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

HEALTH TECHNOLOGY ASSESSMENT

Trodelvy

200 mg powder for concentrate for solution for infusion x 1 vial

INN Sacituzumab govitecan

Therapeutic indication(s)	Monotherapy for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease.
Start/end date of procedure	31.03.2023 – 12.12.2023
Final decision	Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act.

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

Health problem

Triple-negative breast cancer (TNBC) is a basal-like subtype of breast cancer (BC) characterized by the absence of hormone receptor expression (i.e., estrogen receptor [ER]-negative and progesterone receptor [PR]-negative) and the lack of overexpression of human epidermal growth factor receptor 2 (i.e., HER2-negative). It accounts for approximately 10% to 15% of all BC cases. Compared to other BC subtypes, TNBC is associated with rapid tumor proliferation, poor prognosis, and a higher risk of early recurrence, with the disease often being diagnosed at a metastatic stage—about 40% of cases—where the role of systemic antitumor therapy is palliative. Additionally, TNBC is characterized by a larger primary tumor size and a higher degree of cellular dedifferentiation. The levels of programmed cell death-1 (PD-1) protein are higher in TNBC compared to other BC subtypes. Patients diagnosed with TNBC are also more likely to carry BRCA1 gene mutations compared to those with other BC subtypes.

The clinical presentation of TNBC is similar to that of other BC subtypes. The most common manifestation is a new "lump" or mass. Other signs and symptoms of BC include swelling of nearby lymph nodes, changes in the nipples (e.g., discharge), skin changes (e.g., erythema, skin ulcers, eczema), pain or heaviness in the breasts, and other persistent changes in the breasts. The treatment of TNBC depends on the stage of the disease, the molecular subtype, prognostic biomarkers, the degree of tumor malignancy, and the patient's age. In the early stages, treatment includes chemotherapy (adjuvant and neoadjuvant), radiation therapy, or surgery (mastectomy or lumpectomy).

Sacituzumab govitecan (Trodelvy) binds to Trop-2-expressing cancer cells and is internalized, leading to the release of SN-38 from a hydrolyzable linker. SN-38 interacts with topoisomerase I, preventing the re-ligation of topoisomerase I-induced single-strand breaks. The resulting DNA damage leads to apoptosis and cell death. Sacituzumab govitecan is for intravenous administration only.

Epidemiological Data

According to GLOBOCAN, in 2020, the third most common type of cancer in Bulgaria was breast cancer. The number of newly diagnosed patients was 4,061, with 1,533 registered deaths. The five-year survival rate was 425.25 per 100,000 people.

Efficacy data

The therapeutic efficacy and safety profile of sacituzumab govitecan have been analyzed in two clinical trials.

The **IMMU-132-01 clinical trial (NCT01631552)** is a multicenter, open-label, single-group, basket-design Phase I/II trial evaluating the safety and efficacy of sacituzumab govitecan in previously treated patients with advanced epithelial cancer, including metastatic TNBC (mTNBC). The trial involved 108 mTNBC patients. The results showed that 2.8% of the patients with mTNBC achieved a complete response, and 30.6% achieved a partial response. The median progression-free survival (PFS) was 5.5 months, with PFS rates at 6 and 12 months being 41.9% and 15.1%, respectively. The median overall survival (OS) was 13.0 months, with survival rates at 6 and 12 months being 78.5% and 51.3%, respectively. In pretreated mTNBC patients without brain metastases in the ASCENT trial, sacituzumab govitecan demonstrated a significant improvement compared to standard single-agent chemotherapy (physician's choice therapy - TPC), with a median PFS of 5.6 months for patients treated with sacituzumab govitecan compared to 1.7 months for those treated with TPC. The efficacy demonstrated by sacituzumab govitecan compared to TPC led to the early termination of the trial based on the unanimous recommendation of the Data and Safety Monitoring Committee.

The **ASCENT clinical trial (NCT02574455)** is an international, multicenter, open-label, randomized Phase III trial in patients with unresectable, locally advanced, or metastatic TNBC who were refractory or relapsed after receiving ≥2 prior chemotherapy regimens, including ≥1 prior therapy for locally advanced or metastatic disease. The trial results showed that in the intention-to-treat (ITT) population of the ASCENT trial, sacituzumab govitecan demonstrated a significant benefit compared to standard monochemotherapy (TPC) for the primary endpoint of PFS, with a median PFS of 4.8 months for patients treated with sacituzumab govitecan compared to 1.7 months for patients treated with TPC. The high efficacy of the drug led to the early termination of the trial in 2020. In terms of overall survival, sacituzumab govitecan demonstrated a significant benefit over TPC in the ITT population (median OS of 11.8 months versus 6.9 months). A subgroup analysis of ITT patients focused on those treated in the second line (patients who experienced recurrence of BC within 12 months after adjuvant/neoadjuvant chemotherapy as unresectable, locally advanced, or metastatic disease, and who received 1 line of therapy before starting ASCENT); these were early recurrence patients. Of the 34 patients meeting these criteria, sacituzumab govitecan was administered to 34 patients, and TPC to 33 patients. Significant advantages in PFS (median 4.8 versus 1.5 months) and OS (median 10.5 versus 5.0 months) were observed with sacituzumab govitecan compared to TPC. Another subgroup analysis looked at patients treated with ≥3 prior lines of therapy, including ≥2 prior lines in the metastatic setting. This population included 208 patients treated with sacituzumab govitecan and 209 patients treated with TPC. Significant benefits were observed in PFS and OS.

Safety data

The most commonly reported adverse reactions in patients treated with sacituzumab govitecan were diarrhea (64.5%), nausea (64.2%), neutropenia (64.2%), fatigue (52.5%), alopecia (44.3%), anemia (43.2%), vomiting (38.0%), constipation (36.3%), decreased appetite (28.1%), cough (22.7%), and abdominal pain (20.8%).

Data on comparators

Comparative alternatives include eribulin, carboplatin + docetaxel, carboplatin + paclitaxel, carboplatin, cisplatin + gemcitabine, paclitaxel, vinorelbine, and gemcitabine + vinorelbine.

Pharmacoeconomic indicators

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

Four assessments have been published by other government institutions—G-BA (Germany), HAS (France), NICE (UK), and TLV (Sweden), with HAS giving a positive opinion.

Applied analysis
The applied analyses are a cost-effectiveness analysis (CEA), in which the health benefits outcome is presented as life years gained (LYG), and a cost-utility analysis (CUA), in which the health benefits outcome is presented as quality-adjusted life years (QALY). TPC (eribulin) is chosen as the comparative alternative for the primary analysis, and TPC (eribulin, capecitabine) for the additional analysis. The perspective of the analysis is that of the paying institution—the National Health Insurance Fund (NHIF). Health benefits and costs are discounted at an annual discount factor of 3.5%. The time horizon is 10 years. A partitioned survival model with three health states is applied: progression-free, disease progression, and death.

The results of the analyses indicate that the higher treatment costs associated with the evaluated therapeutic regimen are linked to higher health benefits, expressed as more life years gained. In the cost-utility analysis, the ICER of the compared therapies places sacituzumab govitecan above the threshold of favorable cost-effectiveness at 60,636 BGN/QALY (3xGDP per capita).

Costs for the assessed health technology
The included costs in the model are the costs of drug therapy with sacituzumab govitecan (SG), alternative treatment costs, follow-up treatment costs, and palliative care costs.

Subgroup analysis

No subgroup analyses are applied.

Budget impact analysis

The budget impact analysis is conducted from the perspective of the paying institution—the NHIF. The time horizon is 5 years. The target population includes adult patients with inoperable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one for advanced disease. The projected number of patients is 20 in the first year and 40 in the fifth year. Costs are calculated in two variants, each with two scenarios:

Variant 1: Primary analysis. Costs are calculated according to the dosage and administration method per the Summary of Product Characteristics (SPC). A 100% dose intensity is accounted for.

Scenario 1: A world in which the health technology Trodelvy (INN sacituzumab govitecan) is introduced into specialized healthcare and reimbursed by the NHIF for the treatment of adult patients with locally recurrent inoperable or metastatic triple-negative breast cancer ("World with Trodelvy").

Scenario 2: A world where the health technology Trodelvy (INN sacituzumab govitecan) is not introduced into specialized healthcare and is not covered by the NHIF for the treatment of adult patients with locally recurrent inoperable or metastatic triple-negative breast cancer ("World without Trodelvy").

Variant 2: Additional analysis. The costs of therapy with the health technology are calculated with Relative Dose Intensity (RDI), which adjusts the cost per dose of the medicinal product proportionally to the dose received in the ASCENT clinical trial. Similar to real clinical practice, patients in clinical trials do not always receive the prescribed full doses of the medicinal product. Therefore, the data from trials best reflect the efficacy of the doses received compared to the planned doses. This variant reflects the real-world application of the medicinal products, and accordingly, the cost for the payer.

Scenario 1: A world where the health technology Trodelvy (INN sacituzumab govitecan) is introduced into specialized healthcare and is covered by the NHIF for the treatment of adult patients with locally recurrent inoperable or metastatic triple-negative breast cancer ("World with Trodelvy").

Scenario 2: A world where the health technology Trodelvy (INN sacituzumab govitecan) is not introduced into specialized healthcare and is not covered by the NHIF for the treatment of adult patients with locally recurrent inoperable or metastatic triple-negative breast cancer ("World without Trodelvy").

The analysis predicts an increase in costs over a five-year period for the NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The health technology sacituzumab govitecan (Trodelvy) is intended for the treatment of patients with inoperable or metastatic TNBC who have received at least two prior therapies, one of which must have been for metastatic disease. The positive budget impact of Trodelvy can be considered justified, as Trodelvy is the first targeted therapy, representing a Trop-2-directed antibody-drug conjugate, which shows significant benefits in terms of progression-free survival and overall survival compared to standard chemotherapy.