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

HEALTH TECHNOLOGY ASSESSMENT

Cresemba

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

Isavuconazole

Therapeutic indication(s)	Indicated in adults for the treatment of: • invasive aspergillosis • mucormycosis in patients for whom amphotericin B is inappropriate.
Start/end date of procedure	14.11.2019 – 25.06.2020
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 Cresemba

Health problem

Invasive aspergillosis and mucormycosis are rare infections caused by Aspergillus and Mucorales, respectively. Invasive aspergillosis is an infection that generally affects the lungs, while mucormycosis most commonly affects the sinuses or lungs. Invasive fungal infections are more common in immunocompromised or critically ill individuals, and both infections can be fatal with mortality in severe cases reaching 90%. Invasive aspergillosis and mucormycosis are also associated with prolonged hospital stays, requiring significant healthcare expenditure due to long-term treatment and management of treatment-related adverse events.

The differential diagnosis between invasive aspergillosis, mucormycosis and other infections is difficult, which contributes to mortality and to the economic burden of invasive aspergillosis and mucormycosis.

There is a limited number of approved therapies for the treatment of invasive aspergillosis and mucormycosis. Voriconazole and liposomal amphotericin B (L-AMB) are indicated for first-line treatment of invasive aspergillosis. L-AMB is also indicated for the first-line treatment of mucormycosis, whereas voriconazole has no activity against infections caused by Mucorales.

Voriconazole and L-AMB have certain disadvantages in their safety profile, which may limit their use, especially in vulnerable groups of patients. L-AMB is associated with clinically significant toxicity, especially an increase in serum creatinine at high doses, which may require dose reduction and discontinuation of treatment.

CRESEMBA (isavuconazole) is an azole antifungal agent for the treatment of invasive aspergillosis in adults and mucormycosis in patients for whom amphotericin B is inappropriate.

Epidemiological data

Invasive aspergillosis and mucormycosis are rare diseases, globally affecting about 250,000 and 10,000 people per year, respectively.

The incidence of invasive aspergillosis and mucormycosis is increasing as the number and life expectancy of immunocompromised and critically ill patient populations are increasing.

Efficacy data

To assess the therapeutic efficacy and safety of the new health technology CRESEMBA, the outcomes of two main phase III clinical trials and a matched case-control analysis were analyzed and summarized.

Phase III SECURE clinical trial evaluated the efficacy and safety of CRESEMBA (isavuconazole) versus voriconazole in the initial treatment of invasive fungal infection caused by Aspergillus species or other filamentous fungi.

VITAL clinical trial is an open-label one-arm study to evaluate the efficacy and safety of CRESEMBA (isavuconazole) in the treatment of invasive aspergillosis in patients with renal impairment and in the treatment of invasive fungal infection caused by Mucorales and other rare fungi, yeasts or dimorphic fungi. Patients with primary therapy from the VITAL study were also compared by case-control analysis with patients receiving amphotericin B in different pharmaceutical forms in the FungiScope™ registry database for emerging fungal infections.

Clinical trial 9766-CL-0104 (SECURE) - indication "invasive aspergillosis"
Clinical trial 9766-CL-0104 (SECURE) was a randomized, double-blind, active comparator (voriconazole) trial for non-inferiority in which 527 adult patients were randomized with a confirmed, probable or possible invasive fungal infection caused by Aspergillus species or other filamentous fungi. The main findings of the study are that CRESEMBA has comparable efficacy to voriconazole in the treatment of invasive aspergillosis. CRESEMBA has comparable survival to voriconazole in patients with invasive aspergillosis.

SECURE study showed that CRESEMBA and voriconazole had similar mortality rates in patients with invasive aspergillosis. The results of the SECURE study also showed that CRESEMBA and voriconazole had similar success rates in the treatment of invasive aspergillosis.

Clinical trial 9766-CL-0103 (VITAL) - indication "mucormycosis"
The main findings of the study are that CRESEMBA is effective as first-line therapy or rescue therapy in the treatment of mucormycosis. CRESEMBA demonstrated comparable survival to that of amphotericin B in patients with mucormycosis.
The results observed in patients with disease refractory to previous treatment with amphotericin B, or in those with intolerance to previous treatment with amphotericin B, emphasizes the benefit of CRESEMBA in patients for whom amphotericin B is inappropriate.
Data from both studies indicate that CRESEMBA is effective in patients with renal impairment.

FungiScope™ case-control analysis

The FungiScope study is a case-control comparison analysis, evaluating the clinical efficacy of CRESEMBA in the treatment of mucormycosis, using data from the FungiScope registry database for emerging fungal infections.

The results show that CRESEMBA has comparable efficacy to amphotericin B in the primary treatment of mucormycosis.

Safety data

CRESEMBA has been associated with a lower incidence of TEAEs compared to voriconazole mainly in terms of hepatobiliary disorders, laboratory tests, eye disorders and mental disorders. Voriconazole has been associated with a lower incidence of TEAEs with respect to respiratory, thoracic and mediastinal disorders. Less serious TEAEs leading to prolonged hospital stay and a tendency to less serious TEAEs leading to re-hospitalization were observed in CRESEMBA-treated patients compared to voriconazole.

Data on comparators

The main therapeutic alternatives of the new health technology in the treatment of invasive aspergillosis and mucormycosis are voriconazole and amphotericin B. Voriconazole is a well-established comparator and is the preferred antifungal agent for the treatment of invasive aspergillosis. Amphotericin B is not available as a therapy for invasive fungal diseases in Bulgaria. There is an unmet need for alternative treatments with activity against both Aspergillus and Mucorales.

Pharmacoeconomic indicators

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

Seven assessments of the Isavuconazole health technology, performed by governmental institutions for the purposes of the national health systems of France, Sweden, Scotland, are presented, all of them are positive and recommend the reimbursement of the new technology.

Applied analysis

The method used for comparative assessment of the health technology Isavuconazole is cost-utility analysis (CUA). Solution tree modeling was used. The measures used are QALY and LYG. Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were performed.

Voriconazole has been used as comparator in invasive aspergillosis and mucormycosis. Although not indicated for mucormycosis, voriconazole is expected to be used as empirical treatment in the presence of a clinical picture until the causative pathogen is identified. The perspective of the analysis is that of the medical institution for hospital care. A basic principle in the model is the hypothesis that all patients with presumed invasive aspergillosis must have started treatment before the final diagnosis is made, with the percentage of mucormycosis patients in that case being 5.75%. The model is based on a decision tree, in which transition from initial symptoms to the end of the therapy is pre-set. The results are extrapolated to a lifetime horizon.

The results for invasive aspergillosis show an additional expenditure on introducing the technology in a 30-day course of treatment and in a 45-day course of treatment while maintaining the level of life years and QALY.

The results for the indication mucormycosis in a 30-day course and a 45-day course of treatment show an additional expenditure on introducing the technology, with positive LYG and QALY.

The health technology is highly cost effective for both indications.

Probabilistic analyses (1000 Monte Carlo simulations) for the indication invasive aspergillosis, as well as for the indication mucormycosis, confirm the results of the main analysis.

Costs for the assessed health technology

Only medication-related costs (Isavuconazole and Voriconazole) are included in the presented model.

Budget impact analysis

The budget impact analysis perspective is of the public paying institution - the budget of the healthcare facilities, the time horizon is 5 years. The target population is adult patients being treated with the health technology for invasive aspergillosis, as well as mucormycosis in case amphotericin B is inappropriate. 78 patients with invasive aspergillosis are expected in the first year and by the end of the 5-year period their number will amount to 93. For mucormycosis, 7 patients are expected in the first year and a total of 10 by the end of the period. Reimbursement of the new technology will lead to additional costs for both indications.

Conclusion

Invasive aspergillosis and mucormycosis are rare diseases with increasing incidence as the number and life expectancy of immunocompromised and critically ill patient populations are increasing.

Invasive fungal infections usually affect immunocompromised or critically ill people, with both infections being potentially fatal and in severe cases mortality reaches 90%. Invasive aspergillosis and mucormycosis are also associated with prolonged hospital stay and require significant health care expenditure due to long-term treatment and management of treatment-related adverse events.

Advantages of isavuconazole health technology are the broad spectrum of action, good safety profile, availability of intravenous and oral dosage forms, low risk of drug interactions, no therapeutic drug monitoring required, no restrictions in the presence of renal impairment. The health technology is highly cost effective for both indications. The reimbursement of the new technology will lead to additional costs for both indications.