Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies

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ABSTRACT

Objectives: Given the spread of multidrug-resistant tuberculosis (MDR-TB), new therapies are urgently needed, including the repurposing of existing drugs. We aimed to assess key considerations for the clinical and programmatic use of clofazimine (Cfz), a riminophenazine with antimycobacterial activity currently used to treat leprosy.

Design: Fixed and random effects meta-analysis of cohort studies and systematic review.

Setting: Electronic and manual searches were combined.

Inclusion criteria: Observational studies on treatment of multidrug-resistant and extremely drug-resistant tuberculosis with Cfz or a Cfz-containing regimen, and published guidance and documents relating to cost and availability were eligible.

Results: 5 observational studies enrolled 861 patients, of which 602 received Cfz. The pooled proportion of adverse drug reactions requiring discontinuation of Cfz treatment was 0.1% (95% CI (0.0 to 0.6%)), and the median frequency of all adverse events was 5.1%. Cfz showed in vitro efficacy against Mycobacterium tuberculosis, and Cfz-containing regimens may have had a useful role in the treatment of patients with drug-resistant strains and who had limited alternative treatment options. However, Cfz uptake remains insufficient to meet global needs; there is only one internationally quality-assured manufacturer, which produces a limited quantity of the drug prioritised for treatment of leprosy, the only indication for which the drug is registered.

Conclusions: While the data were limited, Cfz was associated with a risk for adverse drug reactions comparable to that of first-line TB treatment, which could be reasonably managed under programmatic conditions. However, low market availability and high cost are important barriers to access to Cfz for patients with MDR-TB.

Strongest and limitations of this study

- We have reviewed a comprehensive body of peer-reviewed literature and policy guidance relating to the safety, use, cost and availability of clofazimine (Cfz) in clinical practice.
- This study shows that the burden of safety issues associated with Cfz use appears to be manageable by national TB programmes. The widespread use of Cfz is limited by low availability and relatively high cost.
- Few studies were included in the meta-analysis since only a smaller number of studies have been conducted with Cfz. Further research is needed.

INTRODUCTION

Drug-resistant strains of tuberculosis (TB) pose a serious obstacle to progress in global TB control.1 In 2011, there were an estimated half a million new cases of multidrug-resistant tuberculosis (MDR-TB; resistance to, at least, rifampicin and isoniazid) worldwide.2 Extensively drug-resistant (XDR-TB) cases, a form of MDR-TB with additional resistance to any fluoroquinolone and an injectable second-line drug, have been identified in 84 countries.2 3 A recent survey from Belarus reported that nearly one in two of all enrolled TB patients had MDR-TB, the highest proportion of MDR ever recorded.4

The recent approval of bedaquiline by the US Food and Drug Administration (FDA), the first drug developed for TB treatment in nearly a half-century and the filing of delamanid with the European Medicines Agency (EMA), are promising developments for the treatment of TB.5 6 However, the management
of drug-resistant strains of *Mycobacterium tuberculosis* (*Mtb*) necessitates new effective treatment regimens, composed of at least four effective drugs. In light of the limited treatment options available for patients affected by severe patterns of drug-resistant TB, some have recommended repurposing older drugs, though there are significant concerns with the adverse drug reaction (ADR) profiles and long-term safety of several agents and conflicting evidence of their efficacy.\(^7\) \(^8\) One potential candidate to be repurposed is clofazimine (Cfz), a raminophenazine derived from a R-substitution at the imino group.\(^9\) Cfz has apparent antimycobacterial and anti-inflammatory activity, though its precise mechanism of action is still unclear.\(^10\) The drug is known to be highly lipophilic, accumulating in fatty tissues with uptake by human mononuclear phagocytes, the same cells infected by *Mtb*.\(^11\) Cfz also appears to exhibit a property uniquely relevant for tuberculosis treatment: despite its long half-life and accumulation in tissue, the risk of developing resistance is relatively low.\(^12\)

Although Cfz was originally developed for the treatment of tuberculosis, its current medical indication is for the treatment of multibacillary and paucibacillary leprosy, including severe erythema nodosum leprosum reactions in patients with leprosy.\(^13\) While in vitro studies suggested high anti-TB activity, poor in vivo results in the mid-1950s led to the abandonment of clinical development as an antituberculosis agent.\(^14\) \(^15\) In the past decade, there has been renewed and growing interest in the use of Cfz as an anti-TB agent. An MDR-TB treatment observational study conducted in Bangladesh showed favourable outcomes, even with a significantly shorter treatment duration than the current WHO recommended regimen.\(^16\) A multicountry randomised control trial to evaluate a standardised 9-month regimen containing Cfz for the treatment of MDR-TB is currently under way, and observational cohort studies are being conducted in some West African countries.\(^17\) Given the growing evidence supporting the use of Cfz in the treatment of patients with MDR-TB and XDR-TB treatment, we sought to assess the key considerations, including safety, effectiveness, management and cost, in relation to the programmatic and clinical use of Cfz by national TB programmes (NTP).

### METHODS

#### Study design and data sources

Our meta-analysis and systematic review were conducted using a prospective protocol according to MOOSE (Meta-analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines for reporting systematic reviews of observational study results (see online supplementary material).\(^18\) \(^19\) Studies published between 1950 and May 2013 were identified from an electronic search of the PubMed, MEDLINE, Embase and Cochrane Library databases. The key words and Medical Subject Heading terms included: ‘clofazimine’, ‘B663’, lamprène’, ‘tuberculosis’, ‘side effects’, ‘adverse events’, ‘adverse drug reactions’, ‘sequela’, ‘toxicity’, ‘tolerability’, ‘outcomes’, ‘treatment’, ‘effectiveness’, ‘efficacy’, ‘cure’, ‘success’, ‘guideline’, ‘treatment’ or ‘safety’. We contacted researchers and manually collected references of all retrieved articles, selected review articles, clinical trial registration notices and conference abstracts, as needed. These additional studies were merged with our search results, following exclusion of non-relevant or duplicate citations. Policy guidelines and drug label information were retrieved from manual searches of WHO publications, as well as those of two stringent regulatory agencies, the US FDA and EMA.

#### Outcome variables and data extraction

The aim of our study was to perform a meta-analysis of the safety of Cfz from published studies and a systematic analysis of the effectiveness, management and cost of Cfz from the peer-reviewed literature as well as published guidance.

For our safety analysis, our primary outcomes of interest were adverse events and ADR. We defined an ADR as an appreciably harmful or unpleasant reaction caused by a drug that is serious enough to warrant the discontinuation or revision of treatment.\(^20\) In contrast, an adverse event included any undesirable reactions reported by patients or clinicians, including mild reactions that had no bearing on treatment. Since the use of the term ‘adverse event’ and ‘serious adverse events’ was inconsistent in the reviewed studies and the criteria for judging an adverse event as serious were not consistently reported, we used ADR as a measure of Cfz’s safety profile. Using methods described previously,\(^21\) we used challenge–dechallenge to evaluate ADR data: a reaction was attributed solely to Cfz if discontinuation of the drug or reducing the dose led to reported disappearance of the toxicity.\(^22\) Prevalence (%) was measured as a proportion relative to the total number of drug-receiving patients.

Data on study characteristics, methodological quality and results were independently extracted from each selected article using a pre-defined extraction form by two authors (TJH and SD). This form captured: author, study location, study design, observation period, number of patients treated, patient age, sex and reported race or ethnicity, drug resistance profile, prior treatment with second-line drugs, HIV status, treatment regimen with Cfz, dosage, duration of treatment, treatment outcomes, reported ADRs by agent and rate of discontinuation. An additional author (DFW) independently assessed the validity of included citations and extracted data.

#### Statistical analysis

We calculated point estimates and 95% CIs for the frequency of adverse events and ADRs. We assessed the heterogeneity between studies using the *I*\(^2\) statistic, which reports the proportion of total variance across studies.
that is due to between-study heterogeneity rather than by randomness (see online supplementary appendix). Based on this assessment, we used the DerSimonian and Laird\textsuperscript{23} random effects model for pooling estimates and calculating 95\% CI of adverse event frequencies, and the inverse-variance weighted fixed effects model for ADRs.\textsuperscript{24} Since some studies reported no ADRs, we also performed a post hoc sensitivity analysis to calculate 95\% CI of adverse events and ADRs using the Wilson score method and found that the intervals did not differ significantly. We defined statistical significance at the p<0.05 level. Forest plots illustrate the distributions of pooling adverse event data by various stratification criteria. Statistical analyses were performed using Stata (V.12.0, Stata Corp).

**RESULTS**

**Safety**

From 1248 citations identified by our search strategy, 147 were selected for full-text review (figure 1). A total of five studies were subsequently included in the review for safety.

The characteristics of the five selected studies with safety data are summarised in table 1.\textsuperscript{16 25–28} Of the total 861 participants, 602 patients received Cfz as part of their TB treatment regimens. The study periods ranged from 1993 to 2012. The average study population was 144 patients (range 10–427). The daily dose range of Cfz administered in clinical settings was 50–100 mg, though one study reported a daily dose of 300 mg.\textsuperscript{25} Drug resistance patterns, duration and extent of prior TB treatment, HIV status and types of ADRs were variably reported.

The two most reported adverse event categories were dermal (skin discolouration) and gastrointestinal. As shown in figure 2, the overall pooled proportion of all adverse events attributed to Cfz was 21.9\% (95\% CI (0.0\% to 46.1\%)), though the median frequency of adverse events was 5-1\%. The pooled proportion was disproportionately affected by an outlier reporting adverse events in 88-6\% (95\% CI (75.4\% to 96.2\%)) of cases.\textsuperscript{27} Not all reported adverse events required discontinuation of Cfz treatment. From our fixed effects model, the pooled proportion of ADRs requiring discontinuation or withdrawal of Cfz was 0.1\% (95\% CI (0.0\% to 0.6\%)), with the frequency of ADRs ranging from 0\% (95\% CI (0.0\% to 1.1\%)) to 11-8\% (95\% CI (2.0\% to 35.6\%).

**Efficacy**

Early in vitro studies of Cfz reported positive bactericidal efficacy of Cfz.\textsuperscript{29–33} More recent in vitro and in vivo evidence suggests that Cfz also has sustained sterilising activity against latent or persistent bacterial populations of \textit{M tuberculosis}.\textsuperscript{34} Currently, novel analogues of Cfz are under investigation with comparable efficacy but shorter half-lives, potentially reducing tissue accumulation and resultant skin pigmentation.\textsuperscript{35}

In vivo studies in mice and hamsters reported significant activity of Cfz, though accumulation in animal tissues may lead to overestimation of drug activity when subsequently plated on solid media.\textsuperscript{12 30 36–38} Earlier studies had shown that Cfz had little or no activity in guinea pig and monkey models.\textsuperscript{15 39} It was later thought that these poor in vivo results and monotherapy-induced resistance in guinea pigs and monkeys may have been a result of low absorption of the drug by the oral route.\textsuperscript{29}

Recently, Cfz combined with bedaquiline and pyrazinamide has been shown to be superior to the current first-line regimen in reducing colony-forming unit counts at 1 month in mice.\textsuperscript{40} Cfz combined with the standard second-line regimen also significantly improved culture conversion and relapse prevention, compared with a regimen without Cfz, in mice.\textsuperscript{41} In addition, the sterilising activity of bedaquiline and pyrazinamide was significantly improved with the addition of Cfz.\textsuperscript{42}

**Effectiveness**

In a recent systematic review and meta-analysis of 3489 patients treated for drug-resistant TB across 10 countries, Dey et al\textsuperscript{43} reported a pooled treatment success rate of 62.0\% (95\% CI (52.8\% to 71.1\%)) from treatment regimens containing Cfz, with success defined as cure and/or treatment completion. The success rate in HIV/MDR-TB coinfected patients was not significantly different from the overall success rate. In another systematic review of patients treated with Cfz-containing regimens, Gupta et al\textsuperscript{4} found no significant differences in the proportions with favourable outcomes between patients with MDR-TB (65\%; 95\% CI (52\% to 79\%)) and patients with XDR-TB (66\%; 95\% CI (42\% to 89\%)).\textsuperscript{44} There was substantial variation in estimates of mortality during treatment with Cfz-containing regimens, ranging from.
<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Country</th>
<th>Study period</th>
<th>Study design</th>
<th>Study included participants</th>
<th>Treatment duration (months)</th>
<th>Regimen</th>
<th>N. given Cfz</th>
<th>Daily Cfz dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goble <em>et al</em> (1993)</td>
<td>USA</td>
<td>1973–1983</td>
<td>Retrospective</td>
<td>171 patients included Age: 46 (17–79) DS: 0; DR: 98</td>
<td>7</td>
<td>Individualised</td>
<td>17</td>
<td>300</td>
</tr>
<tr>
<td>Van Deun <em>et al</em> (2010)</td>
<td>Bangladesh</td>
<td>1997–2007</td>
<td>Prospective</td>
<td>427 patients included Age: 33.8 (mean) DS: 0; DR: 427</td>
<td>3–15</td>
<td>Cfz, Km, Ofx, E, H, Z, Pto</td>
<td>427</td>
<td>50–100</td>
</tr>
<tr>
<td>Xu <em>et al</em> (2012)</td>
<td>People’s Republic of China</td>
<td>2006–2011</td>
<td>Retrospective</td>
<td>144 patients included Age: 38.8±10.8 (Cfz); 47.4±11.8 (non-Cfz) DS: 0; DR: 427</td>
<td>2.2±1.7 (Cfz); 2.1±1.3 (non-Cfz)</td>
<td>Individualised</td>
<td>44</td>
<td>100</td>
</tr>
</tbody>
</table>

Cfz, clofazimine; E, ethambutol; DR, drug-resistant (to at least two agents in standard-line therapy); DS, drug-sensitive; Ga, gatifloxacin; H, isoniazid; Km, kanamycin; Ofx, Ofloxacin; Pto, prothionamide; S, streptomycin; TB, tuberculosis; Z, pyrazinamide.
1.0% (95% CI 0.1% to 2.6%) to 63.4% (95% CI 38.3% to 85.0%), though the risk of death attributed solely to Cfz, after adjusting for covariates, was not reported. Further cohort studies showing a favourable effect of Cfz-containing regimens have been reported in Benin,45 South Africa46 and Ukraine,47 though limited benefit from Cfz was found in studies in Brazil48 and Sri Lanka.49

Two clinical trials are currently ongoing involving the investigation of the efficacy and safety of treatment regimens containing Cfz (table 2). The Global Alliance for TB Drug Development is conducting a Phase 2 study to evaluate the early bactericidal activity of Cfz (dosed at 300 mg for the first 2 days and 100 mg thereafter) combined with bedaquiline and pyrazinamide, compared with first-line treatment.50 The Phase 3 STREAM trial,

**Figure 2** Forest plot of all reported adverse events associated with or ADRs attributed to clofazimine and clofazimine-containing regimens, pooled estimates using inverse-variance weighted fixed effects and random effects models are shown. The random effects model was used for adverse events estimates (I²=98.7%; p<0.001) and fixed effects for ADRs (I²=11.5%; p=0.34). ADRs, adverse drug reactions; FE, fixed effects; RE, random effects.
sponsored by the International Union Against Tuberculosis and Lung Disease, is comparing a modified MDR-TB treatment regimen, based on the shorter treatment regimens assessed in Bangladesh,\textsuperscript{16} with regimens based on the current WHO guidelines for MDR-TB treatment. The STREAM trial involves sites in Ethiopia, India, South Africa and Vietnam.\textsuperscript{17} Follow-up is expected for all patients in the study for 27–33 months, with final results anticipated after October 2016.

**Availability, cost and demand forecast**

Cfz was registered under the trade name Lamprene by Novartis in the USA in 1986.\textsuperscript{51} Quality-assured Cfz is available on very limited quantities for the treatment of patients with MDR-TB on a patient-named basis through the Global Drug Facility (GDF) mechanism of the Stop TB Partnership, which uses a distributor authorised by Novartis.\textsuperscript{52–54} Securing a steady supply of quality-assured Cfz that can meet the increasing demand for MDR-TB treatment, without jeopardising the needs of the global programme for leprosy elimination, is currently a major challenge in the response to MDR-TB.\textsuperscript{55}

The price of the 100 mg product through the GDF mechanism is US$120.86/100 capsules, or roughly US$1.21 per capsule. The cost of a daily dosage of Cfz varies between US$1.21 (when a 100 mg dosage is used) and US$3.63 (when 300 mg is used). Depending on the regimen and dosage, the cost of Cfz can be higher than the cost of a daily dosage of most injectables used in the treatment of intensive phase of MDR-TB treatment. By our calculations, the estimated annual cost of procuring a 24-month-regimen of Cfz will range between US$2–20 million, depending on the number of patients (low estimate: patients with XDR-TB only; high estimate: all patients with MDR-TB) treated.

**Global policy, guidelines and national practices**

From a search of the national, regional and international guidelines and regulations relating to the use of Cfz, two policy sources were retrieved from the WHO\textsuperscript{56–59} and the US FDA (table 3).\textsuperscript{60}

Cfz is currently indicated solely for leprosy by the WHO and the US FDA, and is included in the WHO Model Lists of Essential Medicines for adults and children.\textsuperscript{51, 62} For this use, the drug is provided free to endemic countries through an agreement with the sole manufacturer of quality-assured Cfz, Novartis, first signed in 1999 and renewed in 2010.\textsuperscript{63} The most recent donation, valued at US$26 million, will treat an estimated 1.1 million patients with leprosy over 5 years (2010–2015). In the USA, Cfz can only be obtained through the National Hansen’s Disease Programme under a single-patient treatment investigational new drug protocol administered by the US FDA.\textsuperscript{64}

WHO guidelines currently do not recommend the routine use of Cfz for the treatment of DR-TB, due to insufficient data supporting the drug’s efficacy and long-term safety.\textsuperscript{56, 57} A WHO consultation in early 2012 on diagnostic definition and treatment options for so-called ‘totally drug-resistant TB’ concluded, based on expert opinion, that Cfz (at a daily dose of 100 mg) and linezolid were likely to be the most effective in the group 5

**Table 3 Guidelines and labelling regulations for Cfz**

<table>
<thead>
<tr>
<th>Authority</th>
<th>Region</th>
<th>Indication</th>
<th>Adverse effects</th>
<th>Off-label use</th>
<th>Recommendation for Cfz in TB use</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO\textsuperscript{56, 57}</td>
<td>Global</td>
<td>MDR-TB and XDR-TB</td>
<td>Gastrointestinal intolerance</td>
<td>Named patient basis on ‘exceptional’ grounds</td>
<td>2011: ‘May be used but not included among drugs making up the standard regimen’ 2008: ‘Only if additional drugs are needed to bring the total to four’ ‘…In the treatment of multidrug resistant tuberculosis (MDR TB)…’ WHO has found no evidence of its effectiveness for these forms of treatment\textsuperscript{58} Not stated</td>
</tr>
<tr>
<td>WHO\textsuperscript{58, 59}</td>
<td>Global</td>
<td>Leprosy and severe ENL reactions in leprosy</td>
<td>Discolouration, ichthyosis</td>
<td>Named patient basis on ‘exceptional’ grounds</td>
<td></td>
</tr>
<tr>
<td>Food and Drug Administration\textsuperscript{60}</td>
<td>USA</td>
<td>Lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by ENL</td>
<td>Skin pigmentation, gastrointestinal, conjunctival and corneal pigmentation, discolouration of urine, faeces, sputum and sweat</td>
<td>Single-patient treatment investigational new drug protocol</td>
<td></td>
</tr>
</tbody>
</table>

ENL, erythema nodosum leprosum; MDR-TB, multidrug-resistant tuberculosis; XDR.
category of second-line anti-TB drugs for the treatment of XDR-TB.65

Seven articles were identified from the literature on the national policies, guidelines and practices on the use of Cfz to treat MDR-TB.66–72 There has been virtually no published evidence of the use of Cfz in the Russian Federation. The two articles retrieved from the Russian-language literature mention solely that Cfz is included in international guidelines as a third-line therapy but note that the drug is not currently registered in the country.66 67 Cfz was previously registered with the Russian Ministry of Health for the indication of leprosy in 1977 and reregistered in 1989. In 1995, Cfz’s registration was annulled for unknown reasons and was not identifiable through the State Registry of Medical Substances as of May 2013.73

In India, use of Cfz has been associated with varying degrees of success in a number of settings, including in TB cases with strains described as so-called ‘totally drug-resistant’.68 A survey of the clinical practices in the management of DR-TB cases by chest physicians in the Indian state of Maharashtra found that Cfz was a preferred drug, being included in the treatment regimens by 15 respondents of the 29 surveyed.69 A number of studies have reported the use of aggressive supervised therapies, including Cfz and other group 5 drugs such as linezolid and clarithromycin.70 71 In one such study with 14 patients with XDR-TB, only two cases achieved complete cure (defined to be at least five negative culture results for the final 12 months of treatment), compared with four deaths.72

**DISCUSSION**

While data were limited, this study has shown a low proportion of adverse events requiring discontinuation of treatment attributed to Cfz at doses ranging from 50 mg to 300 mg daily. Our pooled frequency of Cfz ADRs at 0.1% is comparable to the incidence of serious ADRs reported with first-line TB treatment.74

These findings are in line with those made in an unpublished report on spontaneous individual case safety reports (ICSRs) submitted between 1976 and 2012 to the WHO’s International Drug Monitoring Programme, which found that Cfz was associated with 288 ICSRs accounting for 674 ADRs (Wang S et al, unpublished data). The three most frequent systemic categories involved in the TB-specific ADRs were central and peripheral nervous system (23.2%), gastrointestinal (17.9%) and skin (16.1%).

Our review of preclinical studies of Cfz suggests that this drug has sterilising activity against Mtb. Observational cohort studies in Bangladesh, Benin, China, Niger, Peru and Sri Lanka, among other settings, show an association between treatment regimens containing Cfz and favourable outcomes, including shortened treatment duration and add support to its inclusion by WHO in the group 5 of drugs to be considered in the management of MDR-TB.57 A high variance in mortality rates of patients receiving Cfz-containing drug combinations is observed in some studies. While these data might be confounded by indication—as patients who receive Cfz-containing regimens tend to be those with broader-spectrum drug resistance patterns and more advanced disease—the increasing use of Cfz should be coupled with strengthening of active pharmacovigilance systems.22 Results from the Phase 3 STREAM and Phase 2 Global TB Alliance trials will help to elucidate further the long-term safety and effectiveness of Cfz in the treatment of MDR-TB.

Our analysis is limited by the small number of available studies and published materials on Cfz. As ADRs are often rare, the paucity of clinical investigations with Cfz in the treatment of TB means that our results should be interpreted with some caution. While we attempted to categorise ADRs based on resolution after withdrawal or recurrence with rechallenge, reporting varied across studies and different thresholds may have been applied to report adverse events and ADRs. In the Xu et al72 study, for instance, 39 of 44 (87%) patients were reported to have experienced adverse events after starting Cfz. This high level of adverse events could be attributed to the high frequency of reported skin discoloration (36 patients), a known reaction to Cfz treatment, but only two patients discontinued Cfz altogether. There were also insufficient data on the extent of prior treatment, drug susceptibility and HIV status—factors that could result in varying severity of disease. Another limitation was that we considered participants in our meta-analysis as those with at least one ADR while being treated with Cfz, rather than cumulatively counting multiple ADRs that may have been experienced. In addition, to review the global landscape of policies and regulatory actions relating to Cfz, we relied on databases, search engines and manual searches which are biased in favour of English-language publications. Many more national and local policies may exist that were not captured in this article.

The use of Cfz in the clinical settings where patients with MDR-TB are treated has been increasing over the past two decades. The progress countries are making towards universal access to diagnosis and treatment of MDR-TB75 is resulting in sustained and increasing demand for this product, at least until more new and effective drugs are available. The GDF’s projected forecast based on the ongoing global scale-up of MDR-TB management suggests that the current quality-assured supply line is insufficient to meet this demand. GDF and the Global Fund regularly publish joint invitations to manufacturers of first, second and third-line antituberculosis medicines to submit an Expression of Interest for TB drug products evaluation by the Expert Review Panel. However, to date, no successful review of Cfz has been reported through this mechanism. To improve access to the drug, generic manufacturers that can complement Novartis’ production capacity should be identified. The inclusion of more manufacturers in the market may also contribute to a reduction in the cost of the drug, further improving access.

Despite these limitations, this article underscores the potential value of Cfz’s inclusion in the treatment
regimens for MDR-TB and XDR-TB cases. However, even if the ongoing clinical trials and observational studies confirm the earlier findings reviewed here, much more will need to be carried out to make C Iz available and affordable.

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Data sharing statement The dataset is available from the corresponding author.

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Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies

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