54.6%

Results: **UltIMMa-2 (NCT02684357)**

PASI 90 at week 16 - RZB: 74.8%, PBO: 2.0%; *PASI 90 at week 52* - RZB: *80.6%, UST: 50.5%, PBO/RZB: 85.1%; sPGA 0/1 at week 16* - RZB: 83.7%, PBO: 5.1%; *sPGA 0/1 at week 52* - RZB: 83.3%, PBO/RZB: 87.2%; *sPGA 0 at week 16* - RZB: 51.0%, UST: 25.3%, PBO: 3.1%; *sPGA 0 at week 52* - RZB: 59.6%, UST: 30.3%, PBO/RZB: 67.0%; *PASI 100 at week 16* - RZB: 50.7%, UST: 24.2%, PBO: 2.0%; *PASI 100 at week 52* - RZB: 59.5%, UST: 30.3%, PBO/RZB: 67.0%

IMMvent Clinical Trial (NCT02694523)

IMMvent was a randomized, double-blind trial to evaluate the efficacy and safety of **Rizankizumab compared to Adalimumab** after 16 weeks of treatment and after an unsatisfactory response to adalimumab treatment for 44 weeks.

Results: PASI 90 at week 16 - RZB: 72%, ADA: 47%, p <0.001; *PASI 90 at week 44* - RZB: 66%, ADA: 21%, p <0.001; *sPGA 0/1 at week 16* - RZB: 84%, ADA: 60%, p <0.001; *PASI 100 at week 16* - RZB: 40%, ADA: 23%, p <0.001; *PASI 100 at week 44* - RZB: 40%, ADA: 7%, p <0.001

IMMhance Clinical Trial (NCT02672852)

IMMhance was a randomized, double-blind, 104-week trial to evaluate the safety and efficacy of discontinuation and re-treatment with **Rizankizumab**.

Results: PASI 90 at week 4 - RZB: 7.1%, PBO: 0.0% , p <0.001; *PASI 90 at week 16* - RZB: 73.2%, PBO: 2.0%, p <0.001 (NRI analysis); *sPGA 0/1 at week 4* - RZB: 32.9%, PBO: 0.0%, p <0.001; *sPGA 0/1 at week 16* - RZB: 83.5%, PBO: 7.0%, p <0.001 (NRI analysis); *PASI 100 score at week 4* - RZB: 2.2%, PBO: 0.0%, p <0.05; *PASI 100 at week 16* - RZB: 47.2%, PBO: 1.0%, p <0.001 (NRI analysis); *PASI 75 at week 16* - RZB: 88.7%, PBO: 8.0%, p <0.001 (NRI analysis); *sPGA 0 at week 4* - RZB: 2.2%, PBO: 0.0%, p <0.05; ***sPGA 0 at week 8*** - RZB: 21.4%, PBO: 0.0%, p <0.001; *sPGA 0 at week 12* - RZB: 40.0%, PBO: 1.0%, p <0.001; *sPGA 0 at week 16* - RZB: 46.4%, PBO: 1.0%, p <0.001 (NRI analysis); *DLQI 0/1 at week 16* - RZB: 65.4%, PBO: 3.0%

Description of meta-analyzes

The results of a systematic review of the literature are presented in order to assess the short-term and long-term improvements in safety, efficacy and health-related quality of life (HRQoL) observed in these therapies. The following therapies are included: anti-TNF (adalimumab, certolizumab pegol, etanercept and infliximab), anti-IL (brodalumab, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab) and anti-PDE4 (apremilast) and fumaric acid ester (dimethyl fumarate). This Bayesian network meta-analysis (NMA) evaluates probabilities for PASI 90/100, using data obtained from weeks 10-16 of clinical trials. PASI percent at weeks 44-60 is also assessed based on data from ongoing trials.
A total of 60 clinical trials are included. Of the 13 treatments included in the analysis, risankizumab was found to have the highest PASI 90/100 values (71.6% and 40.4%, respectively).

Results of PASI for the treatment of moderate to severe psoriasis

Risankizumab has significantly higher PASI 90/100 levels than etanercept, adalimumab, ustekinumab, certolizumab pegol, tildrakizumab, dimethyl fumarate and apremilast. Risankizumab also had significantly higher values than secukinumab and infliximab at week 16 ($p < 0.05$) – Figure 1.
Long-term PASI data (weeks 44-60) were calculated for 10 therapies by meta-analysis of 23 trials in which initial treatment lasted up to 60 weeks (Figure 2). Long-term data have only been reported for a dose of 50 mg twice weekly for etanercept; PASI 100 has not been reported for apremilast, etanercept and infliximab. Risankizumab had a significantly higher PASI 90/100 response rate at weeks 44-60 compared to etanercept, adalimumab, ustekinumab, and infliximab ($p < 0.05$).
Among these five treatments, risankizumab achieved a significantly higher PASI 90 compared to secukinumab and ixekizumab, as well as a significantly higher PASI 100 compared to secukinumab and guselkumab ($p < 0.05$).

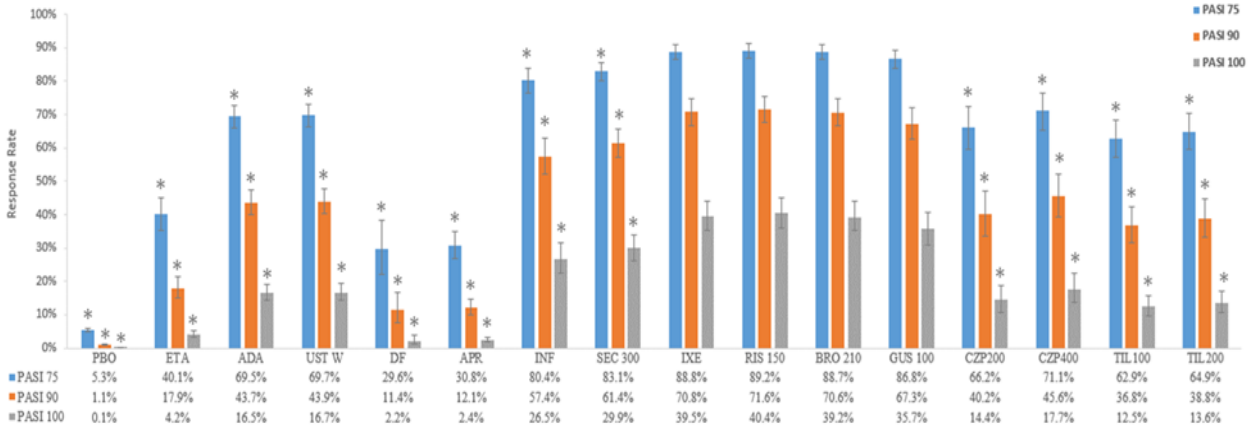

Figure 1. Expected PASI 75/90/100 values in therapies for the treatment of psoriasis at weeks 10-16.

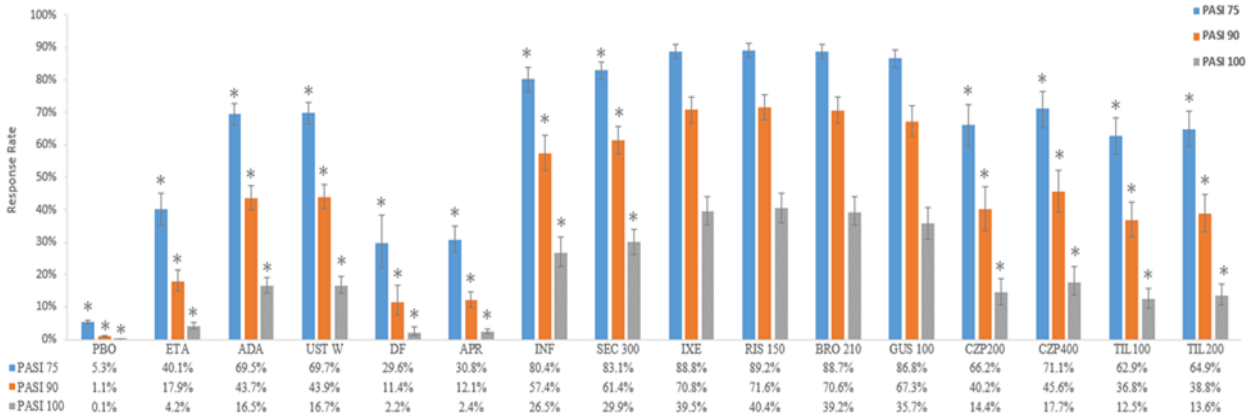

Figure 2. Results of the meta-analysis at weeks 44-60.

Safety data

Summary of the safety profile

A total of 2234 patients with psoriasis in clinical trials received risankizumab, representing 2167 patient-years of exposure. Of these, 1208 participants with psoriasis had exposure to risankizumab for at least one year. A total of 1306 participants in the 150 mg risankizumab group were evaluated. Serious adverse events occurred in 2.4% of the risankizumab group (9.9 events per 100 patient-years), 4.0% of the placebo group (17.4 events per 100 patient-years), 5.0% of the ustekinumab group (18.4 events per 100 patient-years) and 3.0% of the adalimumab group (14.7 events per 100 patient-years).

Adverse reactions for risankizumab according to clinical trials are listed by system organ class and by frequency under the Medical Dictionary for Regulatory Activities (MedDRA) convention:

Infections and infestations:

- Upper respiratory tract infections, includes respiratory tract infections (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis - Very common;
- Tinea infections, includes tinea pedis, tinea cruris, tinea of the body, tinea versicolor, tinea manuum, onychomycosis - Common;
- Folliculitis – Uncommon

Nervous system disorders:

Headache, includes headache, tension headache, sinus headache - Common.

General and administration site conditions:

- Fatigue, includes fatigue, asthenia - Common
- Injection site reactions, including injection site reactions, erythema, haematomas, haemorrhage, irritation, pain, pruritus, reaction, swelling - Common

Compared to the initial 16 weeks of risankizumab treatment, the incidence of adverse reactions was similar and no new adverse reactions were observed in those subjects who were exposed for up to 77 weeks.

Comparators data

The comparators are in accordance with the therapeutic guidelines for the treatment of psoriasis and the medicinal products available in Bulgaria and included in the PDL: adalimumab, etanercept, secukinumab, ustekinumab, ixekizumab and infliximab. The selected comparators cover all classes of biological treatments available in Bulgaria. It is recommended that a TNF-α inhibitor, an IL-17 inhibitor and/or an IL-23 inhibitor be present in the therapeutic sequence.

Table 3. Available biological therapies for the treatment of psoriasis in Bulgaria

Therapy	Mechanism of action	Method of administration
Adalimumab	TNF-α	subcutaneous injection
Etanercept	TNF-α	subcutaneous injection
Infliximab	TNF-α	intravenous infusion
Secukinumab	IL-17A	subcutaneous injection
Ixekizumab	IL-17A	subcutaneous injection
Ustekinumab	IL-12/IL-23 p40	subcutaneous injection

Pharmacoeconomic indicators

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

Health technology assessments performed by: NICE UK, TLV Sweden and CADTH Canada are presented, all of which are positive, with prescription/ reimbursement recommended under certain conditions.

Applied analysis

A pharmacoeconomic cost-benefit analysis with a quality-adjusted life year (QALY) outcome measure was used. Adalimumab, Etanercept, Secukinumab,

Ustekinumab, Ixekizumab, Infliximab, which are used for the treatment of moderate to severe plaque psoriasis, have been used as comparators.
The analysis is from the point of view of the paying institution NHIF with discounting 3.5% of the costs and benefits and including sensitivity analysis. A 10-year time horizon has been chosen.
The applied model is based on an assessment of the change in health benefits compared to baseline. The EQ-5D-5L questionnaire was used to assess quality of life, based on the UltIMMa-1 and UltIMMa-2 trials, which were registered at baseline, week 12, week 16 and week 52.
A network meta-analysis of the comparative therapeutic efficacy of risankizumab for the treatment of patients with psoriasis in the baseline scenario (when after first-line treatment with biologic therapy, patients switch directly to best supportive care - BSC) and the second variant of the baseline scenario (after first-line treatment with biologic therapy, several more lines of biological therapy are included before switching to BSC).
A Markov model was built at a 10-year time horizon. The duration of the cycle is 4 weeks. The model includes the following health conditions: period of primary response in first-line treatment; period supportive care in first-line treatment; second line primary response period; period of primary response in the second line; period of primary response in the third line; period of supportive care in the third line; best supportive care (BSC); death.
Subgroup analysis is not applicable.
Cost-benefit analysis in first-line therapy, baseline scenario in variant 1 (when patients switch directly to BSC in second-line treatment) - the comparison shows that risankizumab therapy is cost-effective over ixekizumab and secukinumab, and relative to other therapeutic alternatives, the incremental cost-effectiveness ratio is above the threshold.
In variant 2 (when two additional lines of biologic therapy were included in the patient's treatment sequence before switching to BSC), risankizumab therapy was cost-effective over secukinumab.
Cost-benefit analysis in second-line therapy, additional scenarios - risankizumab therapy is dominant over ixekizumab therapy and over secukinumab, and a comparison with other alternatives shows more health benefits at a higher cost per patient.
The results of the sensitivity analysis showed that the health benefits had the greatest effect on the value of the incremental cost-effectiveness ratio (ICER) when comparing the therapy to adalimumab and infliximab. Compared to etanercept, ustekinumab was most significantly affected by the health benefits of risankizumab therapy, and with respect to secukinumab therapy, ICER was primarily affected by the cost of both therapies.

Costs for the assessed health technology

All costs generated by the new health technology are included. The prices of the medicinal products are calculated on the basis of registered dosage regimens and prices in the Positive Drug List in Bulgaria as of August 2019. The calculated costs are the costs for drugs administration, disease follow-up, BSC in case of lack of clinical response, for control of adverse drug reactions (ADRs), costs for risankizumab - presented price per package, per vial and cost of therapy for the period of primary response and maintenance treatment and the cost of treatment with comparators.

Budget impact analysis

The analysis is conducted from the perspective of the National Health Insurance Fund, the time horizon is 5 years. According to data from IQVIA, patients with psoriasis on biological treatment in 2018 in Bulgaria are about 25% more than in 2017. Based on this trend, the number of patients is expected to increase, and the number of patients switching to risankizumab therapy each year will increase from 45 in the first year to 400 in the fifth year.
The presented Tornado diagram shows that the variables that are the most significant are the cost of comparators and the cost of risankizumab therapy. The change in the number of patients has a negligible impact. The introduction of the new therapy will lead to savings, based on the assumptions that some patients who are treated with comparators at higher costs will switch to risankizumab therapy.

Conclusion

Skyrizi (risankizumab) is a highly selective IL-23 inhibitor that provides a new and great opportunity in the treatment of chronic plaque psoriasis. In an extensive clinical program, the new health technology leads to significant skin cleansing and relief of psoriasis symptoms only after one month of treatment. The improvement is clinically significant and lasting in all subgroups of patients. In addition, risankizumab has a good safety profile and a simplified mode of administration, which are associated with a favorable change in the quality of life of patients. The analysis of the budget impact from the perspective of National Health Insurance Fund, illustrates savings from the inclusion of the product in the Positive Drug List. For a 5-year period, treatment with Skyrizi leads to savings compared to alternatives for the same period.