WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB388 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg delamanid.

Excipients with potential clinical effect

Each tablet contains 100 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

[TB388 trade name] is a yellow, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have "DLM" debossed (Stamped into) and "50" debossed (Stamped into) on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB388 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Treatment with [TB388 trade name] should be initiated and monitored by a health care provider experienced in the management of multidrug-resistant *Mycobacterium tuberculosis*.

[TB388 trade name] must always be administered as part of an appropriate combination regimen for the treatment of drug-resistant tuberculosis (see section 5.1).

It is recommended that [TB388 trade name] is administered by directly observed therapy (DOT).

Posology

The recommended dose of [TB388 trade name] is given as per the table below for 6 months. In patients who require it, extension beyond 6 months may be considered.

Patient's weight	**Dose**		**Number of tablets of [TB388 trade name]**
3 to less than 5 kg		25 mg daily	0.5* tablet **once** daily
5 to less than 10 kg	*under 3 months old:*	25 mg daily	0.5* tablet **once** daily
	3 months and older:	25 mg twice daily	0.5* tablet **twice** daily

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

10 to less than 16 kg		25 mg twice daily	0.5* tablet **twice** daily
16 to less than 30 kg		50 mg in the morning, 25 mg in the evening	1 tablet in the **morning**, 0.5* tablet in the **evening**
30 to less than 46 kg	*under 15 years:*	50 mg twice daily	1 tablet **twice** daily
	15 years and older:	100 mg twice daily	2 tablets **twice** daily
46 kg or more		100 mg twice daily	2 tablets **twice** daily

* When half a tablet is to be given, the tablet should be crushed and dispersed in 10 mL of water. 5 mL of the mixture should then be taken.

Elderly patients (> 65 years of age)

No data are available in the elderly.

Renal impairment

No dose adjustment is considered necessary in patients with mild or moderate renal impairment. There are no data on the use of delamanid in patients with severe renal impairment and its use is not recommended (see section 5.2).

Hepatic impairment

No dose adjustment is considered necessary in patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment.

Method of administration and missed doses

For oral use.

[TB388 trade name] should be taken with food.

In patients unable to swallow the tablets, or when half a tablet is to be given, [TB388 trade name] can be crushed and dispersed in drinking water before administration of the dose. Each tablet should be dispersed in 10 mL water.

1) The required amount of drinking water should be taken in a small, clean cup and the required number of tablets should be added.
2) The cup should be gently swirled until tablets disperse and then the appropriate amount of the mixture taken immediately.
   - For a dose of half a tablet (25 mg), the tablet should be dispersed in 10 mL of water and 5 mL of the mixture should be measured out using a suitable measuring device before taking. The remainder of the mixture should be discarded.
   - Where all the tablets should be taken, the entire mixture should be swallowed.

In case a dose is missed, this dose should be taken as soon as possible. However, if it is close to the time for the next scheduled dose, then the missed dose may be skipped, and the patient should not take a double dose to make up for a forgotten tablet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Serum albumin < 2.8 g/dL (see section 4.4 regarding use in patients with serum albumin ≥2.8 g/dL)
- Taking medicinal products that are strong inducers of CYP3A4 (e.g. carbamazepine) – see also section 4.5.

4.4 Special warnings and precautions for use

There are no clinical data on the use of delamanid to treat:

- extrapulmonary tuberculosis (e.g. central nervous system, bone)
- infections due to mycobacterial species other than those of the *M. tuberculosis* complex
- latent infection with *M. tuberculosis*

There are no clinical data on the use of delamanid as part of combination regimens used to treat drug-susceptible *M. tuberculosis*.

Resistance to delamanid

Delamanid must only be used in an appropriate combination regimen for MDR-TB to prevent development of resistance to delamanid (see section 5.1).

QT prolongation

QT prolongation has been observed in patients treated with delamanid. This prolongation increases slowly over time in the first 6-10 weeks of treatment and remains stable thereafter. QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively (see Special Considerations below).

General recommendations

It is recommended that electrocardiograms (ECG) should be obtained before initiation of treatment and monthly during the full course of treatment with delamanid. If a QTcF >500 ms is observed either before the first dose of delamanid or during delamanid treatment, treatment with delamanid should either not be started or should be discontinued. If the QTc interval duration exceeds 450/470 ms for male/female patients during delamanid treatment, these patients should have more frequent ECG monitoring. It is also recommended that serum electrolytes, e.g. potassium, are obtained at baseline and corrected if abnormal.

Special considerations

Cardiac risk factors

Treatment with delamanid should not be initiated in patients with the following risk factors unless the possible benefit of delamanid is considered to outweigh the potential risks. Such patients should receive more frequent monitoring of ECG throughout the full delamanid treatment period.

- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval or QTc > 500 ms.
- History of symptomatic cardiac arrhythmias or the presence of clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Taking medicinal products that are known to prolong the QTc interval (see section 4.5).

The complete metabolic profile of delamanid in man has not yet been fully elucidated (see sections 4.5 and 5.2). Therefore, the potential for drug-drug interactions of clinical significance to occur with delamanid and the possible consequences, including the total effect on the QTc interval, cannot be predicted with confidence.

Hypoalbuminaemia

In a clinical study, the presence of hypoalbuminaemia was associated with an increased risk of prolongation of the QTc interval in delamanid-treated patients. Delamanid is contraindicated in patients with albumin <2.8 g/dL (see section 4.3). Patients who start delamanid with serum albumin <3.4 g/dL or experience a fall in serum albumin into this range during treatment should receive more frequent monitoring of ECGs throughout the full delamanid treatment period.

Co-administration with strong inhibitors of CYP3A4

Co-administration of delamanid with a strong inhibitor of CYP3A4 (lopinavir/ritonavir) was associated with a 30% higher exposure to the metabolite DM-6705, which has been associated with QTc prolongation.

Therefore, if co-administration of delamanid with any strong inhibitor of CYP3A4 is considered necessary it is recommended that there is very frequent monitoring of ECGs, throughout the full delamanid treatment period.

Use with quinolones and bedaquiline in MDR-TB regimens

There are no added safety concerns for concurrent use of bedaquiline and delamanid and therefore both medicines may be used concurrently in patients who have limited other treatment options available to them, provided that sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place.

QTcF prolongations above 60 ms were associated with concomitant fluoroquinolone use with delamanid. Therefore, if co- administration is considered to be unavoidable in order to construct an adequate treatment regimen for MDR-TB it is recommended that there is more frequent monitoring of ECGs throughout the full delamanid treatment period. Levofloxacin is often preferred because of moxifloxacin's slightly higher potential for cardiotoxicity.

Neuropsychiatric adverse events

Neuropsychiatric adverse events such as hallucinations have been reported with delamanid (see section 4.8).

Children should be monitored for neuropsychiatric adverse events, including hallucinations. This is particularly important when administering delamanid and cycloserine concurrently.

Hepatic impairment

[TB388 trade name] is not recommended in patients with moderate to severe hepatic impairment.

Renal impairment

There are no data on the use of delamanid in patients with severe renal impairment and its use is not recommended (see section 5.2).

Paradoxical drug reaction

Post-marketing cases of paradoxical drug reactions (clinical or radiological worsening of existing lesions or development of new lesions in a patient who had previously shown improvement with appropriate antimycobacterial treatment) have been reported with delamanid. Paradoxical drug reactions are often transient and should not be misinterpreted as failure to respond to treatment. If a paradoxical response is suspected, continuation of planned combination therapy is recommended and symptomatic therapy to suppress the exaggerated immune reaction should be initiated if necessary (see section 4.8).

Excipients

Each tablet of [TB388 trade name] contains 100 mg of lactose monohydrate. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

The complete metabolic profile and mode of elimination of delamanid has not yet been fully elucidated (see sections 4.4 and 5.2).

Effects of other medicinal products on [TB388 trade name]

Cytochrome P450 3A4 inducers

[TB388 trade name] is **contraindicated** in people taking strong inducers of CYP3A4 (e.g. carbamazepine and rifampicin).

Clinical drug-drug interactions studies in healthy subjects indicated a reduced exposure to delamanid, of up to 45% following 15 days of concomitant administration of the strong inducer of cytochrome P450 (CYP) 3A4 (rifampicin 300 mg daily) with delamanid (200 mg daily).

No clinically relevant reduction in delamanid exposure was observed with the weak inducer efavirenz when administered at a dose of 600 mg daily for 10 days in combination with delamanid 100 mg twice daily. A higher rate of neuropsychiatric adverse events (e.g., euphoric mood and abnormal dreams) was observed with delamanid plus efavirenz compared to either drug alone, but no subject discontinued the study because of neuropsychiatric events or had serious neuropsychiatric adverse events.

HIV medicines

In clinical drug-drug interaction studies in healthy subjects, delamanid was administered alone (100 mg twice daily) and with tenofovir disoproxil (245 mg daily) or lopinavir/ritonavir (400/100 mg daily) for 14 days and with efavirenz for 10 days (600 mg daily). Delamanid exposure remained unchanged (<25% difference) with anti-HIV medicines tenofovir disoproxil and efavirenz but was slightly increased with the combination anti-HIV medicine containing lopinavir/ritonavir.

Cycloserine

For the importance of carefully monitoring neuropsychiatric side-effects in patients receiving both delamanid and cycloserine, see section 4.4.

Effects of [TB388 trade name] on other medicinal products

In-vitro studies showed that delamanid did not inhibit CYP450 isozymes.

In-vitro studies showed that delamanid and metabolites did not have any effect on the transporters MDR1(p- gp), BCRP, OATP1, OATP3, OCT1, OCT2, OATP1B1, OATP1B3 and BSEP, at concentrations of approximately 5 to 20 fold greater than the C_{max} at steady state. However, since the concentrations in the gut can potentially be much greater than these multiples of the C_{max}, delamanid may have an effect on these transporters.

Tuberculosis medicines

In a clinical drug-drug interaction study in healthy subjects, delamanid was administered alone (200 mg daily) and with rifampicin/isoniazid/pyrazinamide (300/720/180 mg daily) or ethambutol (1100 mg daily) for 15 days. Exposure of concomitant anti-TB drugs (rifampicin [R]/ isoniazid [H]/ pyrazinamide [Z]) was not affected. Co-administration with delamanid significantly increased steady state plasma concentrations of ethambutol by approximately 25%, the clinical relevance is unknown.

HIV medicines

In a clinical drug-drug interaction study in healthy subjects, delamanid was administered alone (100 mg twice daily) and tenofovir disoproxil (245 mg daily), lopinavir/ritonavir (400/100 mg daily) for 14 days and with efavirenz for 10 days (600 mg daily). Delamanid given in combination with the HIV-medicines, tenofovir disoproxil, lopinavir/ritonavir and efavirenz, did not affect the exposure to these medicinal products.

Medicinal products with the potential to prolong QTc

Co-administration of moxifloxacin and delamanid in MDR-TB patients has not been studied. Moxifloxacin is therefore not recommended for use in patients treated with delamanid.

Care must be taken in using delamanid in patients already receiving other medicines associated with QT prolongation (see section 4.4). Patients taking these medicines should receive more frequent monitoring of ECG throughout the full delamanid treatment period. These medicines may include, but are not limited to:

- Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
- Neuroleptics (e.g. phenothiazines such as chlorpromazine, sertindole, sultopride, haloperidol,

mesoridazine, pimozide, or thioridazine).

- Antidepressants.
- Certain antimicrobial agents, including:
    - macrolides (e.g. erythromycin, clarithromycin)
    - moxifloxacin, sparfloxacin (see also Use with quinolones and bedaquiline, below, regarding use with other fluoroquinolones)
    - bedaquiline (see Use with quinolones and bedaquiline, below)
    - triazole antifungal agents
    - pentamidine
- Protease inhibitors: atazanavir/ritonavir, darunavir/ ritonavir, or lopinavir/ ritonavir
- Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine)
- Certain antimalarials with QT-prolonging potential (e.g. halofantrine, quinine, chloroquine, artesunate/amodiaquine, dihydroartemisinin/piperaquine).
- Droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

This medicine may be used as part of a treatment regimen for drug-resistant tuberculosis in pregnant women. Tuberculosis can be particularly dangerous in pregnancy and the benefits (to both mother and fetus) of effective treatment are considered to outweigh the potential risks posed by these medications to the fetus. Close monitoring during and immediately after pregnancy will allow any concerns to be managed promptly.

Studies with delamanid in animals have shown potential reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown whether this medicinal product or its metabolites are excreted in human milk. This medicine may be used for drug-resistant tuberculosis in breast-feeding women in accordance with official guidance.

Available pharmacokinetic data in animals have shown excretion of delamanid and/or its metabolites in milk.

Fertility

Delamanid had no effect on male or female fertility in animals (see section 5.3). There are no clinical data on the effects of delamanid on fertility in humans.

4.7 Effects on ability to drive and use machines

[TB388 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (i.e. incidence > 10%) in patients treated with delamanid plus Optimised Background Regimen (OBR) are nausea: (32.9%), vomiting (29.9%), headache (28.4%), sleep disorders and disturbances (28.2%), dizziness (22.4%), gastritis (15.9%), and decreased appetite (13.1%).

Tabulated list of adverse reactions

The list of adverse drug reactions and frequencies are based on the results from 2 double-blind placebo controlled clinical trials (delamanid plus OBR, n = 662 vs placebo plus OBR n = 330). The adverse drug reactions are listed by MedDRA System Organ Class and Preferred Term. Within each System Organ Class, adverse reactions are listed under frequency categories of very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Endocrine disorders	
Common	Hypothyroidism
Metabolism and nutrition disorders	
Very common	Decreased appetite
Psychiatric disorders	
Very common	Sleep disorders and disturbances
Common	Psychotic disorder
	Anxiety
	Depression
	Hallucination
Nervous system disorders	
Very common	Dizziness
	Headache
Common	Hypoaesthesia
	Tremor
Uncommon	Lethargy
Cardiac disorders	
Common	Atrioventricular block, first degree
	Ventricular extrasystoles
	Palpitations
Respiratory, thoracic and mediastinal disorders	
Common	Throat irritation
Gastrointestinal disorders	
Very common	Nausea
	Vomiting
	Gastritis
Common	Dyspepsia
Musculoskeletal and connective tissue disorders	
Common	Muscular weakness
	Muscle spasms
General disorders and administration site conditions	
Common	Chest pain
Not known	Paradoxical drug reaction
Investigations	
Common	Cortisol increased
	Electrocardiogram QT prolonged

Description of selected adverse reactions

ECG QT interval prolongation

In patients receiving 200 mg delamanid total daily dose in the phase 2 and 3 trials, the mean placebo corrected increase in QTcF from baseline ranged from 4.7 – 7.6 ms at 1 month and 5.3 ms – 12.1 ms at 2 months, respectively. The incidence of a QTcF interval > 500 ms ranged from 0.6% (1/161) – 2.1% (7/341)

in patients receiving delamanid 200 mg total daily dose versus 0% (0/160) – 1.2% (2/170) of patients receiving placebo + OBR, while the incidence of QTcF change from baseline > 60 ms ranged from 3.1% (5/161) – 10.3% (35/341) in patients receiving delamanid 200 mg total daily dose versus 0% (0/160) – 7.1% (12/170) in patients receiving placebo.

Palpitations

In patients receiving 100 mg delamanid + OBR twice daily, the frequency was 7.9% (frequency category common) in comparison to a frequency of 6.7% in patients receiving placebo + OBR twice daily.

Paediatric population

Based on a study (see section 5.1) in 37 paediatric patients aged 0 to 17 years, the frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Nightmares and hallucinations have been both seen mainly in children in post-marketing reports. The incidence of hallucination in clinical trials was 5.4% in children and 1% in adults (both common).

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

No cases of delamanid overdose have been observed in clinical trials. However, additional clinical data showed that in patients receiving 200 mg twice daily, i.e. total 400 mg delamanid per day, the overall safety profile is comparable to that in patients receiving the recommended dose of 100 mg twice daily. Some reactions were observed at a higher frequency and the rate of QT-prolongation increased in a dose-related manner.

Treatment of overdose involves appropriate symptomatic and supportive care. Frequent ECG monitoring should be performed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, antibiotics, ATC code: J04AK06.

Mode of action

The pharmacological mode of action of delamanid involves inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. The identified metabolites of delamanid do not show anti-mycobacterial activity.

Activity against specific pathogens

Delamanid has no in vitro activity against bacterial species other than mycobacteria.

Resistance

Mutation in one of the 5 coenzyme F420 genes is suggested as the mechanism for resistance against delamanid in mycobacteria. In mycobacteria, the *in vitro* frequencies of spontaneous resistance to delamanid were similar to those for isoniazid and were higher than those for rifampicin. Resistance to delamanid has been documented to occur during treatment. Delamanid does not show cross-resistance with any of the currently used anti-tuberculosis drugs.

Susceptibility testing breakpoints

In clinical trials resistance to delamanid has been defined as any growth in the presence of a delamanid concentration of 0.2 μg/mL that is greater than 1% of that on drug-free control cultures on Middlebrook 7H11 medium.

Data from clinical studies

Delamanid has been evaluated in two, double-blind, placebo-controlled trials for the treatment of MDR TB. The analyses of sputum culture conversion (SCC) were conducted on the modified intent to treat population which included patients who had positive cultures at baseline and the isolate was resistant to both isoniazid and rifampicin, i.e., had MDR TB.

In the first trial (Trial 204), 64/141 (45.4%) patients randomised to receive delamanid 100 mg twice daily + optimised background regimen (OBR) and 37/125 (29.6%) of patients randomised to receive placebo (PLC) + OBR achieved two-month sputum culture conversion (SCC) (i.e. growth of *Mycobacterium tuberculosis* to no growth over the first 2 months and maintained for 1 more month) (p=0.0083). The time to SCC for the group randomised to 100 mg twice daily was also found to be faster than for the group randomised to receive placebo + OBR (p=0.0056).

In the second trial (Trial 213), delamanid was administered orally at 100 mg twice daily an add-on therapy to an OBR for 2 months followed by 200 mg once daily for 4 months. The median time to SCC was 51 days in the delamanid + OBR group compared with 57 days in the PLC + OBR group (p = 0.0562 using the stratified modified Peto-Peto modification of Gehan's Wilcoxon rank sum test). The proportion of patients achieving SCC (sputum culture conversion) after the 6-month treatment period was 87.6% (198/226) in the delamanid+ OBR treatment group compared to 86.1% (87/101) in the placebo + OBR treatment group (p=0.7131).

All missing cultures up to the time of SCC were assumed to be positive cultures in the primary analysis. Two sensitivity analyses were conducted - a last-observation-carried-forward (LOCF) analysis and an analysis using "bookending" methodology (which required that the previous and subsequent cultures were both observed negative cultures to impute a negative result, otherwise a positive result was imputed). Both showed a 13-day shorter median time to SCC in the delamanid + OBR group (p=0.0281 for LOCF and p=0.0052 for "bookending").

Delamanid resistance (defined as MIC ≥ 0.2 μg/ml) was observed at baseline in 2 of 316 patients in Trial 204 and 2 of 511 patients in Trial 213 (4 of 827 patients [0.48%]). Delamanid resistance emerged in 4 of 341 patients (1.2%) randomised to receive delamanid for 6 months in Trial 213. These four patients were only receiving two other medicinal products in addition to delamanid.

<u>End-TB (Evaluating Newly approved Drugs for multidrug resistant TB) study</u>

End-TB was a multi-country open label randomised, controlled non-inferiority study in patients aged 15 years and older with rifampicin-resistant pulmonary TB that was susceptible to fluoroquinolones.

The study evaluated 3 regimens that included delamanid 100mg twice daily: BDLLfxZ (bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide), DCLLfxZ (delamanid, clofazimine, linezolid, levofloxacin and pyrazinamide) and DCMZ (delamanid, clofazimine, moxifloxacin and pyrazinamide). Treatment was given for 9 months and compared with the WHO-recommended standard of care.

The primary efficacy outcome was the proportion of participants with a favourable outcome at week 73 (negative cultures or a favourable disease evolution). The modified intention-to-treat (mITT) population (37.8% female) included all the participants who underwent randomisation and received at least one dose of trial treatment and who had a pre-randomization culture positive for Mycobacterium tuberculosis. The median age of the mITT population was 32 years, and 25 participants (3.6%) were younger than 18 years of age; 14.0% were living with HIV infection and 57.1% of the participants had cavitation on chest radiography.

The outcome of the primary efficacy analysis for end TB (mITT) is presented in the table below.

	BDLLfxZ (N=122)	DCLLfxZ (N=118)	DCMZ (N=107)	Standard therapy (N=1119)
Participants with favourable outcome — n (%)	104 (85.2)	93 (78.8)	89 (83.2)	96 (80.7)
Difference from standard therapy (95% CI)	4.6 (-4.9 to 14.1)	- 1.9 (- 12.1 to 8.4)	2.5)-7.5 to 12.5)	

Non-inferiority to standard therapy was established for two of the three delamanid-containing regimens (BDLLfxZ and DCMZ). Week 104 data confirmed these results.

However, WHO analysis of week 104 data showed that both the DCMZ and DCLLfxZ regimens had higher levels of failure (failure to culture convert or culture reversion) or recurrence and higher levels of amplified resistance than the SoC group and are not preferred over the SoC treatment.

Levels of failure or recurrence were 2.5% for SoC, 1.6% for BDLLfxZ, 11.0% for DCLLfxZ and 11.2% for DCMZ. Amplification of drug resistance was shown in 0.0% for SoC and BDLLfxZ, 4.0% for DCLLfxZ and 6.7% for DCMZ.

BEAT-TB

An open-label, phase 3, non-inferiority randomised controlled trial (BEAT-TB) established the efficacy and safety of a regimen comprising 6 months (24 weeks) of bedaquiline, delamanid, and linezolid, with levofloxacin and clofazimine (BDLLfxC) compared with a standard regimen for the treatment of MDR/RR-TB or pre-XDR TB.

Outcomes among patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) receiving the BDLLfxC regimen were compared to those receiving the SoC (9–12-month) all-oral regimens with linezolid for patients with MDR/RR-TB; 18–20-month all-oral regimens for patients with pre-XDR-TB).

Participants with MDR/RR-TB (with or without quinolone resistance) receiving the BDLLfxC regimen (n=202) compared to participants receiving the standard regimen used in the BEAT-TB trial (n=200) experienced:

- higher levels of failure or recurrence: 8.4% vs 7.0%; risk difference = 14 more per 1,000, 95% CI: 38 fewer to 66 more per 1,000)
- lower levels of death: 5.0% vs 5.0%; risk difference = 0.5 fewer per 1,000 (95% CI: from 43 fewer to 42 more per 1,000);
- lower levels of loss to follow up: 1.0% vs 2.0%; risk difference = 10 fewer per 1,000 (95% CI: from 34 fewer to 14 more per 1,000);
- lower levels of grade 3–5 adverse events: 34% vs 38%; risk difference = 38 fewer per 1,000 (95% CI: 132 fewer to 55 more per 1,000); and

- lower levels of amplified resistance: 2.5% vs 3.0%; risk difference = 5 fewer per 1,000 (95% CI: 37 fewer to 27 more per 1,000).

Paediatric population

The pharmacokinetics, safety and efficacy of delamanid in combination with a background regimen (BR) were evaluated in trial 242-12 -232 (10 days pharmacokinetics) followed by trial -233 (pharmacokinetics, efficacy and safety), both single-arm, open-label trials, which included 37 patients who had a median age of 4.55 years (range 0.78 to 17.60 years), 25 (67.6%) were Asian and 19 (51.4%) were female.

Paediatric patients were enrolled in four groups:

Group 1: 12 to 17 years (7 patients), group 2: 6 to 11 years (6 patients), group 3: 3 to 5 years (12 patients) and group 4: 0 to 2 years (12 patients). The overall mean baseline body weight of subjects was 19.5 kg and in groups 1, 2, 3, and 4 the mean body weights were 38.4, 25.1, 14.8, and 10.3 kg, respectively.

The patients had confirmed or probable MDR-TB infection and were to complete 26 weeks of treatment with delamanid + OBR, followed by OBR only in accordance with the WHO recommendation. Patients in groups 1 and 2 received film-coated tablets. The delamanid dose in group 1 was 100 mg twice daily and 50 mg twice daily in group 2. The doses administered were higher than the currently recommended weight-based dosage in the paediatric population. Patients in groups 3 and 4 received dispersible tablets. This paediatric formulation is not bio-equivalent with the film-coated tablets. Patients in group 3 were administered 25 mg twice daily and patients in group 4 were administered doses between 10 mg twice daily and 5 mg once daily based on body weight. The doses administered in group 4 were below the currently recommended weight-based dosage in the paediatric population.

A population PK analysis was performed on data from the 2 paediatric trials to determine the doses in paediatric subjects which would provide delamanid exposures similar to those observed in adult subjects with MDR-TB. Data in children with a body weight of less than 10 kg were too limited to determine doses for that patient population.

5.2 Pharmacokinetic properties

Pharmacokinetics of delamanid

	Delamanid
Absorption	
Absolute bioavailability	Unknown
Oral bioavailability	Estimated to be between 25% and 47%
Food effect	2.7-fold increase
Distribution.	
Volume of distribution (mean)	Vz/F of 2100 L
Plasma protein-binding *in vitro*	≥99.5%
Metabolism	
	Delamanid is primarily metabolised in plasma by albumin and to a lesser extent by CYP3A4. Identified metabolites do not show anti-mycobacterial activity, some contribute to QTc prolongation, namely DM—6705. Concentration of identified metabolites progressively increase to steady state after 6-10 weeks

Elimination	
Elimination half life	$t_{1/2}$ of 30-38 hours.
Mean systemic clearance (Cl/F)	approximately 300 - 400 ml/h/kg (at a 100 mg bid dose)
% of dose excreted in urine	less than 5%
% of dose excreted in faeces	Primarily excreted in stools
Pharmacokinetic linearity	Plasma exposure increases less proportionately with increasing dose
Drug interactions *(in vitro*)	Inhibition of P-gp in the gut seems low, however not fully elucidated. The metabolic profile is not elucidated and there may be a potential for drug interactions with co-administered medicines.

NA* = Information not available

Special populations

Patients with renal impairment

Less than 5% of an oral dose of delamanid is recovered from urine. Mild renal impairment (50 mL/min < CrCLN < 80 mL/min) does not appear to affect delamanid exposure. Therefore, no dose adjustment is needed for patients with mild or moderate renal impairment. It is not known whether delamanid and metabolites will be significantly removed by haemodialysis or peritoneal dialysis.

Patients with hepatic impairment

No dose adjustment is considered necessary for patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment.

Elderly patients (≥ 65 years)

No patients of ≥ 65 years of age were included in clinical trials.

5.3 Preclinical safety data

Delamanid and/or its metabolites have the potential to affect cardiac repolarisation via blockade of hERG potassium channels. In the dog, foamy macrophages were observed in lymphoid tissue of various organs during repeat-dose toxicity studies. The finding was shown to be partially reversible; the clinical relevance of this finding is unknown. Repeat-dose toxicity studies in rabbits revealed an inhibitory effect of delamanid and/or its metabolites on vitamin K-dependent blood clotting.

Non-clinical data reveal no specific hazard for humans based on conventional studies for genotoxicity and carcinogenic potential.

In rabbit reproductive studies, embryofetal toxicity was observed at maternally toxic dosages. Pharmacokinetic data in animals have shown excretion of delamanid or its metabolites into breast milk. In lactating rats, the C_{max} for delamanid in breast milk was 4-fold higher than that in blood.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Hypromellose phthalate
Povidone
All-rac- α-tocopherol
Microcrystalline cellulose
Colloidal hydrated silica
Lactose monohydrate
Sodium starch glycolate
Carmellose calcium
Magnesium stearate

Film coat: Hypromellose
Macrogol /polyethylene glycol
Titanium dioxide
Iron oxide yellow (E172)
Talc

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per *tablet*.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

8's CF O2 1.16% blister - 36 months

8's CF O2 3-5% blister - 24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Alu /Alu blisters

[TB388 trade name] is available in cold form aluminium (Alu /Alu) blisters containing 8 tablets. Such 6 blister cards are packed in a carton (6 x 8).

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Mylan Laboratories Limited

Plot No. 564/A/22, Road No. 92

Jubilee Hills

Hyderabad - 500096

Telangana, India

Email: ProductSafety@viatris.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB388

9. DATE OF PREQUALIFICATION

24 November 2022

10. DATE OF REVISION OF THE TEXT

March 2026

References

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Section 4.5:

Liverpool HIV Drug Interactions Checker (https://www.hiv-druginteractions.org/, accessed 26 Jan 2026)

Mallikaarjun S, Wells C, Petersen C, et al. Delamanid coadministered with antiretroviral drugs or antituberculosis drugs shows no clinically relevant drug-drug interactions in healthy subjects. Antimicrob Agents Chemother, 2016; 60: 5976-85 (available at https://pmc.ncbi.nlm.nih.gov/articles/PMC5038266/, accessed 26 Jan 2026).

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products