June 10th, 2019

Dear Tereza,

The Union, the Institute of Tropical Medicine and the Damien Foundation are writing to express their interest in including gatifloxacin in the WHO Essential Medicines List (EML) and to maintain it in the WHO Expression of Interest List (EOI).

The drug is still included in the current WHO DR-TB guidelines and in the companion handbook to the WHO guidelines. However, at the present time, there are no quality-assured formulations of gatifloxacin available.

In 2006, Bristol Myers Squibb announced that it was withdrawing gatifloxacin from the market[1] because an observational study[2] reported that gatifloxacin was associated with dysglycaemia in the treatment of pneumonia among the elderly (mean age 78 years). Consequently, moxifloxacin replaced gatifloxacin in the treatment of MDR-TB in observational studies[3] and in a clinical trial (STREAM)[4].

The short treatment regimen for multidrug resistant tuberculosis (MDR-TB) piloted in Bangladesh[5] and used, with modifications, in Niger[6] and Cameroon[7], was based on gatifloxacin and achieved treatment success in a very large proportion of patients. Gatifloxacin is likely to have played a critical role in this success.

A recent analysis comparing short treatment regimens based on gatifloxacin, moxifloxacin and levofloxacin in the same countries revealed that gatifloxacin -based regimens had significantly superior bacteriological effectiveness compared to moxifloxacin -based or levofloxacin -based regimens halving the risk for failure and relapse and not allowing amplification of resistance to fluoroquinolones in those patients treated with gatifloxacin [8].

Pharmacodynamic hollow-fiber model studies also showed that gatifloxacin has a higher bactericidal capacity than levofloxacin or moxifloxacin[9]. Also in vitro susceptibility testing results consistently indicate lower MICs for gatifloxacin than moxifloxacin[10].

In terms of safety we may point out that the use of gatifloxacin was associated with dysglycaemia in the elderly[1]. The findings of that study may have less significance for the majority of MDR-TB patients living in high-incidence countries who are much younger, have a lower risk of dysglycaemia and suffer from a highly fatal condition. Gatifloxacin associated dysglycemia was manageable and reversible among those MDR-TB patients treated with high dose in Bangladesh[5] and Niger[6] in whom it occurred.

Gatifloxacin was also used in a large clinical trial (OFLOTUB)[11] comparing a 4-month normal dose gatifloxacin-based regimen with the standard 6-month regimen for the treatment of rifampicin-susceptible pulmonary TB. The OFLOTUB trial reported that the vast majority of the patients had

normal blood glucose levels throughout the course of treatment, and that there was no significant difference in the risk of hyperglycaemia between the 4-month gatifloxacin-based regimen and the standard 6-month regimen.

The OFLOTUB study reported that a 4-month gatifloxacin-based regimen did not have a sizable risk of QT prolongation and this finding was confirmed by a further study[12].

It might be easier to use gatifloxacin than moxifloxacin in resource-limited settings where the burden of MDR-TB is high but the capacity for monitoring and management of QT prolongation is limited, and monitoring plasma glucose is required with either medication anyway.

Given that a superior efficacy and excellent safety profile of gatifloxacin has been demonstrated in observational MDR-TB treatment studies, it will be critical to make gatifloxacin available again for MDR-TB treatment. Bringing back gatifloxacin, the strongest anti-tuberculosis FQ, will moreover likely preserve this critical class of core drugs longer, given gatifloxacin's superior ability to suppress resistance to FQ.

Several National Tuberculosis Programs in West and Central Africa, Latin America and Asia have manifested their interest in having gatifloxacin back in informal discussions with technical partners, such as The Union and Damien Foundation.

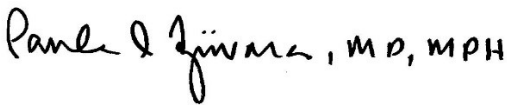
In addition, SVIZERA, a generic manufacturer, showed interest in producing gatifloxacin and to submit the product to the pre-qualification department of WHO.

In 2017, the Global TB Programme and the Global Drug Facility had submitted an application to include gatifloxacin in the WHO Essential Medicines List without success[13]. The main concerns for non-inclusion were: gatifloxacin safety, availability of equivalent drugs and lack of prequalified gatifloxacin on the market[14]. We think that recent evidence, as summarized in this letter, provides the elements needed to justify making gatifloxacin availability an urgent priority, to provide high quality care to people affected by drug-resistant tuberculosis.

We are confident that this letter may retain your attention.

Sincerely,

Paula Fujiwara, Scientific Director, The Union



Bouke de Jong, Head of Mycobacteriology Unit, Institute of Tropical Medicine of Antwerp

Patrick Suykerbuyk, Projects Director of Damien Foundation, Brussels

1 Chiang CY, Van Deun A, Rieder HL. Gatifloxacin for short, effective treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2016;20:1143-7.

2 Park-Wyllie L Y, Juurlink D N, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med 2006; 354: 1352–1361.

3 Trébucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis* 2018; **22**: 17-25.

4 Nunn AJ, Philipps PPJ, Meredith SK, Chiang CY et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Eng J Med 2019. DOI: 10.1056/NEJMoa1811867.

5 Aung K J M, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 2014; 18:1180-1187.

6 Piubello A, Hassane Harouna S, Souleymane M B, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis 2014;18:1188-1194.

7 Kuaban C, Noeske J, Rieder H L, Aït-Khaled N, Abena Foe J L, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis 2015;19:517-524.

8 Van Deun A , Decroo T, Kuaban C, Noeske J , Piubello A, Maug A , Rieder H Gatifloxacin is superior to levofloxacin and moxifloxacin in shorter treatment regimens for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. In Press

9 Deshpande D, Pasipanodya J G, Mpagama S G, et al. Levofloxacin pharmacokinetics/pharmacodynamics, dosing, susceptibility breakpoints, and artificial intelligence in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2018;67(Suppl 3):S293-S302.

10. L. Rigouts, N. Coeck, M. Gumusboga, et al. Specific gyrA gene mutations predict poor treatment outcome in MDR-TB. J Antimicrob Chemother2016;71: 314–323.

11 Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med 2014; 371: 1588–1598.

12 Olliaro PL, Merle C, Mthiyane T, et al. Effect on the QT interval of a gatifloxacin-containing regimen versus standard treatment of pulmonary tuberculosis. Antimicrob Agents Chemother 2017; 61: e01834–e01816.

13 World Health Organization. Gatifloxacin – EML and EMLc. 21st Expert Committee on the Selection and Use of Essential Medicines. 2017. https://www.who.int/selection_medicines/committees/expert/21/applications/gatifloxacin_ad/en/ (accessed 05/06/2019).

14 Chiang C-Y, Trébucq A, Piubello A, Rieder HL, Van Deun A. Should gatifloxacin be included in the model list of essential medicines? Eur Respir J 2018;51:1702329