Gatifloxacin

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.5. Antituberculosis medicines

EMLc | ATC codes: J01MA16

Indication	Multi-drug resistant Mycobacterium tuberculosis ICD11 code: MG52.00
INN	Gatifloxacin
Medicine type	Chemical agent
Antibiotic groups	WATCH
List type	Core
Formulations	**Oral > Solid:** 200 mg ; 400 mg
EML status history	Application rejected 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	Gatifloxacin
DrugBank	Gatifloxacin

Expert Committee recommendation

The Expert Committee did not recommend the addition of gatifloxacin to the Complementary List of the EML and EMLc as a reserve second-line drug for the treatment of multidrug-resistant tuberculosis. The Committee noted that gatifloxacin, in short therapy regimens, did not show superiority in benefit–harm ratio to alternative fluoroquinolones currently listed on the EML and EMLc (levofloxacin and moxifloxacin).

Background

The application requested addition of gatifloxacin to the Complementary List of the EML and EMLc as a reserve second-line drug for the treatment of multidrug-resistant tuberculosis. The 2016 update of the WHO treatment guidelines for drug-resistant tuberculosis positions gatifloxacin as an alternative to other fluoroquinolones (specifically levofloxacin and moxifloxacin) in Group A. Gatifloxacin may be included as part of both shorter regimens for multidrug-resistant tuberculosis (MDR-TB) and longer regimens for MDR-TB and extensively drug-resistant TB (XDR-TB) (1, 2). Currently, the EML and EMLc include the fluoroquinolone, levofloxacin, for this indication, with an asterisk and a note specifying that ofloxacin and moxifloxacin may be alternatives based on availability and programme considerations. Ofloxacin was proposed for removal from the Model Lists in a separate application to this meeting on the basis that it is no longer recommended in the updated WHO treatment guidelines.

Public health relevance

It is estimated that 580 000 patients develop rifampicin-resistant or MDR-TB globally each year and would need second-line TB treatment regimens to increase the likelihood of a successful treatment outcome (3). In many low-resource settings, there are often too few medicines available to compose a suitable regimen for drug-resistant TB, and stock-outs of second-line drugs occur regularly (3). Gatifloxacin was a mainstay fluoroquinolone of the shorter MDR-TB regimen until a global shortage of quality-assured formulations of the medicine occurred following safety concerns (4). Clinicians had to replace gatifloxacin with other later-generation fluoroquinolones in both shorter and longer MDR-TB regimens. Given that gatifloxacin is cheaper to manufacture than other later-generation fluoroquinolones, the inclusion of gatifloxacin on the EML should encourage pharmaceutical manufacturers to produce this medicine.

Benefits

A review of the available evidence for the effectiveness of, and adverse reactions to, gatifloxacin was undertaken for the 2016 revision of the WHO treatment guidelines for MDR-TB (1). The GRADE table of the evidence was presented in Annex 2 of the application and the findings are summarized below. There are few data on the effectiveness of gatifloxacin in either conventional 24-month MDR-TB regimens or shorter MDR-TB regimens. Four observational studies were presented (5–8); all were assessed as being of very low quality. The studies reported treatment success versus failure, relapse or death in gatifloxacin-treated patients versus no gatifloxacin in rifampicin-resistant or MDR-TB. (In the no gatifloxacin group, the other fluoroquinolone used was ofloxacin, levofloxacin or moxifloxacin.) Treatment success was reported as 84% for regimens with gatifloxacin compared with 64.9% for regimens without (relative benefit not estimable; absolute effect 191 more successes per 1000; 95% confidence interval (CI) 116–265). Deaths among patients treated with gatifloxacin (2.7%) were lower than those in patients who received another fluoroquinolone or no fluoroquinolone (8.6%), suggesting improved outcome rather than any risk of excess mortality in patients exposed to gatifloxacin (relative benefit not estimable; absolute effect 59 fewer per 1000; 95% CI 20–99).

Harms

Safety data were derived from five observational studies (5, 9–12). Serious adverse events (Grade 3 or 4 or treatment stopped because of adverse effects) were reported in 3.6% of gatifloxacin-treated patients compared with 8% of patients given treatments that did not include gatifloxacin (relative and absolute effects were not estimable). Adverse events are likely to be incompletely reported in some of the studies included in the review. Reports of blood glucose disorders in patients treated with gatifloxacin for conditions other than drug-resistant TB led the manufacturer to stop production of the drug in 2006 (4). Reports of severe dysglycaemia, hypoglycaemia and hyperglycaemia and diabetes led to some countries removing gatifloxacin from their national formularies. A global shortage in quality-assured formulations of this medicine ensued, with consequent negative impacts on MDR-TB treatment regimens that included gatifloxacin. More recent reports of treatment regimens for drug-susceptible TB that included gatifloxacin (400 mg once daily) have shown no significant risk of hyperglycaemia associated with exposure (13).

Cost / cost effectiveness

A restart of the manufacture of quality-assured formulations of the medicine could substantially lower the costs of TB treatment regimens by substituting for more expensive fluoroquinolone options.

WHO guidelines

The application suggested that gatifloxacin could be an important component of both the intensive and the continuation phase of the shorter MDR-TB regimen recommended by WHO (1, 2). The regimen is usually composed of pyrazinamide, ethambutol, isoniazid, gatifloxacin (or moxifloxacin), kanamycin (or amikacin), protionamide (or ethionamide) and clofazimine for 4 months (extended to 6 months in case of failure of sputum

conversion), followed by a continuation phase of pyrazinamide, ethambutol, gatifloxacin (or moxifloxacin), and clofazimine for 5 months. Since May 2016, WHO has recommended the shorter MDR-TB regimen in selected patients; gatifloxacin could thus have a central role in a regimen that is offered to patients as a standard of care unless they have specific exclusion criteria. Moreover, gatifloxacin could be the fluoroquinolone of choice for the longer regimens for both MDR-TB and XDR-TB, which are usually composed of pyrazinamide plus at least four second-line anti-TB drugs considered to be effective, including a latergeneration fluoroquinolone, a second-line injectable, and two or more of: ethionamide (or protionamide), cycloserine, linezolid or clofazimine. In August 2012, WHO advised countries to introduce shorter MDR-TB regimen only under operational research conditions, subject to the approval of a national ethics review and with an appropriate assessment of the effectiveness and safety of treatment. In May 2016, following a review of evidence that accrued from such studies, WHO conditionally recommended the use of a shorter MDR-TB regimen under normal programmatic conditions in patients who fulfil the eligibility criteria for this treatment.

Availability

Generic manufacturers in India and Bangladesh are known to produce gatifloxacin tablets for export; however, these manufacturers are not yet quality-assured. In October 2016, WHO added gatifloxacin to the list of anti-TB medicines for which manufacturers will be invited to submit an Expression of Interest for Active Pharmaceutical Ingredient (API) or Finished Pharmaceutical Products to the WHO Prequalification Team. It is expected that a number of manufacturers will respond to this invitation.

Other considerations

Listing of gatifloxacin was proposed as an alternative fluoroquinolone to levofloxacin and moxifloxacin which are already included as reserve second-line medicines on the EML and EMLc. With the recommended deletion of ofloxacin, separate EML listings could be considered for fluoroquinolones recommended as Group A alternatives in the updated WHO guidelines.

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