Voriconazole

Section: 6. Anti-infective medicines > 6.3. Antifungal medicines

EMLc | ATC codes: J02AC03

Indication	Invasive aspergillosis ICD11 code: 1F20.0
INN	Voriconazole
Medicine type	Chemical agent
List type	Core
Additional notes	*for treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis
Formulations	**Parenteral > General injections > IV:** 200 mg in vial powder for injection **Oral > Liquid:** 40 mg per mL powder for oral liquid **Oral > Solid:** 50 mg tablet ; 200 mg tablet
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Voriconazole
DrugBank	Voriconazole

Expert Committee recommendation

The Expert Committee recommended the addition of voriconazole to the EML and EMLc for the treatment of acute invasive aspergillosis and chronic pulmonary aspergillosis. The Committee acknowledged that voriconazole is currently the recommended treatment of choice for acute invasive aspergillosis in available guidelines.

Background

Voriconazole has not previously been considered for addition to the EML and EMLc. The current EML and EMLc include fluconazole with a square box as the representative of the pharmacological class of azole antifungals. However, fluconazole has no activity against infections caused by filamentous fungi including chronic pulmonary aspergillosis and invasive aspergillosis.

Public health relevance

Chronic pulmonary aspergillosis (CPA) is estimated to affect more than 3 million people worldwide, of whom approximately 1.2 million have had tuberculosis (1). Following pulmonary tuberculosis, 25–33% of patients are left with residual cavitation in the lung and, of these, 10–35% develop CPA. Five-year survival without antifungal treatment is approximately 20% (2, 3). It is estimated that more than 200 000 people develop acute invasive aspergillosis annually (4). The disease is common in people with acute leukaemia, those who have haematopoietic stem cell transplantation (HSCT) and other transplant recipients (5). Less commonly, invasive aspergillosis occurs

in people receiving corticosteroids for many reasons including chronic obstructive pulmonary disease (>1.2% of admissions to hospital), lung cancer and autoimmune disorders (such as systemic lupus erythematosus) (6). Other significant risk factors include medical intensive care, liver failure and severe burns (7). However, as some of these conditions are more prevalent than haematological cancer and transplantations, the number of individuals with invasive aspergillosis may be higher than estimated. Mortality without antifungal treatment is 100%.

Benefits

The application summarized the outcomes of prospective studies of voriconazole in chronic and invasive pulmonary aspergillosis. Chronic pulmonary aspergillosis The efficacy and safety of voriconazole were evaluated in a prospective, open, multicentre trial of 41 minimally or non-immunocompromised patients with proven CPA (8). The primary end-point was global success at 6 months, defined as complete or partial (≥50% improvement) radiological response and mycological eradication. Global success at 6 months was reported in 13/41 (32%) patients (95% confidence interval (CI) 18.1–48.1 %): 10/19 (53%) with chronic necrotizing aspergillosis and 3/22 (14%) with chronic cavitary aspergillosis ($P = 0.01$). The respective success rates at the end of therapy were 58% and 32%. Acute invasive aspergillosis Voriconazole and amphotericin B were compared as primary therapy for invasive aspergillosis in 277 treated patients in a randomized, unblinded trial (9). Most patients had underlying allogeneic HSCT, acute leukaemia or other haematological diseases. At week 12, for the modified intention-to-treat population, a complete or partial response to therapy (“successful outcome”) was achieved in 52.8% of the patients in the voriconazole group compared with 31.6% of patients in the amphotericin B group (absolute difference 21.2%; 95% CI 10.4–32.9). Survival rates at 12 weeks for voriconazole and amphotericin B were 70.8% and 57.9%, respectively (hazard ratio (HR) 0.59; 95% CI 0.40–0.88). As the lower bound of the 95% CI was above zero, the authors concluded that voriconazole was non-inferior and superior to amphotericin B. A subsequent study followed the same population and reported the outcomes for patients who switched from voriconazole or amphotericin B to other licensed antifungal therapies (OLAT) (10). Of voriconazole-treated patients, 36% switched to OLAT, compared with 80% of amphotericin B treated patients. Switches were made because of intolerance or insufficient response in 24% and 70% of the voriconazole and amphotericin B groups, respectively. The application also summarized international guideline recommendations for voriconazole in adults and children. The Infectious Diseases Society of America (IDSA) recommends voriconazole for treatment of invasive aspergillosis in adults and children (strong recommendation, high-quality evidence) (11). ISDA and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) also recommend voriconazole for treatment of CPA in adults and children (strong recommendation, high-quality evidence) (11, 12).

Harms

Known adverse events associated with voriconazole include transient visual disturbances, potentially dose-limiting hepatotoxicity, skin rash, erythroderma, photosensitivity, cheilitis and perioral excoriations, nausea, vomiting, diarrhoea, visual or auditory hallucinations, and cardiovascular events including tachyarrhythmias and QT-interval prolongations on electrocardiography. There have also been rare cases of arrhythmia (including torsade de pointes and bradycardia), cardiac arrest and sudden death in patients taking voriconazole, probably related to excessive plasma concentrations; these cases usually involve patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia, and concomitant medication (e.g. quinolones) that may be contributory. Reversible central and peripheral neurological symptoms and hallucinations may be observed in association with higher drug concentrations but with significant variability; these may be confused with other etiologies of CNS dysfunction. Voriconazole concentrations may be a predictor of CNS neurotoxicity, which is reversible. Peripheral neuropathy – usually sensory, sometimes motor or mixed – may occur after months of therapy and may be concentration-dependent. Prolonged use of voriconazole (e.g. for osteomyelitis or meningitis) for prophylaxis has revealed newer toxicities including periostitis with severe pain in bones or joints and elevated serum fluoride levels. The risk for squamous cell carcinoma or melanoma in sun-exposed areas is increased by concomitant immunosuppression and chronic voriconazole use, especially in fair-skinned individuals (11). Voriconazole is metabolized via cytochrome P450 3A4, 2C9 and 2C19 pathways and is thus associated with a number of drug–drug interactions including (but not limited to) selected antiretroviral

medicines, rifampicin, antiepileptic medicines, ciclosporin, statins, opioids, warfarin and prednisolone. Care is required in its prescribing and therapeutic drug monitoring (TDM) is often recommended.

Additional evidence

N/A

Cost / cost effectiveness

The application stated that generic voriconazole has recently been introduced and that prices are consequently changing in many countries although they remain generally high. Daily treatment costs for oral voriconazole are estimated to vary from US$ 2.08 in Pakistan to US$ 94.00 in Thailand.

WHO guidelines

N/A

Availability

Widely available.

Other considerations

The Expert Committee considered that TDM, where available, may help inform management considerations, especially with regard to preventing underdosing. In severe infections, however, the Committee felt that the clinical benefits of unmonitored therapy would often outweigh the benefits of additional TDM, and thus considered that core listing on the EML (as opposed to complementary listing) was appropriate.

Implementation considerations

The Committee recommended that, with the addition of new azoles (itraconazole and voriconazole) to the Model Lists, the square box should be removed from the current listing for fluconazole.

1. Denning DW, Park S, Lass-Florl C, Fraczek MG, Kirwan M, Gore R et al. High-frequency triazole resistance found In nonculturable Aspergillus fumigatus from lungs of patients with chronic fungal disease. Clin Infect Dis. 2011;52(9):1123–9.
2. Ohba H, Miwa S, Shirai M, Kanai M, Eifuku T, Suda T et al. Clinical characteristics and prognosis of chronic pulmonary aspergillosis. Respir Med. 2012;106(5):724–9.
3. Nam HS, Jeon K, Um SW, Suh GY, Chung MP, Kim H et al. Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: a review of 43 cases. Int J Infect Dis. 2010;14(6):e479–82.
4. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med. 2012;4(165):165rv13.
5. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis. 2008;47(8):1041–50.
6. Guinea J, Torres-Narbona M, Gijon P, Munoz P, Pozo F, Pelaez T et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Clin Microbiol Infect. 2010;16(7):870–7.
7. Denning DW. Invasive aspergillosis. Clin Infect Dis. 1998;26(4):781–803.
8. Cadranel J, Philippe B, Hennequin C, Bergeron A, Bergot E, Bourdin A et al. Voriconazole for chronic pulmonary aspergillosis: a prospective multicenter trial. Eur J Clin Microbiol Infect Dis. 2012;31(11):3231–9.
9. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408–15.
10. Patterson TF, Boucher HW, Herbrecht R, Denning DW, Lortholary O, Ribaud P et al. Strategy of following voriconazole versus amphotericin B therapy with other licensed antifungal therapy for primary treatment of invasive aspergillosis: impact of other therapies on outcome. Clin Infect Dis. 2005;41(10):1448–52.
11. Patterson TF, Thompson GR, 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–60.
12. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J. 2016;47(1):45–68.