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

HEALTH TECHNOLOGY ASSESSMENT

Xgeva
120 mg/1.7 ml solution for injection x 1
denosumab

Therapeutic indication(s)	Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with multiple myeloma.
Start/end date of procedure	20.06.2019 – 23.12.2019
Final decision	To add a therapeutic indication 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 beyond the value of the rendered medical services.

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

Health problem

Multiple myeloma (MM) is a malignant disease of plasma cells with low proliferative potential, accumulation in the bone marrow and secretion of structurally homogeneous immunoglobulins (Ig) or fragments thereof. It generally involves the skeletal and renal systems and progresses with a diverse clinical spectrum ranging from asymptomatic through aggressive forms. The diagnosis is made if ≥10% clonal plasma cells are present in the bone marrow or there is a biopsy-proven bone or extramedullary plasmacytoma involvement and ≥1 of the following criteria:

A. Evidence of organ damage (CRAB)

- Hypercalcaemia: serum calcium> 0.25 mmol/l (> 1 mg/dl) higher than the upper reference limit or > 2.75 mmol / l (> 11 mg/dl)
- Renal insufficiency: creatinine clearance < 40 ml per min or serum creatinine > 177 μmol/l (> 2 mg/dl)
- Anemia: hemoglobin value > 20 g/l below the lower limit of normal or hemoglobin values <100 g/l
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT

B. One or more of the following tumor volume biomarkers:

- ≥ 60% clonal plasma cells in the bone marrow
- κ/λ ratio ≥100 (monoclonal to heterogeneous light chain) or absolute value of monoclonal LV > 100mg / l
- > 1 focal lesions ≥ 5 mm, detected by MRI

Although osteolytic lesions can occur anywhere on the skeleton, the most frequently affected sites include the central skeleton (spine, ribs, pelvis), skull, and proximal long bones (elbow and femur). Diffuse osteoporosis may also be a presenting symptom in MM. Bone pain, most commonly in the back due to vertebral fractures, is present in approximately 60% of patients with MM at the time of diagnosis.

Epidemiological data

MM is a rare disease that accounts for only 1% of all carcinomas globally and 15-20% of malignant hemopathies. Traditionally, MM affects older people, with a mean age of 69 years at the time of diagnosis (34.8% of patients diagnosed with MM are over 75 years of age and 9.6% are over 85 years of age), with incidence increasing with age. Annual morbidity is 4-6/ 100,000 population, increasing with age and in patients over 75 years reaching a rate of 30-35/100,000.

In Bulgaria, in 2018 there were 160 new cases of MM and 117 deaths. In 2018 in Bulgaria the number of frequently encountered 5-year cases of diagnosed with MM among all ages is 388. Despite significant improvements in the treatment of MM, the disease remains incurable. It is associated with increased mortality, enormous pain and decreased health-related quality of life (HRQOL), and due to spontaneous fractures, spinal cord compression, osteolytic lesions, recurrent infections, renal failure, anemia, mood disorders, it is accompanied by reduced physical function and side effects of various treatments used to control the disease. Myeloma bone disease is associated with impaired survival with skeletal-related events that increase the risk of death by more than 20%.

In patients with MM, the most important element of supportive care is prevention or reducing the number of skeletal lesions. The goal of treatment of bone lesions in patients with MM is to delay the onset of skeletal events, reduce the recurrence of skeletal events, control of bone pain, and preserving HRQOL. Reduction of bone damage is particularly important in patients with MM with osteolytic bone lesions, as myeloma cells are associated with greater inhibition of bone formation, leading to greater bone loss and a higher rate of fractures, compared to patients with solid tumors and bone metastases.

XGEVA (denosumab) is an innovative therapy for the prevention of skeletal-related events in patients with MM. It is the first and only inhibitor of RANKL, which is a key mediator in the vicious cycle of bone destruction and myeloma cell growth in patients with MM. RANKL is an essential mediator for osteoclast formation, activation and survival. It also has direct expression through myeloma cells. Excessive amount of RANKL is associated with increased bone disease and reduced survival in patients with MM.

Efficacy data

Study 482 is a pilot study, demonstrating the efficacy of denosumab in the MM patient population. Two main trials have been presented, which include data on the efficacy of denosumab in the prevention of skeletal-related events in patients with MM.

The efficacy and safety of denosumab for the prevention of skeletal events in patients with MM was first evaluated in a post hoc subgroup analysis of Study 244. This study was a double-blind, phase 3 randomized controlled trial that assessed denosumab versus zoledronate in 1 776 patients with solid tumors or MM. Although denosumab was shown to be statistically superior to zoledronate for the prevention of skeletal events in patients with advanced bone cancer metastases, the inclusion of participants in the MM component in study 244 was limited to 10% (n = 180) of the general study population and it was not sufficient to definitively evaluate the efficacy of denosumab in MM.

To extend the assessment of the efficacy and safety of denosumab compared to bisphosphonates in the treatment of patients with MM, another specialized, large phase 3 trial of denosumab versus zoledronate was conducted. The results of Study 482 offer a better understanding of clinical outcomes, including survival, with denosumab or bisphosphonate treatment in patients with newly diagnosed MM. At the time of the initial analysis of the study, it was the largest international study ever conducted for patients with MM, including 1,718 patients in 259 centers in 29 countries. Therefore, details on results and employed methods have been provided only for study 482.

Study 482 was a randomized, double-blind, multicenter study comparing denosumab with zoledronate in the treatment of bone disease in patients with newly diagnosed multiple myeloma. A total of 1,718 eligible participants were randomly assigned in a 1:1 ratio to two treatment arms: denosumab 120 mg SC and IV placebo infusion every 4 weeks (Q4W) for at least 15 minutes or a single, minimum 15-minute IV infusion of zoledronate 4 mg (dose adjusted at RI) + placebo SC Q4W.

In Study 482, OS was a secondary additional endpoint, and PFS and time to overall disease progression were research endpoints.

It has been shown that MM cells directly secrete RANKL, and the concentration of RANKL is commensurate with the survival of patients with MM. The hypothesis is that bone-targeted therapies significantly modify the endosteal niche, creating an environment that is inhibitory for myeloma cell growth, leading to a possible indirect antitumor effect on myeloma cells.

In patients with MM, denosumab prolongs PFS compared to zoledronate. Denosumab slows the overall progression of the disease (study endpoint) in patients with MM compared with zoledronate (mean time to overall disease progression 46.1 to 38.8 months [HR = 0.80; 95% CI 0.65 to 0 , 97; p = 0.027]. OS is a secondary endpoint in Study 482 and in the initial HR analysis between denosumab and zoledronate it was 0.90 (95% CI 0.70 to 1.16). There were fewer deaths in the arm of denosumab than in the arm of zoledronate (14.1% versus 15.0%), but the difference was not statistically significant.

Analysis of data reported by patients

The abbreviated form of the The Brief Pain Inventory (BPI-SF) was included in Study 482 to elucidate both the severity of the pain and the perception of how pain interferes with the daily lives of denosumab-treated patients compared to those receiving zoledronate. The severity of the pain was assessed at baseline, on day 8, day 29 (week 5) and every 4 weeks until the end of the trial. Denosumab had a greater reduction in pain severity score than zoledronate, with a therapeutic difference of -0.32 (95% CI -0.60 to -0.04; p = 0.024). Denosumab and

zoledronate show similar results for the time before visit and visit rate for ≥ 2-point decrease, ≥ 2-point increase, and > 4 points for worst pain score.

Safety data

The risk-benefit profile of denosumab remains favorable in both clinical trials and in real world clinical practice for the approved indications for the prevention of skeletal events in adults with advanced bone malignancies and for the treatment of adults and adolescents with developed skeleton with giant cell bone tumor, which is inoperable or where surgery is likely to lead to severe morbidity.

The overall safety profile is consistent with all approved indications for denosumab. The analysis shows the frequency of adverse events for the indications based on the rate of occurence in four phase 3, two phase 2 clinical trials and postmarketing experience, as indicated in the summary of product characteristics.

Adverse events with denosumab are: new primary malignancy, hypersensitivity to the medicinal product, hypocalcaemia, hypophosphatemia, post-treatment hypercalcaemia in patients with giant cell tumor of the bone (GCC), dyspnea, diarrhea, tooth extraction, hyperhidrosis, musculoskeletal pain, osteonecrosis of the jaw, atypical fracture of the femur, osteonecrosis of the external auditory canal.

Data on comparators

The bisphosphonate zoledronate is a comparative alternative used in phase 3 clinical trials of denosumab. Worldwide, it is the most commonly used therapy for the prevention of skeletal-related events in patients with advanced malignancies affecting the bones, including MM.

Pharmacoeconomic indicators

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

In Germany, Sweden, Croatia and Belgium, the drug XGEVA is reimbursed with an indication for the prevention of skeletal-related events (SRE) in adult patients with advanced malignancies (multiple myeloma) affecting the bones.

In Finland, Denmark, the Netherlands and Austria, Xgeva is administered in patients with multiple myeloma.

Applied analysis

A pharmacoeconomic cost-benefit analysis of Xgeva in patients with multiple myeloma (MM) was applied, with a measure of outcome being the cost of QALY and the cost of avoided skeletal-related events. The comparative alternative is zoledronate. The perspective of the analysis is that of the paying institution - NHIF, the time horizon is lifelong and a discounting of costs and health benefits by 3.5% has been carried out.

A five-component model for the development of the disease has been presented that includes the following conditions: administration of bone targeting agents (BTA), no BTA, before progression of MM (no progression), after progression of MM (progression) and death, which are not mutually exclusive. Sensitivity analysis has been attached.

The results of the applied model show that in the lifetime horizon in the baseline scenario, savings were realized and the added QALY was 0.1841, which confirms that denosumab is superior, compared to zoledronate.

With respect to denosumab, patients were estimated to have 0.01 fewer skeletal-related events than those treated with zoledronate, corresponding to a mean deducted year of life of 6.81 years and an additional 12.0 months on average PFS (53.7 to 41.7 months).

The deterministic sensitivity analysis shows that the most significant influence was exerted by the level of utility after progression of MM and the annual frequency of skeletal-related events in both products, while the probabilistic sensitivity analysis shows that denosumab was 61% likely to be dominant and 75% to be cost-effective at the established break-even point.

Costs for the assessed health technology

The analysis includes costs for the acquisition and administration of drugs, for control of adverse events, for the treatment of MM and control of skeletal-related events.
The analysis is based on once every 4 weeks intake.

Budget impact analysis

The analysis of the budget impact has been prepared from the perspective of the National Health Insurance Fund with a time horizon of 5 years. Included are newly diagnosed patients with MM. A 5-year survival rate of 5.51 per 100,000 man-years has been adopted, according to the WHO database. The number of patients to be treated with denosumab is projected to be 95 in the first year through 196 in the fifth year. The effect on the budget is gradually increasing over the years as a result of the increase in the number of patients, expected to start denosumab therapy, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

There exists a medical need for a preventive therapy of skeletal-related events, to be used in all patients with MM, irrespective of renal function or concomitant use of nephrotoxic drugs. Reducing the number of skeletal-related events and improving clinically significant endpoints without further renal function impairment is of primary importance in patients with MM. Xgeva is the first and only inhibitor of RANKL, a key mediator in the vicious cycle of bone destruction and myeloma cell growth in patients with MM.

The presented budget impact analysis illustrates the expected change in costs after the inclusion of the MM indication in Xgeva therapy. The increase in the number of patients who might possibly be treated with it would lead to an increase in the cost of therapy compared to the cost of zoledronate. At the same time, the costs of treatment of multiple myeloma would be reduced, due to the costs generated by alternative product therapy being significantly higher.