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

HEALTH TECHNOLOGY ASSESSMENT

Imnovid
4 mg capsule, hard
Pomalidomide

Therapeutic indications	In combination with dexamethasone, indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.
Start date - end date of procedure	19.04.2019 - 23.12.2019
Final decision	Inclusion in Annex 2 of the Positive Drug List (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 outside of the value of the rendered medical services, with an obligation to monitor the effect of therapy in line with adopted conditions and criteria.

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

Health problem

Multiple myeloma (MM) refers to malignant proliferation of mutated plasma cells in the bone marrow and secretion of structurally homogeneous immunoglobulins (Ig) or their fragments (so-called paraproteins). It generally involves the skeletal and renal systems in the form of debilitating myeloma bone disease and light chain nephropathy respectively, and progresses with various organ dysfunctions.

The disease clinical syndrome complex involves many organs and systems, the main targets being the bones and kidneys. The clinical manifestation ranges from almost asymptomatic forms to severe aggressive course with rapid evolution and fatal outcome. The disease affects middle-aged and elderly patients and most often develops against the background of concomitant comorbidity with varying degrees of organ dysfunction, susceptibility to intercurrent diseases, more frequent side effects of therapy, the need for specific care, limited potential for self-care due to debilitating bone lesions. Such a clinical picture of the disease denotes MM as currently incurable, progressive disease, characterized by multiple relapses.

MM has become one of the rare malignant hemopathies for which a definite benefit of modern treatment has been achieved.
The main groups of medicinal products for the treatment of MM are:
- Immunomodulators (IMiDs) - thalidomide, lenalidomide and pomalidomide
- Proteasome inhibitors (PIs) - bortezomib, carfilzomib and ixazomib
- Monoclonal antibodies (mAb) - daratumumab and elotuzumab
- Histone deacytylase inhibitors (HDAC) - panobinostat

Pomalidomide in combination with dexamethasone is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression with the last therapy.

Epidemiological data

MM is a rare disease with a relative proportion of 1% of all malignancies and 15-20% of all malignant hemopathies. The annual incidence is 4-6/100000 population, increasing with age and in patients over 75 years of age reaches 30-35/100000.
The average age at the time of diagnosis is 65 years with 75% of patients being over 70 years. Male to female ratio is 1.5:1.0. Studies predict an increase in the incidence of MM for Europe by approximately 23% for the period 2015-2030 and by about 60% for the United States for

the period 2012-2033. According to the Bulgarian National Cancer Registry, the standardized incidence in Bulgaria of multiple myeloma and malignant plasma cells neoplasms in 2015 was 2.7/100000 men and 2.1/ 100000 women. The relative 5-year survival of patients ≥ 15 years of age with multiple myeloma in Bulgaria is 22.8%, which is 13.7 percentage points lower than the European average.

Efficacy data

To assess the therapeutic efficacy and safety of Imnovid (pomalidomide) health technology for the treatment of recurrent and refractory multiple myeloma (RRMM), an analysis of results of four clinical trials and one meta-analysis were performed, including 8 complete publications (4 non-comparative and 4 randomized trials).

Data from the initial drug registration study MM-003 (NIMBUS, NCT01311687), which compared the efficacy and safety of pomalidomide + low-dose dexamethasone versus high-dose dexamethasone in patients with PPMM, and the final results of the study OPTIMISxtem + pomD, which compared with bortezomib + dexamethasone in patients with RRMM have been analyzed.

Registration study MM-003 (NIMBUS)
Patients were randomized 2:1 to receive 28-day cycles of pomalidomide (4 mg/day on days 1–21, p.o.) plus low doses of dexamethasone (40 mg/day on days 1, 8, 15, and 22 p.o.) against 28-day cycles of high doses of dexamethasone (40 mg/day on days 1–4, 9–12, and 17–20). Treatment was continued until disease progression or occurrence of unacceptable toxicity.

At a follow-up period of 10 months, the group with POM + LD + DEX demonstrated an advantage in terms of progression-free survival (PFS) compared to the group with HD-DEX: 4 months compared to 1.9 months. PFS in the POM + LD + DEX group was significantly higher regardless of previous treatment.

Overall survival (OS) was significantly higher in the POM + LD + DEX group than in the HD-DEX group: 12.7 months versus 8.1 months.

A higher OS was found in the POM + LD + DEX group in patients refractory to lenalidomide and patients with recent lenalidomide therapy. There were no significant differences between the groups in lenalidomide-refractory and bortezomib patients (11.1 months versus 7.7 months), in patients intolerant to bortezomib (15.5 months versus 8.6 months), and in those with recent bortezomib therapy (13,1 month versus 12.3 months).

Therapeutic response. Of the 302 patients, randomized in the P3 + LoDEX arm at C3, 19.2% achieved ≥ PR, 38.4% SD, and 14.6% progression versus 10% in the HD-DEX arm. Patients with stable disease C3 (17.4%) and C5 (13.6%) improved their therapeutic response to C7. In the groups of patients refractory to Lenalidomide, Boretzomib and both, the therapeutic response was maintained at about 30% in the POM + LD + DEX arm versus 9-12% in the HD-DEX arm.

OPTIMISMM clinical trial

The study included adult patients > 18 years, ECOG 0-2 who had received the following previous treatment:

- Patients with RRMM who received 1–3 previous lines of therapy, all with previous lenalidomide exposure (lenalidomide refractory was also allowed)
- Patients with previous bortezomib therapy if the disease had not progressed during treatment or within 60 days of the last dose of bortezomib at a dose of 1.3 mg/m² body surface area twice weekly.

Patients were randomized 1:1 to receive POM + BOR + LD + DEX or BOR + LD + DEX in 21-day cycles until disease progression or occurrence of unacceptable toxicity. Patients who discontinued therapy prior to disease progression were monitored for response to treatment until progression. All patients were followed up until death or for 5 years, making the assessment of PFS possible in real time after the next line of therapy (PFS2) and OS.

POM + BOR + DEX significantly prolongs PFS: 11.2 months versus 7.1 months for BOR + DEX, including lenalidomide-refractory patients; POM + BOR + DEX significantly reduced the risk of progression or death by 39%; early administration of pomalidomide is associated with greater benefit in all subgroups with adverse cytogenetic risk. The therapeutic response after POM + BOR + DEX was significantly higher (82.2% vs. 50.0%), the mean time to therapeutic response (0.9 months vs. 1.4 months) was significantly shorter, and the time to next treatment (22.2 versus 8.5 months) significantly longer.

Studies with data from real practice. A review of the literature identified 6 retrospective observational studies in patients with prior lenalidomide treatment. The group size in these studies ranged from 39 to 1682 patients with RRMM. The largest of the studies, MIROIR, provided data on 1,682 patients, 97% of whom had received prior treatment with lenalidomide. In that study, patients were followed for 23.7 months. The smallest size study included 39 patients, all of whom previously treated with lenalidomide and followed for 13.1 months. The results of the studies provided further evidence of the efficacy and safety of pomalidomide in a contingent of patients with no other realistic treatment options.

Factors that predict long-term survival with pomalidomide treatment in a univariate analysis are the time from diagnosis to initiation of treatment, particularly over a period of >3 years, serum beta-2 microglobulin levels, unfavorable cytogenetic profile and the presence of plasmacytoma/EMD, although the latter did not reach statistical significance. In the multivariate analysis, the time from diagnosis to the start of therapy with pomalidomide, especially over a period of >3 years, has a negative effect on long-term survival with pomalidomide and represents a separate prognostic factor.

Safety data

Fatal outcome occurred in 144 (48%) in the POM + LD + DEX group and in 80 (53%) patients in the HD-DEX group, most commonly caused by disease progression of 68% and 64%, respectively, and infection, 10% and 19%. There were 4% treatment-related deaths in the POM + LD + DEX group and 5% in the HD-DEX group. ADRs are typical of the class of immunomodulators, but those typical for thalidomide peripheral polyneuropathy and thromboembolism have not been registered. The contingent of pre-treated severely immunocompromised patients who underwent > 2 lines of therapy manifests infectious and inflammatory complications as the most common, 68%. In the HD-DEX arm every other patient has a similar frequency of infectious complications.

Data on comparators

There is no third line drug therapy in Bulgaria for the treatment of RRMM. Pomalidomide can be viewed as technology with no alternative and more specifically as a 'salvage regimen'.

Pharmacoeconomic indicators

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

Pomalidomide in combination with dexamethasone for the treatment of recurrent and refractory multiple myeloma in adult patients who have received at least two prior treatments, including lenalidomide and bortezomib, and whose disease has progressed since the last treatment, has been reviewed and evaluated by NICE (UK), HAS (France), G-BA/ IQWiG (Germany) and SMC (Scotland), all assessments being positive and recommending reimbursement of Imnovid.

Applied analysis

A cost-benefit and cost-effectiveness pharmacoeconomic analysis has been performed. The outcome measures are the acquired QALY, LYG and years without disease progression. The analysis was performed from the perspective of the paying institution, the NHIF. The time

horizon is lifelong. An annual discount factor of 3.5% has been applied for results and costs. Pomalidomide has a unique therapeutic indication that includes adult patients with relapsed refractory multiple myeloma (RRMM) who have received at least two prior treatment regimens, including lenalidomide and bortezomib. The treatment options for these patients are very limited and the evaluation considers pomalidomide as an alternative therapy in the target group of patients.

Pomalidomide in combination with low-dose dexamethason meets the need for third-line treatment of patients with RRMM. Due to the lack of comparative alternatives, pomalidomide was compared to Best Supportive Care (BSC). To assess the cost-effectiveness of Imnovid (pomalidomide), a survival model was applied with three mutually exclusive health conditions - stable disease (before progression), progressive disease and absorbing state (death). Patient quality of life data come from study MM-003 and were reported using EQ-5D.

Despite the high cost of pomalidomide therapy (administered with low dose of dexamethasone), and the fact that it is not defined as cost-effective, compared to BSC, it remains value-effective because it has no alternative for patients with failure of two or more treatment regimens (including lenalidomide and bortezomib). With pomalidomide therapy, a greater proportion of patients remain in a state of PFS and progression, compared to BSC, namely improved survival and acquired additional QALY, an improved quality of life.

Analyzes of subgroups
No subgroup analysis was performed.

Costs for the assessed health technology
Included are costs for drug therapy, costs for control of adverse events, palliative care and complications as a result of the underlying disease or ongoing treatment.

Budget impact analysis
The budget impact analysis was conducted from the point of view of the paying institution, the NHIF. The time horizon of the budget impact is 5 years. The estimated number of patients suitable for treatment with the assessed health technology is 25 in the first year, expected to reach 35 in the fifth year. The inclusion of the new technology in the Positive Drug List will lead to additional costs for the NHIF for a period of 5 years, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The evaluated medicinal product Imnovid (pomalidomide) represents a rescue regimen without alternative. Results from a significant number of clinical trials in RRMM show significant advantages in terms of therapeutic response (ORR, CR), a short time for its achievement, longer PFS and OS in the framework of studies and follow-up, including a 5-year period. With pomalidomide, only the specific side effects characteristic of this class have been registered, against the background of bone marrow insufficiency and immunosuppression from prior lines of therapy and concomitant comorbidity with varying degrees of organ dysfunction in adult patients.

The medicinal product Imnovid (pomalidomide) meets the requirements for a modern therapeutic strategy in a small but problematic number of patients with refractoriness or recurrence from prior therapy.