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

HEALTH TECHNOLOGY ASSESSMENT

Onivyde pegylated liposomal

4.3 mg/ml – 10 ml concentrate for dispersion for infusion x 1 vial

Irinotecan anhydrous free base

Therapeutic indication(s)	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.
Start/end date of procedure	20.01.2020 – 20.11.2020
Final decision	Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act.

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

Health problem

Pancreatic cancer is an aggressive disease with a relatively low survival rate. Due to the lack of characteristic early symptoms, the disease is often diagnosed at an advanced stage, when the main therapeutic options are specific drug antitumor treatment, combined in some cases with palliative radiotherapy. Only 10%-15% of patients are eligible for radical surgery at the time of diagnosis, with a similarly significant high risk of recurrence or long-term spread of the disease - over 70%. The majority of patients are diagnosed at a locally advanced or metastatic stage, with a total five-year survival rate of 6.7%.

The most common risk factor for development of pancreatic cancer is the cigarette smoke, with smoking leading to a 66% increased risk of pancreatic cancer in current smokers compared to non-smokers. Similar to lung cancer, smoking cessation significantly reduces the risk of developing pancreatic cancer. Other risk factors are male gender and age.

The pancreas has both endocrine and exocrine glands, with exocrine glands making up the majority of the pancreas (> 95%). Exocrine tumors are the most common type of pancreatic cancer (96%); 80% to 90% of exocrine tumors are pancreatic ductal adenocarcinomas). Endocrine carcinomas (4%) are rare, have a better prognosis and are often diagnosed at a younger age, with a different approach to clinical management.

Anatomically, pancreatic cancer can be classified into 3 groups based on tumor location: tumors of the head, body or tail. The majority (60% to 70%) of pancreatic tumors are found in the head of the pancreas, while 20% to 25% are found in the body or tail of the pancreas, with the remaining 10% to 20% diffusely involving the pancreas. Common symptoms of pancreatic cancer include abdominal pain, weight loss, asthenia, anorexia, steatorrhea, and new onset diabetes, and jaundice is common in patients with tumors of the head of the pancreas, resulting from obstruction of the common bile duct.

ONIVYDE represents a nanoliposome encapsulation of the cytotoxic irinotecan, a topoisomerase inhibitor that has clinical activity against several solid tumors, including pancreatic cancer. The nanoliposome dosage form of irinotecan has a design that aims to prolong its circulation in plasma and the tumor by protecting irinotecan inside the liposome capsule, to increase the tumor uptake of ONIVYDE, taking advantage of the compromised circulatory system to increase the conversion of irinotecan to the active product SN-38 in the tumors themselves.

Epidemiological data

Compared to other cancers, the incidence and prevalence of pancreatic cancer are relatively low. In Bulgaria, according to the National Cancer Registry, of all cancers, pancreatic cancer has a 4% prevalence in men and 3.9% in women. As a cause of death it is 6% and 6.9% for men and women, respectively. The incidence is 17.2 individuals per 100,000.

Efficacy data

NAPOLI-1 is an open, global, phase III trial, which included patients with metastatic pancreatic cancer previously treated with gemcitabine who were randomized to receive ONIVYDE, 5-FU/LV or ONIVYDE plus 5-FU/LV. The primary endpoint is OS (overall survival), while secondary endpoints are: PFS (progression free survival), time to treatment failure (TTF), overall response rate (ORR), CA 19-9 response, clinical benefit response (CBR), patient-reported outcomes (PROs), and safety.

Eligible patients included those with metastatic adenocarcinoma of the exocrine pancreas that had progressed after gemcitabine-based treatment, and in addition, patients had to have a functional status on the KPS scale ≥70 and adequate bone marrow, liver, and kidney function.

In the ITT (total randomized population), the addition of ONIVYDE resulted in a significant improvement in the median OS (6.1 months for ONIVYDE plus 5-FU/LV versus 4.2 months for 5-FU/LV). The mean overall survival was similar for ONIVYDE monotherapy and 5-FU/LV (4.9 months vs. 4.2 months).

Regarding the secondary endpoints of the study, the results showed that a statistically significant benefit was demonstrated in terms of the median PFS and ORR in patients treated with ONIVYDE + 5-FU/LV compared to those treated with 5-FU/LV alone. In addition, a higher response rate in terms of tumor markers was observed in patients receiving ONIVYDE + 5-FU/LV compared to only 5-FU-LV (29% vs. 9%).

Patient-reported outcomes

The assessment of the Health-related Quality of Life (HRQoL) showed that the median scores in Week 6 and Week 12 were close to baseline (before starting treatment), suggesting negligible effects of treatment on QoL. There were no significant differences in the proportion of patients who had improvement, stabilization or reduction in QoL scores between the two treatment arms.

Safety data

The overall incidence of grade 4 adverse events was comparable between ONIVYDE + 5-FU/ LV and 5-FU/LV arms (10% vs. 7%), despite the higher dose of 5-FU/LV in the 5-FU/LV arm in the first 6 weeks of treatment. The most common grade ≥ 3 adverse events (frequency ≥ 10%) observed with ONIVYDE in combination with 5-FU/LV were neutropenia (27%), fatigue (14%), diarrhea (13%) and vomiting (11%). More patients in the ONIVYDE-containing combination arm (compared to 5-FU/LV) required dose reduction (33% vs. 4%) and discontinuation of treatment (11% vs. 7%) due to treatment-related adverse events. The majority of patients were exposed to treatment for at least 6 weeks.

Data on comparators

5-FU/LV is the basic comparator. FOLFOX is a possible additional alternative to expand the functionality of the model.

Pharmacoeconomic indicators

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

Assessments, made for other healthcare systems are presented, with reimbursement decisions being positive in Sweden and France.

Applied analysis

Cost-effectiveness and cost-utility analyses are applied, with outcome measures LYs and QALYs, respectively. The perspective of the paying institution, the NHIF, is presented. The time horizon is 10 years. As comparators, 5-FU/LV as the main alternative and FOLFOX as an additional alternative were used. Health outcomes and costs are discounted at an annual discount factor of 3.5%. In the applied survival model, 4 health conditions were used, and for each individual condition, costs and benefits were considered, based on which the expected costs and QALY for the respective patients were determined. Deterministic and probabilistic sensitivity analyses have been applied.

The results of the analysis show that the costs of using Onivyde + 5FU/LV are higher than the use of 5-FU/LV alone or FOLFOX. The incremental cost per year of life gained ratio and cost per QALY is above the break-even point 3 times GDP per capita.
Subgroup analysis is not presented.

Costs of the assessed health technology

In the model, medication costs have been included, as well as:

- the hospital chemotherapy clinical pathway cost
- follow-up costs - outpatient consultations, scanner, CBC, tests, ultrasound
- ADR treatment cost

Budget impact analysis

The budget impact analysis has been prepared, using the perspective of the National Health Insurance Fund with the time horizon 5 years. The estimated number of patients, eligible for treatment with Onivyde in the first year is 16, reaching 48 patients in the fifth year.

The budget impact analysis shows an increase in the costs of the paying institution, the NHIF, for a period of 5 years after the inclusion of Onivyde in clinical practice, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

In conclusion, ONIVYDE + 5-FU/LV showed a clinically significant improvement in mean overall survival of up to 3.8 months in patients after gemcitabine based therapy as second-line treatment of metastatic pancreatic cancer. Additionally, the mean progression-free survival in patients, treated with ONIVYDE + 5-FU/LV has doubled. The therapy is not associated with reduced quality of life. The cost of therapy is higher than the alternatives and the inclusion of the medicinal product in the PDL is associated with an increase in the NHIF budget, without taking into account risk-sharing agreements and patient access schemes.