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

HEALTH TECHNOLOGY ASSESSMENT

HUMIRA

40 mg/0.4 ml solution for injection x 2 pre filled syringes + 2 alcohol pads

Adalimumab

Therapeutic indications	Treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in whom corticosteroids need to be avoided, or in whom corticosteroid treatment is inappropriate; Treatment of chronic non-infectious anterior uveitis in pediatric patients over 2 years of age who have had an inadequate response or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.
Start - end of the procedure	25.03.2019 – 20.12.2019
Final decision	Positive for an addition of a new therapeutic indication of the medicinal product in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF).

Report on the clinical and pharmacoeconomic evaluation of the health technology of the medicinal product Humira

Health problem

1. Introduction

1.1. Health problem

Uveitis is an inflammation of the uvea (iris, ciliary body, choroid), often involving neighboring eye structures (retina, optic nerve, vitreous, sclera). In most cases, the etiology remains unclear, with the disease being predominantly autoimmune in nature. Infectious agents or eye injuries are among the most common causes with a clear etiology. The differential diagnosis is extensive and the treatment in idiopathic cases is difficult.

Uveitis is one of the leading causes of decreased vision, with patients at high risk for ocular complications, including glaucoma, cystoid macular edema, and cataract. Inflammatory recurrences of the iris, ciliary body and / or choroid can lead to severely reduced vision or blindness, and associated emotional and physical suffering as well as social and economic problems. Oral corticosteroids remain the treatment of choice for the treatment of non-infectious uveitis (NIU), despite the serious side effects of long-term use of high doses. Topical administration of corticosteroids, such as peribulbar or intravitreal injections, severely limits systemic side effects, but is associated with topical ones such as ocular hypertension, glaucoma, cataract, and sterile endophthalmitis. Immunosuppressants are used in patients with severe, prolonged or recurrent uveitis who do not respond to steroids or with complications associated with conventional therapy. The latest therapeutic approaches for uveitis are drugs targeting specific mediators of the immune response. Their effect has been studied mainly in patients with autoimmune diseases such as rheumatoid arthritis, psoriasis and Crohn's disease. The similarities in their pathogenesis with that of uveitis determine the interest in the use of such drugs for the treatment of various ocular inflammatory diseases. Molecules that block TNF-α (adalimumab, infliximab, etc.) have been shown to effectively modulate the immune response in patients with uveitis. In June 2016, the FDA approved adalimumab (Humira) for the treatment of non-infectious intermediate uveitis, posterior uveitis and panuveitis, with patients having a significantly lower risk of treatment failure, expressed in anterior chamber inflammatory cells and reduced visual acuity compared to with those of placebo. In 2018, consensus recommendations were published by FOCUS - Fundamentals Of Care for Uveitis Initiative for the treatment of NIU with immunomodulators, based on published studies, expert opinions and practical experience.

Positioning of health technology in relation to the analyzed disease

Adalimumab (ADA) is a recombinant humanized monoclonal antibody (IgG1) against tumor necrosis factor alpha (TNF-α) expressed in Chinese hamster ovary cells. TNF-α is thought to play a key role in the pathogenesis of non-infectious uveitis, contributing to retinal and choroidal damage and subsequent vision loss. The mechanism of action of adalimumab is its specific binding to TNF-α and subsequent blocking of its interaction with cell surface receptors p55 and p75. ADA also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration. Through these mechanisms of action, the drug contributes to the reduction of the inflammatory reaction.

ATC code

ADA has the ATC code: L04AB04, and belongs to the pharmacotherapeutic group of immunosuppressants, TNF-α inhibitors. The product is approved for the treatment of many autoimmune diseases in over 80 countries around the world. It is indicated in: juvenile idiopathic arthritis, psoriasis in adults and children, psoriatic arthritis, Crohn's disease in children and non-infectious, intermediate, posterior and panuveitis.
In Bulgaria, adalimumab is promoted under the Humira brand. The marketing authorization holder is AbbVie Ltd, Vanwall Road, Maidenhead, SL6 4UB, United Kingdom.

ADA marketing authorization number: EU / 1/03/256/021

Codes for Uveitis according to ICD-10

H20.0 Acute and subacute iridocyclitis

Anterior uveitis, cyclitis, iritis - acute, recurrent or subacute

H20.1 Chronic iridocyclitis

H20.8 Other iridocyclitis

H20.9 Iridocyclitis, unspecified

H22.1Iridocyclitis in diseases classified elsewhere

Ankylosing spondylitis M45

Sarcoidosis D 86.8

H30.0 Focal chorioretinal inflammation

H30.1 Disseminated chorioretinal inflammation

H30.2 Rear cyclitis

H30.8 Other chorioretinal inflammation

H30.9 Chorioretinal inflammation, unspecified

H31.0 Chorioretinal scars

H32.8 Other chorioretinal disorders in diseases classified elsewhere

H35.0 Background retinopathy and retinal vascular changes

H44.1 Other endophthalmitis

Sympathetic uveitis

Classification of uveitis

Classification and standardization of the diagnosis of uveitis is essential for higher accuracy and comparability of clinical trials from different centers, the course of the disease and their response to treatment. The most widely used classification of uveitis is that developed by the International Uveitis Study Group (IUSG) in 1987 based on the anatomical location of the inflammation. It includes anterior uveitis (iritis, iridocyclitis and anterior cyclitis), intermediate uveitis (parsplanitis, posterior cyclitis and hyalitis) and posterior uveitis (focal, multifocal or diffuse choroiditis, chorioretinitis, retinitis and neuroretinitis). Panuveitis (an inflammatory reaction in the anterior chamber, vitreous, retina and choroid) has also been described. The International Ocular Inflammation Society (IOIS) also publishes detailed clinical guidelines on anterior and posterior segment inflammation. In 2005, the Standardization of Uveitis Nomenclature (SUN) Working Group standardized methods for reporting clinical data on uveitis (diagnostic terminology, inflammation grading schema, and outcome measures). The group reached a consensus that the anatomical classification of uveitis should be used based on the criteria set by the IUSG. A standardized scheme has been developed to describe the severity of intraocular inflammation, ie the number of cells in the anterior chamber, opalescence of the anterior chamber fluid and opacities in the vitreous. The method of evaluation of the results, including the change of the visual acuity, is standardized and approved. In 2008, IUSG developed a simplified clinical system for classifying uveitis based on etiological criteria. It has 3 main

categories: infectious (bacterial, viral, fungal, parasitic), non-infectious (associated with systemic diseases, not associated with systemic diseases) and masquerade (neoplastic, non-neoplastic).
The pathogenesis of non-infectious uveitis is thought to involve both the innate and the adaptive immune system. Inflammation in NIU is controlled by a T-cell mediated autoimmune process and is maintained by proinflammatory cytokines. Upward regulation of inflammatory cytokines and release of toxic agents cause damage to retinal photoreceptor cells. The main risk factors that are associated with the disease include: genetic predisposition, smoking, autoimmune or inflammatory disorders, infections associated with uveitis, eye injuries (most often the injury leads to anterior uveitis).
Non-infectious uveitis involving the posterior segment has a different etiology, which is systemic or locally limited to the eyeball. They demonstrate a different response to immunosuppressive therapy. Systemic autoimmune diseases associated with NSAIDs include Behçet's disease, ankylosing spondylitis, and other HIU antigens-B27-associated disease syndromes and multiple sclerosis. Some patients may have ocular autoimmune disease without systemic associations with diseases such as birdshot retinochoroidopathy, multifocal choroiditis, and other white dot syndromes.

1.2. Epidemiological data, medical and social burden of the disease

Uveitis is a rare disease, but is associated with a high risk of vision loss. It is thought to be responsible for 5% to 20% of all cases of legal blindness in the United States and Europe and 25% of blindness in the developing world. Uveitis mainly affects people at a young or mature age, e.g. in a cohort study of 2619 patients with uveitis treated in a clinic in Austria, two thirds of the cases of uveitis (infectious or non-infectious) were between 17 and 60 years old. This distribution differs from that of more common eye diseases with vision loss, such as diabetic retinopathy and age-related macular degeneration, in which the incidence increases with age.
In developed countries, the etiology of uveitis is non-infectious in approximately 80% to 90% of cases. Epidemiological data on the anatomical location of the disease show that up to 50% of the posterior segment is affected. Data have been published that NIU was diagnosed in approximately 298,801 adults (95% CI, 290512-307324) and 21,879 children (95% CI, 19360-24626) in the United States in 2015, with an approximate prevalence of the disease of 121 per 100,000 and 29 per 100,000. Women are more likely to get sick than men, more often adults than children. Most cases are of anterior uveitis, and about 10% of adult patients with anterior NIU are severe cases. The predominant combined prevalence of NIU is 23 per 100,000, with pan-NIU and posterior NIU being the most common.
The prevalence of uveitis in general is 113.5-115.3 per 100,000 population. 22.3 -26% of children with NIU have a systemic disease - juvenile idiopathic arthritis.

There are no data on the number of patients with NIU in Bulgaria.
Treatment of posterior segment NIU is a challenge and can be a significant burden on patients, the health care system and society. Topical therapy is easy to apply, but it does not penetrate effectively to the posterior segment and is considered an adjunct treatment for patients with posterior segmental NIU who also have inflammation of the anterior segment of the eye. Drugs aimed at the posterior segment of the eye are difficult to apply on this part of the eye, their effectiveness is not universal, and the available options have their risks. In addition, the chronic or recurrent nature of NIU may require years of treatment.
Systemic corticosteroids are the standard of care for acute NIU, and these drugs can control inflammation in most patients. According to a recent study, 30% of patients with NIU of the posterior segment receiving systemic corticosteroid therapy with standard immunosuppression continue to have active inflammation after 24 months of treatment. The potential for disabling side effects from long-term use of systemic corticosteroids is well known, including the increased risk of osteoporosis, hypertension, diabetes, gastritis and ulcers, infections, weight gain, and sleep and mood disorders, among others. Recommendations for long-term use of systemic corticosteroids in uveitis are for maintenance doses not higher than 10 mg / day in order to reduce serious adverse reactions, but the doses used in actual clinical practice are often much higher.
Non-corticosteroid immunosuppressive agents have been shown to be effective in suppressing inflammation and reducing corticosteroid exposure, but at the same time have a narrow therapeutic index and may have specific side effects that require monitoring. The SITE cohort study evaluates the results of treatment in patients with ocular inflammation - incl. uveitis, scleritis and ocular pemphigoid. Inflammation control with a prednisone dose of 10 mg / day or less was maintained for 1 year by 55% of the mycophenolate group, 36% of the cyclosporine group, 61% of the cyclophosphamide group, 58% of the methotrexate group and 47% of the azathioprine group. During the same period, the percentage of dropouts due to adverse events was 12% for mycophenolate, 11% for cyclosporine, 34% for cyclophosphamide, 16% for methotrexate and 24% for azathioprine. Specific safety concerns with these agents include bone marrow toxicity and elevated liver enzymes (mycophenolate, methotrexate and azathioprine), renal impairment (cyclosporine) and malignancy and haemorrhagic cystitis (cyclophosphamide).
Intravitreal corticosteroid implants lead to improved vision and a reduced inflammatory response, but they are associated with an increased risk of developing ocular hypertension, glaucoma and cataracts.

Therapeutic standards

There are currently no consensus on treatment specifically aimed at treating non-infectious, intermediate, posterior and panuveitis. Treatment decisions can be guided by available

recommendations from an expert group or country-specific guidelines for ocular inflammatory diseases. Non-infectious uveitis is often treated in combination with systemic autoimmune disease. For this reason, there is currently no consensus on treatment that takes into account all types of uveitis and all possible treatments. Recommendations for the treatment of ocular inflammatory diseases, including uveitis (Table 1) have been developed.

Country	Professional body / expert group	Year of publication	Scope	References
US	Expert panel (12 ophthalmologists, pediatricians, and rheumatologists)(referred to as primary guideline)	2000	Use of immunosuppressive drugs in patients with ocular inflammatory disorders	Jabs *et al. /43/*
US	American Uveitis Society	2013	Use of anti-TNF-α biologic agents in patients with ocular inflammatory disorders	Levy-Clarke *et al.*/44/
US	American College of Rheumatology	2015	Treatment recommendations for axial SpA patients presenting with **comorbid iritis**.	Ward *et al.* /45/
Germany	Professional Association of German Ophthalmologists Association (BVA) and German Ophthalmic Society (GOD)	Updated in 2010	Guideline for the management of **anterior uveitis** (guideline 14)	BVA webpage /46/
Germany		2001	Management of **intermediate and posterior uveitis** (guideline 24)(refers only to guideline 14)	BVA webpage /47/
Germany		2011	Management of **uveitis associated with JIA**	Heiligenhaus *et al. /48/*

Table 1. National and international guidelines and consensus for the treatment of uveitis

As a result of the adverse drug reactions of corticosteroids, consensus recommend other immunosuppressants and biological agents as adjuvant treatment to corticosteroids in the early stages of disease treatment.

Efficacy data

Description of clinical trial results

Clinical study	VISUAL I (25) M10-877	VISUAL II (25) M10-880	VISUAL III (25,26) M11-327
Design	Phase III, double blind, randomized, placebo controlled	Phase III, double blind, randomized, multicenter, placebo controlled	Open, multicenter, an extended study of VISUAL I and VISUAL II
Duration	80 weeks	80 weeks	66 weeks
Goal	To evaluate the therapeutic efficacy and safety profile of ADA compared to PBO in patients with **active** NIPP of at least one eye requiring treatment with high doses of systemic corticosteroids.	To evaluate the therapeutic efficacy and safety profile of ADA versus PBO in patients with **inactive** NIPP in at least 1 eye requiring treatment with high doses of systemic corticosteroids.	To evaluate the long-term safety of ADA in patients with active or inactive NIPP.
Criteria for inclusion and exclusion	Patients with active disease at baseline, defined as the presence of at least one of the following parameters in at least one eye despite ≥2 weeks of maintenance therapy with oral prednisone, dose ≥10 mg / day to ≤60 mg / day (or oral equivalent): Active, inflammatory, chorioretinal and / or inflammatory retinal vascular lesion ≥2 + degree according to the cells in the anterior chamber (according to SUN criteria) ≥2 + degree of vitreous opacity (according to NEI /	Patients who are with inactive disease for > 28 days prior to baseline visit and receive ≥10 mg oral prednisone and meet all three of the following criteria in the screening and baseline visit for both eyes: Patients without active inflammatory chorioretinal and / or inflammatory retinal vascular lesion Patients with a degree according to the cells in the anterior chamber ≤0.5 + (according to the SUN criteria) Patients with a	• Patients who were successfully included in VISUAL I or II and reached the endpoint (treatment failure) or completed the study. Exclusion criteria: Patients who discontinued VISUAL I or II prematurely for a reason other than a treatment failure event Patients with vitreous or lens opacity that interferes with fundus visualization or requires surgical treatment of cataracts during the study

	SUN criteria) Patients on oral prednisone therapy, dose ≥10 mg / day to ≤60 mg / day (or oral equivalent) for at least 2 weeks prior to screening and remain at the same dose from screening to baseline. Patients with documented previous adequate response to oral corticosteroids (oral prednisone equivalent up to 1mg / kg / day) Patients without previous, active or latent tuberculosis **Exclusion criteria:** Patients with isolated anterior uveitis Patients with confirmed or suspected infectious uveitis Patients with previous exposure to anti-TNF therapy or any biological therapy (excluding intravitreal anti-VEGF therapy) with a potential therapeutic effect in non-infectious uveitis. Patients with a previous inadequate response to high doses of oral corticosteroids Patients on more than one immunosuppressive therapy (without corticosteroids) at baseline. Patients on concomitant immunosuppressive therapy other than methotrexate, cyclosporine, mycophenolate mofetil or an equivalent drug to mycophenolate mofetil, azathioprine, or tacrolimus at baseline Patients receiving corticosteroid therapy with intraocular or periocular administration within 30 days before the initial visit Patients with severe vitreous opacity that interferes with baseline visualization of the fundus	degree of vitreous opacity ≤0.5 + (according to the NEI / SUN criteria) Patients on therapy with oral prednisone 10 to 35 mg / day (or oral equivalent)) at baseline and in which the dose has not been increased in the last 28 days or increased in the last 14 days. Patients with at least one exacerbation of the disease within 18 months of the screening visit. Exacerbations should occur during or up to a maximum of 28 days after dose reduction of oral corticosteroids. Exclusion criteria: Patients with isolated anterior uveitis Patients with confirmed or suspected infectious uveitis Patients with previous exposure to anti-TNF therapy or any biological therapy (excluding intravitreal anti-VEGF therapy) with a potential therapeutic effect in non-infectious uveitis Patients on more than one immunosuppressive therapy (without corticosteroids) within the last 28 days before the initial visit Patients on concomitant immunosuppressive therapy other than methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, or tacrolimus within 28 days of baseline or who have discontinued immunosuppressive therapy, including methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, or tacrolimus within 28 days of baseline. Patients receiving corticosteroid therapy with intraocular or periocular administration within 90 days before the initial visit. Patients with cystic macular edema, unless retinal changes are persistent according to SUN criteria (> 3	Patients with intraocular pressure ≥25 mmHg and on therapy with ≥2 glaucoma medication or evidence of optic nerve damage due to glaucoma. Patients with proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy. Patients with neovascular / wet age-related macular degeneration Patients with vitreoretinal abnormalities with the potential for structural damage to the macula, regardless of the inflammatory process Patients with systemic inflammatory disease requiring treatment with an unauthorized immunosuppressive agent at study inclusion

		months).	
Endpoints	Primary endpoint Time to treatment failure, defined as worsening of at least one of the following criteria in comparison to the baseline:Worsening of at least one of the following: • Inflammatory retinal lesions - new active lesions in comparison to the baseline • Degree according to the cells in the anterior chamber - inability to reach ≤0.5 + in week 6, an increase of 2 degrees compared to the best condition after week 6 • Degree of vitreous opacity - inability to reach ≤0.5 + in week 6, an increase of 2 degrees compared to the best condition after week 6 • Visual acuity - worsening of BCVA by ≥15 letters compared to the best condition Secondary endpoint OCT data for macular edema, change in central retinal thickness, quality of life associated with vision	Primary endpoint Time to treatment failure, defined as a manifestation of exacerbation of uveitis (inability to maintain control of the disease). Treatment failure is based on at least one of the following criteria: • Inflammatory chorioretinal and / or inflammatory retinal vascular lesions - new active lesions relative to baseline • Degree according to the cells in the anterior chamber of the eye - increase by 2 degrees compared to baseline • Degree of vitreous opacity- increase by 2 degrees compared to baseline • Visual acuity - deterioration of BCVA by ≥15 letters relative to baseline Secondary endpoint Time to OCT data for macular edema of at least one eye in patients without baseline macular edema, percentage change in central retinal thickness in each eye in patients without baseline macular edema, quality of life associated with vision	Primary endpoint Proportion of patients at each time point in the study without new disease progression assessed on the basis of: inflammatory lesions, degree according to the cells in the anterior chamber, vitreous opacity, visual acuity, central retinal thickness and VFQ-25.

Initial characteristics of patients	Women: 57% Average age: 42.7 years Average duration of the disease: 46 months Patients with intermediate uveitis: 22% Patients with posterior uveitis: 33% Patients with panuveitis: 45%	Women: 61.1% Average age: 42.5 years Average duration of the disease: 61.2 months Patients with intermediate uveitis: 20.8% Patients with posterior uveitis: 32.3% Patients with intermediate / posterior uveitis: 1.3% Patients with panuveitis: 45.6%	
Arms	217 patients randomized 1:1 to ADA or PBO: stratification according to baseline immunosuppressive therapy.	226 patients	

Table 2. Description of the results of clinical trials

ADA - adalimumab, PBO - placebo, NIPP - Non-infectious intermediate, posterior and panuveitis, SUN - Standardization of uveitis nomenclature, NEI - National EYE Institute, TNF - tumor necrosis factor, VEGF - vascular endothelial growth factor, BCVA – best corrected visual acuity, VFQ-25 - Visual Functioning Questionnaire 25 National Health Insurance Fund

Data for comparators

According to the published pharmacotherapeutic guideline for eye diseases, adopted by Ordinance № 5 of September 19, 2019 for the adoption of a pharmacotherapeutic guideline for eye diseases, prom. in SG, issue 80 of 11.10.2019 the following approach is recommended in the treatment of uveitis:

- steroid drops - Dexamethasone, Fluorometholone, Prednisolone 1%

- subconjunctival or oral steroid - Dexamethasone, Prednisolone acetate

- NSAIDs - topically (Diclofenac sodium 0.1%, Indomethacine, Nepafenac 1 mg / ml), Bromfenac and / or total (Diclofenac)

- cycloplegia - Cyclopentolate

- immunosuppressants in recurrences - Cyclosporin, Methotrexate - after consultation with a rheumatologist.

Pharmacoeconomic indicators

The aim and perspective of the analysis is to evaluate the cost-effectiveness of Humira (adalimumab) in the treatment of patients with non-infectious intermediate, posterior and panuveitis from the point of view of the paying institution - NHIF.

3.1. Description of the conducted pharmacoeconomic analyzes with the assessed health technology in other countries.

A systematic review by keywords (adalimumab, uveitis, cost-effectiveness) in scientific databases is applied in order to identify published complete pharmacoeconomic analyzes of the type of cost-utility, cost-effectiveness or cost-benefit and cost-consequences. The process of selecting publications follows the PRISMA methodology and detailed exclusion criteria (different indication, scores without results or demographic characteristics that do not meet the assessed indication).
Two studies have been identified that meet the pre-established criteria for literary search. The main parameters - target population, comparative alternatives, perspective, costs, results, are described in detail in a table in the provided HTA and are summarized in the following table.

Study	*Purpose*	*Method*	*Alternatives*	*Measure*	*Conclusion*
Squires H et al. 2017, Great Britain	Evaluation of the cost-effectiveness of adalimumab from the perspective of the paying institution	Cost-utility	Adalimumab vs current standard of treatment	QALY	ICER varies in range £ 94 523 - £ 317 5470 QALY in patients with active uveitis and inactive uveitis, respectively
Bermejo I et al. 2018, GreatBritain	Evaluation of the cost-effectiveness of adalimumab from the perspective of the paying institution	Cost-utility	Adalimumab vs current standard of treatment (antibiotics, corticosteroids, aseptics, topical therapy)	QALY	ICER varies in range £ 92,600 - £ 318,075 QALY in patients with active and inactive uveitis

Table 3. Description of the identified studies

3.2. Description of published health technology assessments (HTAs) performed by state institutions for the purposes of another national healthcare system

This HTA provides an assessment of health technology from the relevant institutions of the United Kingdom (NICE) and France (HAS). The point of view of the published HTA, the target population and the conclusion of the respective agency are presented in the following table.

Institution that carried out the assessment	***Perspective***	***Affected population***	***Comparators***	***Access scheme***	***Conclusion and decision***
NICE 2017	Payer	For the treatment of non-infectious intermediate, posterior and panuveitis in adult patients with insufficient response to corticosteroid therapy or who are not indicated for such treatment	Injections with corticosteroids and implants, systemic immunosuppressive therapies, tumor necrosis factor alpha inhibitors	Not applicable	Adalimumab is recommended as an option for the treatment of non-infectious uveitis in the posterior segment of the eye in adult patients with an inadequate response to corticosteroid therapy, only in the presence of: active disease and insufficient response or intolerance to immunosuppressive therapy, and systemic disease or when both eyes are affected
HAS, 2017	Payer	For the treatment of non-infectious intermediate, posterior and panuveitis in adult patients with insufficient response to corticosteroid therapy or who are not indicated for such treatment	Topical periocular corticosteroid treatments or intravitreal injections, but these are insufficient in case of systemic disease.	Not applicable	The Commission recommends the inclusion of the medicinal product in the list of products subject to reimbursement for this indication.

Table 4. Description of the decisions of other HTA agencies

3.3. Applied analysis

The applied analysis is of the type of cost-effectiveness, as it is adapted for the Bulgarian therapeutic practice.

3.4. Purpose of the analysis

The stated goal is to evaluate the value efficacy of adalimumab in the treatment of non-infectious intermediate, posterior and panuveitis (NIPP).

3.5. Comparators

The chosen comparator is the current standard of therapy related to disease control through hospital treatment of complications of long-term systemic corticosteroid therapy - CP No. 133 (Conservative treatment of glaucoma, vascular diseases of the eye and non-perforating injuries) and CP No. 19 (Surgical removal of cataracts). According to experts, cataracts and glaucoma are considered to be the most common complications of long-term systemic treatment with corticosteroids (CS), but currently this treatment and the use of some topical antibiotics are the main standard of treatment. Systemic corticosteroid therapy is used in exacerbate symptoms according to certain regimens, but it is not included in the comparators.

3.6. Perspective

The perspective of the analysis is that of the paying institution - NHIF, as the expected level of reimbursement of 75% is set in the model.

3.7. Time horizon

The selected time horizon of the model is 1 year, the choice is based on data for the period until treatment failure - 5.52 months. The SmPC noted that the long-term benefits and risks of treatment should be reassessed on an annual basis.

3.8. Methods used

A cost-effectiveness analysis was performed on the basis of the efficacy data described in section 2.

3.9. Costs for the assessed health technology and the alternatives used for comparison

The costs included in the model correspond to the perspective of the analysis - NHIF. These are the direct costs of drug therapy, as well as the costs associated with the application of the treatment standard. According to the SmPC, as there is limited experience with starting Humira

monotherapy, it is recommended that the product be started together with corticosteroids, which should be reduced two weeks after the start of the treatment.
The costs are calculated for a 1-year period for 1 person in order to more correctly calculate and present. In the VISUAL I study, the duration of treatment was 80 weeks or until treatment failure, therefore the cost was calculated for a 1-year period.
The cost of systemic corticosteroid therapy was calculated based on their dosing schedule in the VISUAL I and II studies - 60 mg / day until week 15 of treatment.

Medicinal product	**Dose**	**Amount mg for 1-year period**	**Cost for 1 mg**	**Total cost for 1-year period**	**Total cost at 75% reimbursement**	**Cost to be paid by the patient**
Adalimumab	80 mg starting dose, followed by 40 mg per week, starting one week after the initial dose	1120 mg	13.14875	14 726.39	11 044.80	3681.60
Methylprednisolone	60 mg / day for 15 weeks	6300 mg	0.025027	158	79	79

Table 5. Cost for 1-year treatment for 1 patient with adalimumab

Other health resources included in the analysis and the assumptions related to them are presented in the following table.

Health resource	Unit cost	Number per year	Total cost for 1-year period	Source	Note
CP No. 133: Conservative treatment of glaucoma, vascular diseases of the eye and non-perforating injuries	273 BGN	3	819 BGN	National Framework Agreement (NFA); expert opinion	In treatment without adalimumab
CP No. 133: Conservative treatment of glaucoma, vascular diseases of the eye and non-perforating injuries	273 BGN	1	273	NFA; VISUAL III	In the VISUAL III study, published in 2018, 66% of patients entered the study without CS, which is why it has been suggested that adalimumab reduces the risk of hospitalizations by 0.66

Table 6. Cost for 1-year treatment of other direct costs related to the compators

3.10. Discounting

Discounting of costs and results is not applied, as the time horizon of the analysis is 1 year.

3.11. Outcome measures

The selection of outcome measures is based on the VISUAL I and VISUAL II studies.

To perform the present cost-effectiveness analysis, the number of patients in remission at week 52 and time to treatment failure (median) were used as a outcome measure - Table 5.

Measure	Adalimumab + CS	CS	Source
% of patients with remission and without CS	12%	4%	VISUAL I and II
Time to treatment failure (median)	24 weeks	12 weeks	VISUAL I and II

Table 7. Outcome measures

3.12. Presentation of the results of the applied analysis

Alternative	Cost per 1 year 1 patient	ΔC	Result	ΔE	CER/ ICER
% of patients in remission					
SoC (CS	898		0.04		
Adalimumab + CS	11396.80	10499	0.12	0.08	131235
Time to treatment failure (in years)					
SoC (CS	898		0.25		
Adalimumab + CS	11396.80	10499	0.46	0.21	499942

Table 8. Incremental ratio

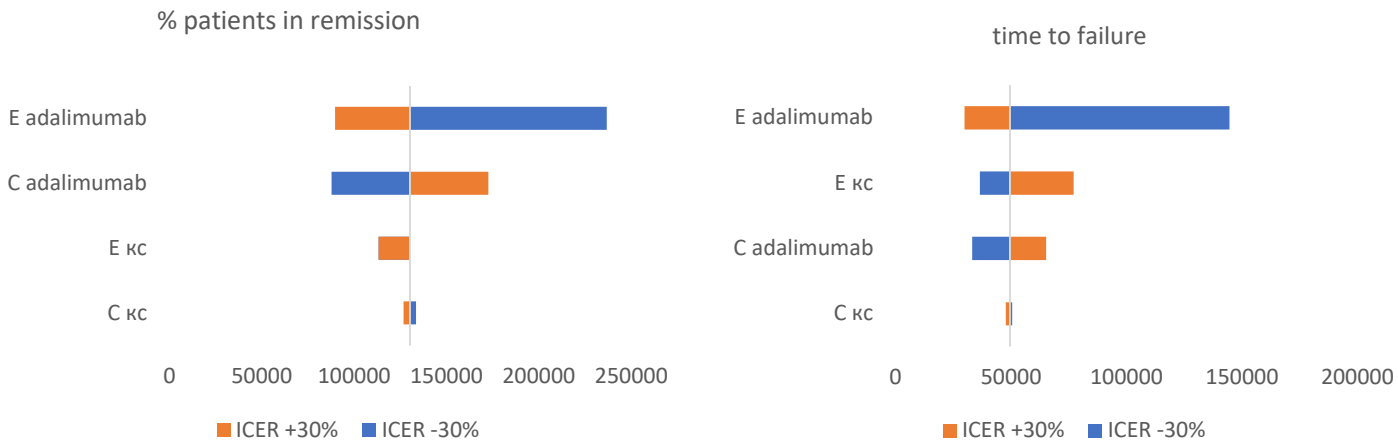

Figure 1. Tornado diagram

The cost-effectiveness analysis shows that according to the WHO methodology, ICER is above the profitability threshold (3x GDP / capita) in terms of the "time to failure" measure, but the applied analysis shows that when the price of adalimumab decreases or increases of efficacy, ICER falls below the profitability threshold.

4. Analysis of the budget impact

4.1. Perspective

The analysis of the budget impact is performed from the point of view of the paying institution - NHIF.

4.2. Time horizon

The time horizon is 5 years.

4.3. Elements of the budget impact analysis

The budget impact analysis (BIA) includes the following elements:

- size and characteristics of the target population

- current therapeutic practice

- new therapeutic practice after the introduction of the new technology

- costs for a treatment with the applicant health technology and SOC

- presentation of the results of BIA

- sensitivity analysis.

4.4. Data sources

The main sources of data used in the analysis of budget impact are the databases of the National council on prices and reimbursement of medicinal products, the NHIF (National Health Insurance Fund) and the National statistical institute (NSI).

4.5. Size and characteristics of the target population

The assumptions in the BIA model are based on global epidemiological data used for NIPP, due to the lack of local ones.

Despite the high incidence of uveitis, NIPP subpopulations are small and belong to patients with rare diseases. **Approximately half of patients with NIPP are also diagnosed with autoimmune disease.** Between 15% and 40% of cases of non-infectious uveitis are intermediate, posterior and panuveitis (depending on the studied population).

The expected number of patients for the considered 5-year period is presented in the following table.

Health Technology	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Humira (adalimumab)	30	35	40	45	50

Table 9. Prognosed number of patients

4.6. BIA scenarios

The Budgetary Impact Analysis (BIA) is based on two scenarios: “World with Health Technology”, in which Humira is reimbursed for the treatment of uveitis with 75% reimbursement, and “World without New Technology”, in which the expected number of patients remains on the standard treatment (described in cost-effectiveness analysis) - CP 133 and treatment with systemic CS.

4.8. Costs

As treatment with systemic CS and CP 313 is determined individually for each patient, the costs are calculated based on the assumptions described in section 3.9.

4.9. Results

	Year 1	Year 2	Year 3	Year 4	Year 5
World with Humira	341904	398888	455872	512856	569840
World without Humira	26940	31430	35920	40410	44900
Budget impact	314964	367458	419952	472446	524940

Table 10. Budget impact

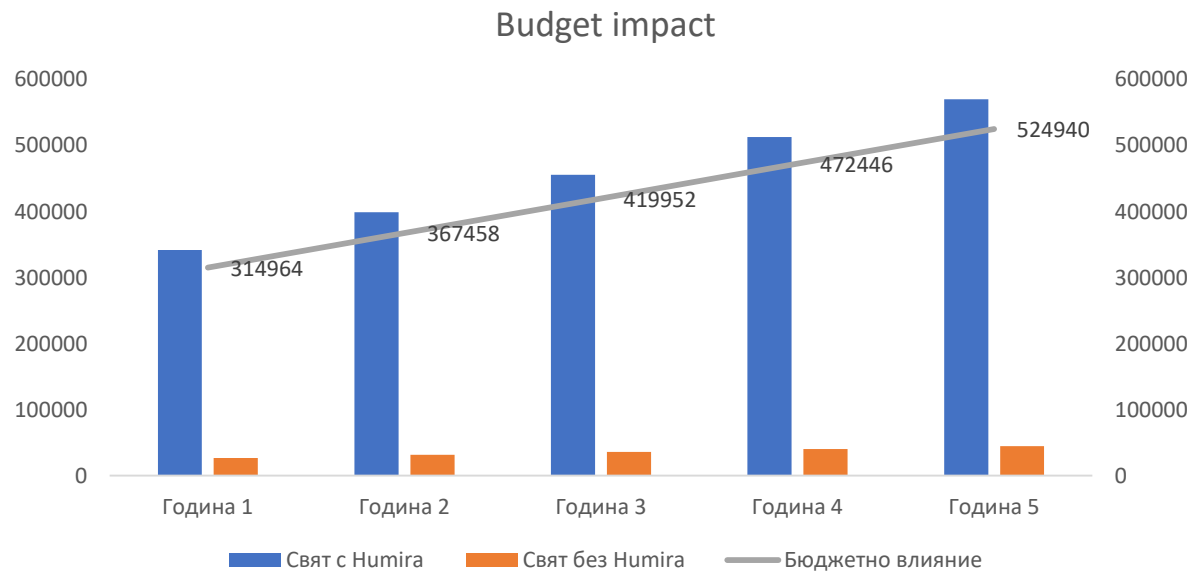

Fig. 2. Budget Impact

The conducted budget impact analysis shows that the treatment of uveitis with Humira will increase the budget by an average of about BGN 420,000 per year.

Conclusion

Uveitis is a disease that affects many aspects of patients' lives, including the daily activities they perform and their overall social and professional functioning. Its negative impact affects the general health of patients, with up to 50% of them losing 25% of their vision and 10-15% remaining blind. As the disease mainly affects people of working age, their professional functioning is reduced, which in turn leads to indirect costs for society due to the numerous days off or reduced productivity in the workplace.

Treatment with Humira significantly reduced the risk of treatment failure in patients with non-infectious intermediate, posterior and panuveitis (NIPP).

Long-term treatment with Humira reduces the inflammatory process and relieves the burden of corticosteroid therapy in patients with NIPP.

The pharmacoeconomic assessment, despite the limitations based on the model, shows that with longer treatment with CS and more frequent hospitalizations, the costs of the current treatment standard are expected to increase and this will lead to a reduction in ICER below the profitability threshold. At present, Humira is the only therapeutic option approved for the treatment of NIPP, which significantly reduces the duration of treatment with systemic CS, and at the same time reduces the risk of complications and ADRs. In addition, adalimumab treatment significantly improved the patient's condition and delayed treatment failure. Humira also meets the concept of unmet medical needs.