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

HEALTH TECHNOLOGY ASSESSMENT

MabThera

500mg/50ml concentrate for solution for infusion x 1 vial

Rituximab

Therapeutic indications	Treatment of patients with moderate to severe pemphigus vulgaris
Start- end of the procedure	08.05.2019-29.11.2019
Final decision	Positive for the indication - treatment of patients with moderate to severe pemphigus vulgaris in Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF).

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

Health problem

Pemphigus is a group of life-threatening autoimmune diseases that most commonly affect the active age (30 to 50 years) and show a chronic recurrent course and sometimes a severe prognosis. It is caused by autoantibodies directed against desmosomal proteins of the cadherin family: desmoglein 1 and desmoglein 3. Deposition of antibodies to antigens in the area of desmosomes lead to a disturbance of their basic function and acantholysis (separation of cells in the epidermis) and the occurrence of intra-epidermal vesicle. Three main variants of pemphigus are known: pemphigus vulgaris (PV), pemphigus foliaceus and paraneoplastic pemphigus, which differ in their clinical picture, histology, immunology and prognosis.

Pemphigus vulgaris (PV) is the most severe variant of the disease, affecting the skin and visible mucous membranes. It is found among all racial and ethnic groups, with the highest frequency among Ashkenazi Jews. There are 3 subtypes:

- With predominant mucosal involvement - blisters are observed in the deep layers of the oral mucosa, which are due to anti-desmoglein 3 IgG autoantibodies;
- With involvement of the mucous membranes and skin - there are blisters in the deep layers of the mucous membrane of the oral cavity and epidermis, which are due to anti-desmoglein 3 and anti-desmoglein 1 IgG autoantibodies, respectively;
- With predominant skin involvement - blisters are observed in the deep layers of the epidermis of the oral cavity, which are due to anti-desmoglein 1 IgG autoantibodies.

Other types of pemphigus are:

- Pemphigus vegetans, which is a subvariant of PV
- Pemphigus erythematosus, a subvariant of pemphigus foliaceus;
- Drug-induced pemphigus, etc.

Diagnostic tests for pemphigus include histology (blister edge biopsy or erosion), direct immunofluorescence, and immuno-serological tests (the most

commonly used serological test for diagnosing pemphigus is ELISA). Prior to the introduction of corticosteroid (CS) therapy in clinical practice in the 1950s, PV was a high-mortality disease. At present, CSs still the main therapeutic alternative. Currently, mortality rates are significantly lower and are mainly due to adverse drug reactions from therapy.

Pemphigus can lead to a deterioration in the quality of life of patients, as the severity of the disease is unpredictable, varies from case to case and can cause life-threatening conditions. There are two most widely used tools for assessing changes in disease severity: 1. Pemphigus Disease Area Index (PDAI) and 2. Autoimmune Bullous Skin Disorder Intensity Score (ABSIS).

The development of pemphigus is thought to be associated with the occurrence of a fixed number of autoreactive B cells that do not change over the years. Removal of these autoimmune B cells may result in long-term remission as seen with Rituximab-treated patients.

In 2018 an international panel of 39 experts from 21 countries (including Bulgaria) presents updated recommendations for the diagnosis and treatment of pemphigus. The anti-CD20 monoclonal antibodies, representative of which is rituximab, are recommended as first-line treatment in newly diagnosed patients with moderate to severe pemphigus and/or in patients who have not achieved remission after treatment with systemic CS and/or immunosuppressants. These recommendations emphasize that Rituximab is the only monoclonal anti-CD20 antibody in which randomized clinical trials were conducted and that allows a faster reduction in the dose of CS compared to other alternatives.

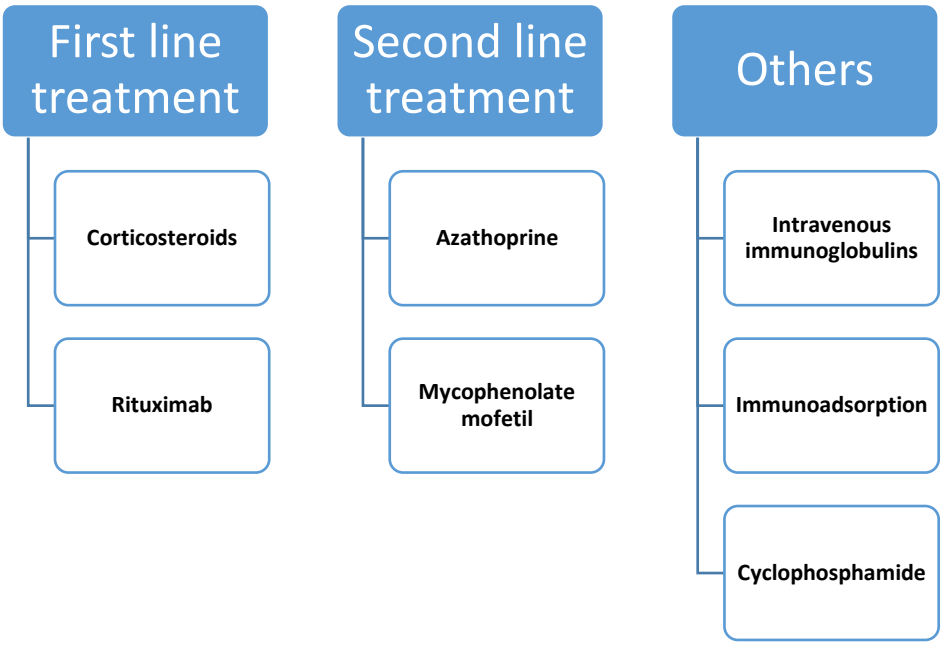

Figure 1. International recommendations for the treatment of patients with pemphigus – 2018

Epidemiological data

The incidence rates of pemphigus vary considerably in different parts of the world. PV is the most common subtype in Europe, the United States and Japan. Patients are more often women, aged between 50-60 years at the time of diagnosis. Epidemiological studies conducted in various European countries show that the incidence of PV is lower at higher altitudes and higher at lower altitudes. The incidence rates range from 0.5/1,000,000 in Germany to 8/100,000 in Greece. Data for the Bulgarian population from a retrospective study by Tsankov et al., show an average incidence of 0.47/100,000 people in the general population and 0.51/100,000 people for the age group over 20 years. The prevalence is estimated at 0.38/100,000 people. The mean age of diagnosis was 72.4 years.

The target population of patients eligible for rituximab treatment is patients with moderate to severe pemphigus vulgaris.

Efficacy data

The efficacy and safety of MabThera in combination with short-term low-dose glucocorticoid therapy (prednisone) have been evaluated in newly diagnosed patients with moderate to severe pemphigus (74 with pemphigus vulgaris and 16 with pemphigus foliaceus [PF]), in a randomized, open-label, controlled, multicenter trial. The patients were between 19 and 79 years of age and had not previously received treatment for pemphigus. In the PV population, 5 (13%) patients in the MabThera group and 3 (8%) patients in the standard dose prednisone group had moderate disease, and 33 (87%) patients in the MabThera group and 33 (92%) patients in the standard dose group prednisone had severe disease according to Harman's disease severity criteria.

A systematic review of the literature identifies the following study:
Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicenter, parallel-group, open-label randomized trial. The Lancet 2017; 389 (10083): 2031-40.
The RITUX-3 study was a randomized, open-label, controlled, multicenter trial evaluating the efficacy and safety of MabThera in combination with short-term low-dose glucocorticoid therapy (prednisone) evaluated in newly diagnosed patients with moderate to severe pemphigus. Description of the RITUX-3 trial:

Table 1. Description of the RITUX-3 trial

Clinical trial	RITUX-3 (NCT00784589)
Country	France
Participants	90 patients
Type of the trial, duration	randomized, open-label, controlled, multicenter trial
Intervention	Rituximab iv
Comparators	Prednisone short course Prednisone long course
Results	Primary endpoint ➢ patients in complete remission at month 24 Secondary endpoints

	➢ number of patients in complete remission with minimal treatment at month 24 ➢ time to achieve complete remission when treatment is stopped ➢ cumulative duration of complete remission when treatment was discontinued during the trial ➢ relapse ➢ cumulative dose of prednisone during the trial ➢ change in quality of life ➢ concentration of desmoglein-specific B-lymphocytes and desmoglein-specific antibodies at months 12 and 24 ➢ occurrence of severe adverse drug reactions

The main characteristics of the patients included in RITUX-3 are presented in the table:

Table 2. Characteristics of patients in the RITUX-3 trial

	Prednisone (n=44)	Rituximab + Prednisone short course (n=46)
Age	53·1 (13·8)	53·5 (16·2)
Gender		
Women	19 (43%)	31 (67%)
Men	25 (57%)	15 (33%)
Pemphigus		
Pemphigus vulgaris	36 (82%)	38 (83%)
Pemphigus foliaceus	8 (18%)	8 (17%)
Severity (according		

to Harman's criteria)		
Moderate form	5 (11%)	6 (13%)
Severe form	39 (89%)	40 (87%)
ABSIS score	43·6 (24·1)	34·4 (20·6)
PDAI score (scale is from 0 to 250)	46·0 (23·7)	33·5 (28·1)
PGA score	6·9 (1·4)	6·4 (1·6)
Quality of life		
Skindex score	60·3 (23·7)	54·4 (24·3)
DLQI score	11·6 (7·0)	10·2 (6·4)
Duration of retention of mucosal lesions (days)	83·0 (41·0 – 127·5)	112·5 (42·5 – 186·5)
Duration of retention of skin lesions (days)	83·5 (43·0 – 206·5)	105·0 (37·5 – 215·5)

The study showed statistically significant results of MabThera and a low dose of prednisone compared to a standard dose of prednisone when achieving CRoff ≥ 2 months at month 24 in patients with PV (primary endpoint).

Table 3. Percentage of patients with PV who achieved complete remission without corticosteroid therapy for two or more months, at month 24 (Intent-to-treat population) – PV

	Rituximab + Prednisone N=38	Prednisone N=36	p-value[a]	95% CI[b]
Number of responders (response rate [%])	34 (89.5%)	10 (27.8%)	<0.0001	61.7% (38.4; 76.5)
[a] The p-value was obtained from an accurate Fisher's exact test with mid-p correction [b] 95% confidence interval is corrected Newcomb interval				

At month 24 of the trial, 89% of patients taking rituximab + prednisone short course achieved complete remission compared to 28% of patients treated with prednisone alone (absolute difference 61.7%, 95% CI, p <0.0001).

Secondary endpoints:

The average time to achieve complete remission without therapy was 677 days (420-713, IQR 577-687) in the prednisone group and 277 days (177-751) in the rituximab + prednisone short course group (p <0.0001). Kaplan-Meyer curves show that patients treated with rituximab + prednisone short course have a higher cumulative probability of achieving complete remission without therapy than prednisone patients (Figure 2).

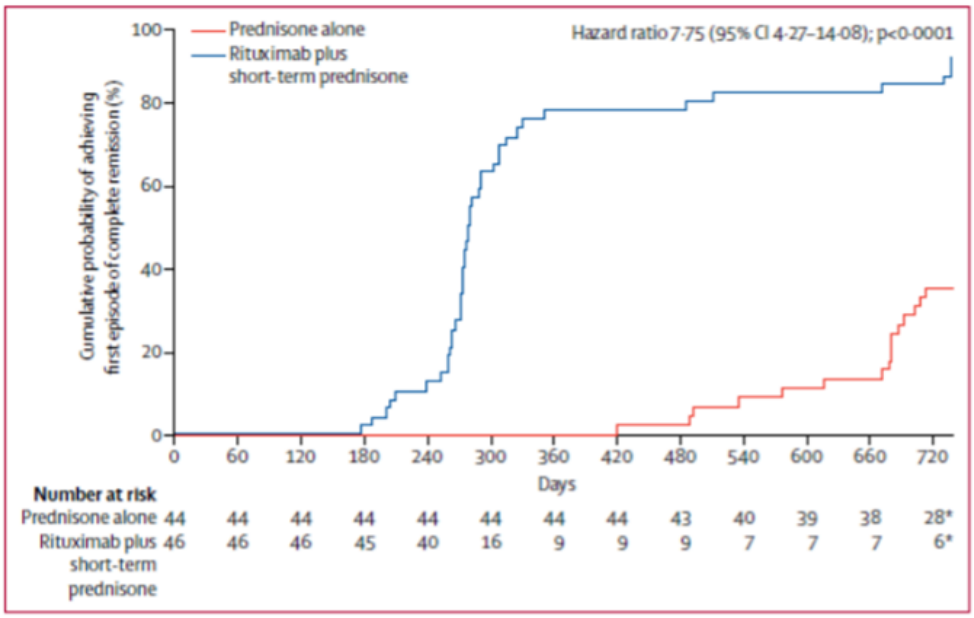

Figure 2. Cumulative probability of achieving complete remission without corticosteroid therapy

The average cumulative duration of complete remission in patients without CS was 7-fold higher in the rituximab + prednisone short course group:

Table 4. The average cumulative duration of complete remission without CS

Group	Value

Rituxmab + Prednisone short course	446 days (0-567, 401-475)
Prednisone	62 days (0-608, IQR 49-178; p<0.0001)

Table 5. Relapse at month 24

Group	Value
Rituxmab + Prednisone short course	24 % (9% severe PV, 15% moderate)
Prednisone	45 % (11% severe PV, 34% moderate)

In the third year of follow-up, relapse was observed in 1 patient (2%) who was in complete remission at month 24 (from the rituximab group) and in 27% of prednisone patients who were in complete remission at month 24.

Table 6. Cumulative dose of corticosteroids for the duration of the study.

Group	Cumulative dose of CS
Rituxmab + Prednisone short course	6143.1 mg (SD 2411)
Prednisone	17973.6 mg (SD 7272.5)

An increase in Dermatology Life Quality Index (DLQI) and Skindex score was observed in patients treated with rituximab + prednisone.
MabThera (rituximab) for the treatment of PV will be administered in specialized pre-hospital care and is expected to partially displace/reduce the dose of corticosteroids used.

Safety data

The safety profile of MabThera in patients with PV is consistent with that observed in patients with Rheumatoid Arthritis (RA) and Granulomatosis with polyangiitis/Microscopic Polyangiitis (GPA/MPA). Adverse drug reactions (ADRs) are adverse events that occurred with a frequency of ≥ 5% in patients with PV treated with MabThera, with an ≥ 2% absolute difference in frequency

between the MabThera-treated group and the prednisone standard dose group up to month 24. There are no patients withdrawn due to ADRs.
No deaths were reported during the study. 14 patients dropped out of the study. In the prednisone group, more ADRs grade 3 and 4 were reported - 53 events in 29 patients (mean 1.2 events per patient). In the rituximab group, grade 3 and 4 ADRs averaged 0.59 per patient. The most commonly reported ADRs in both groups were diabetes and endocrine disorders, myopathy and bone structure disorders.

Table 7. Adverse drug reactions in patients with pemphigus vulgaris treated with MabThera in a clinical trial up to month 24.

System Organ Class **Adverse drug reaction**	**MabThera + low dose prednisone (n = 38)**
Injuries, poisonings and complications resulting from interventions	
Infusion-related reactions	58%
Skin and subcutaneous tissue disorders	
Alopecia	13%
Pruritus	5%
Urticaria	5%
Skin disorder	5%
Mental disorders	
Persistent depressive disorder	13%
Major depression	5%
Irritability	5%
Infections and infestations	
Herpes virus infection	8%

Herpes zoster	5%
Oral herpes	5%
Conjunctivitis	5%
General disorders and administration site conditions	
Fatigue	8%
Pyrexia	5%
Nervous system disorders	
Headache	5%
Dizziness	5%
Gastrointestinal disorders	
Upper abdominal pain	5%
Cardiac disorders	
Tachycardia	5%
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	5%
Neoplasms - benign, malignant and unspecified (including cysts and polyps)	
Skin papilloma	5%
Infusion-related reactions include symptoms collected on the next scheduled visit after each infusion and adverse events occurring on the day of or one day after the infusion. The most common symptoms/preferred terms of infusion-related reactions include headache, chills, high blood pressure, nausea, asthenia and pain.	

Comparators data

At present, one therapeutic alternative for the treatment of patients with pemphigus vulgaris - methylprednisolone - is included in Appendix 1 of PDL. Drug therapy with methylprednisolone is accepted as a comparator. The choice of the comparator - methylprednisolone, is consistent with the recommended alternatives from the presentation of clinical trials, as it is based on the RITUX-3 trial. In addition, it reflects the Bulgarian therapeutic practice because, according to the Draft of Pharmacotherapeutic Guideline for the treatment of skin and sexually transmitted diseases, the current standard for the treatment of PV in Bulgaria is systemic corticosteroid therapy. Methylprednisolone is included in Annex 1 of the PDL for the treatment of patients with PV.

Pharmacoeconomic indicators

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

Rituximab is a medicine with well-established use and there are biologically similar medicines available on the EU market. Pemphigus vulgaris is a disease with a low prevalence in the general population and affects a small number of patients.
At the time of reviewing the Health Technology Assessment, the Guidelines of the British Dermatology Association were published on the NICE website, in which rituximab was recommended as first-line therapy in patients with PV. This guideline is also accredited by NICE.

Applied analysis

The applied pharmacoeconomic analysis is of the cost-effectiveness type and was performed from the perspective of the paying institution (NHIF), estimating the additional costs of rituximab administration for 1 additional patient who is in remission without corticosteroids at month 24 of treatment. The model has an expected reimbursement level of 100%, the time horizon is 24 months, and the evidence for therapeutic results is based on the RITUX-3 trial, with efficacy data being transferred.

The outcome measure was the number of patients who achieved complete remission (complete epithelialization and no new and/or established lesions) at month 24 without treatment for two months or more (CRoff for ≥2 months).

No modeling applied. The results are presented as an incremental cost-effectiveness ratio. A sensitivity analysis of the Tornado type was performed, which shows how the incremental ratio changes with a change in the value of treatment with the applicant health technology and the outcome measure. The values of the uncertain data are varied in the direction of +/- 5%, +/- 10% and +/- 15%.

The conclusion is that the treatment of patients with rituximab is considered to be cost-effective, as the additional cost for an additional patient who has achieved complete remission at month 24 is BGN 18, 827.94, which is below the threshold of 3 times Gross Domestic Product (GDP) per capita.

The cost structure for the administration of the comparator used (methylprednisolone) does not include the direct cost of treating ADRs due to the specifics of the incidence and the individual therapeutic approach, but they would significantly increase the overall cost of treatment with CS, and this would lead to further reduction of the incremental cost-benefit ratio.

The short time horizon of 24 months can also be considered as a limitation of the analysis, but its choice is justified by the clinical trial selected for the database, as well as the planned period of treatment with the applicant health technology.

Costs for the assessed health technology

The costs included in the model are the direct costs of drug therapy, premedication and outpatient procedures related to the administration of the applied health technology and the costs of treatment with the selected comparators.

Budget impact

The budgetary impact assessment is based on national statistics, data from registers and published epidemiological studies and was conducted from the point of view of the NHIF.

The time horizon of the budgetary impact analysis is 5 years and the target population in this analysis is selected on the basis of the applied epidemiological model. It has been suggested that the introduction of specific therapy will also lead to an increase in the number of patients to be treated. The "World with the New Health Technology" scenario is based on the following assumptions:

- Patients treated with rituximab or CS are equal number - 50:50 from the whole population with the moderate to severe form
- For patients treated with rituximab, a mean dose of CS and a mean duration of treatment until discontinuation of CS was accepted.

The costs of premedication, accompanying CS therapy in decreasing doses for the first year and the cost of premedication and outpatient procedures for parenteral administration are also described for the new health technology.
A sensitivity analysis of the Tornado type was performed, which assessed the change in the values of the selected input parameters and assumptions and their influence on the budget. The change in the number of packages of medicinal products used to treat the disease in both scenarios was mainly varied. Variation of this input parameter indirectly affects the number of patients. The biggest influence on the budget has the variation by +/- 30% of the selected parameter.

The estimated number of patients for a five-year period is 41 for the first year, which will increase to 92 for the fifth year, and the NHIF budget is expected to increase with the addition of the indication pemphigus vulgaris.

Conclusion

The inclusion of the therapeutic indication pemphigus vulgaris for Rituximab in the PDL will lead to an increase in the budget, without taking into account risk-sharing agreements and patient access schemes. At the same time, the use of rituximab is expected to increase the number of patients treated as well as those who achieve remission and is expected to reduce the intake of CSs, which will lead to both a reduction in the direct cost of treatment with them and to a reduction in ADRs that require treatment and respectively reduce the costs of the NHIF in this regard.