1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

DELTYBA™ (50 mg, film-coated tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each film-coated tablet contains 50 mg delamanid.

Contains an antioxidant: All-*rac*-α-tocopherol.

Contains sugar: Lactose monohydrate 100 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Yellow, round film coated tablets, debossed with “DLM” and “50” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DELTYBA is indicated for use as part of an appropriate combination regimen for the treatment of pulmonary multi-drug-resistant tuberculosis (MDR-TB) in adult patients, adolescents and children with a body mass of at least 30 kg, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability *(see sections 4.2 & 4.4)*.

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4.2 Posology and method of administration

Posology

The recommended dose for adults is 100 mg twice daily for 24 weeks.

Paediatric population

- Adolescents and children with a body weight of 50 kg or above: the recommended dose is 100 mg twice daily for 24 weeks.
- 30 kg or above and less than 50 kg: the recommended dose is 50 mg twice daily for 24 weeks.

DELTYBA must always be administered as part of an appropriate combination regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB), preferably by Direct Observed Therapy (DOT).

Special populations

Elderly patients (> 65 years of age)

Safety and efficacy have not been established in older patients.

Renal impairment

No dose adjustment is considered necessary in patients with mild or moderate renal impairment. There is no data on the use of DELTYBA in patients with severe renal impairment and its use is not recommended.

Hepatic impairment

No dose adjustment is considered necessary in patients with mild hepatic impairment. DELTYBA is not recommended in patients with moderate to severe hepatic impairment *(see section 4.3)*.

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Paediatric population

The safety and efficacy of DELTYBA in children with a body weight below 30 kg have not yet been established.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation posology can be made.

Method of administration

Oral use.

DELTYBA should be taken with food.

4.3 Contraindications

- Hypersensitivity to delamanid or any of the excipients.
- Serum albumin < 2,8 g/dL.
- Severe hepatic impairment.
- Cardiac failure.
- Uncontrolled brady- or tachydysrhythmias.
- Congenital QT prolongation.
- Concomitant use with medicines known to prolong the QTc interval to time intervals known to induce serious dysrhythmias.
- Patients taking medicines that are strong inducers of CYP3A4 (e.g. carbamazepine).

4.4 Special warnings and precautions for use

There is no data on treatment with DELTYBA for more than 24 consecutive weeks.

There is no clinical data on the use of DELTYBA to treat:

- extra pulmonary tuberculosis (e.g. central nervous system, bone);

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- infections due to Mycobacterial species other than those of the *M. tuberculosis* complex;
- latent infection with *M. tuberculosis.*

There is no clinical data on the use of DELTYBA 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 treatment to prevent development of resistance to delamanid.

QT prolongation

- QT interval 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 or a QTcF interval increase of > 60 ms from the baseline with treatment, treatment with delamanid should either not be started or should be discontinued.

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- If the QTc interval duration exceeds 450/470 ms for male/female patients during delamanid treatment, these patients should be administered 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 DELTYBA should not be initiated in patients with the following risk factors:

- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval or QTc > 500 ms *(see section 4.3).*
- History of symptomatic cardiac dysrhythmias or with clinically relevant bradycardia *(see section 4.3).*
- Any predisposing cardiac conditions for dysrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction *(see section 4.3).*
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Taking medicines that are known to prolong the QTc interval. These include (but are not limited to):

- Antidysrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
- Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive medicines.
- Certain antimicrobial medicines, including e.g.:

- macrolides (e.g. erythromycin, clarithromycin);
- moxifloxacin, sparfloxacin or other fluoro-quinolones);
- bedaquiline;
- triazole antifungal medicines;
- pentamidine;
- saquinavir.

- Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
- Certain antimalarials with QT-prolonging potential (e.g. halofantrine, quinine, chloroquine, artesunate/amodiaquine, dihydroartemisinin/piperaquine).

- Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

Hypoalbuminaemia

- The presence of hypoalbuminaemia is associated with an increased risk of prolongation of the QTc interval in DELTYBA treated patients.
- DELTYBA is contraindicated in patients with albumin < 2,8 g/dL *(see section 4.3).*
- Patients who commence DELTYBA with serum albumin < 3,4 g/dL or experience a fall in serum albumin into this range during treatment should receive very frequent monitoring of ECGs throughout the full DELTYBA 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.

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- 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.

Co-administration of delamanid with quinolones

- All QTcF prolongations above 60 ms were associated with concomitant fluoroquinolone use.
- 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 very frequent monitoring of ECGs throughout the full delamanid treatment period.

Hepatic impairment

- Deltyba is not recommended in patients with moderate and contraindicated in patients with severe hepatic impairment *(see section 4.3).*

Metabolism and elimination

- The complete metabolic profile of delamanid in man has not yet been fully elucidated. Therefore, the potential for 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.

Lactose warning:

DELTYBA contains lactose monohydrate that may have an effect on the glycaemic control of patients with diabetes mellitus. Consequently, patients with rare hereditary problems of galactose intolerance (e.g. galactosaemia), total lactase deficiency, or glucose-galactose malabsorption should not be treated with DELTYBA.

4.5 Interaction with other medicines and other forms of Interaction

Effects of other medicines on Deltyba:

- *Cytochrome P450 3A4 inducers*

Clinical interactions studies in healthy subjects indicated a reduced exposure to DELTYBA, of up to 45 % following 15 days of concomitant administration of the strong inducer of cytochrome P450 (CYP) 3A4 (Rifampicin 300 mg daily) with DELTYBA (200 mg daily). No clinically relevant reduction in DELTYBA exposure was observed with the weak inducer efavirenz when administered at a dose of 600 mg daily for 10 days in combination with DELTYBA 100 mg twice daily.

- *Anti-HIV medicines*

In clinical interaction studies in healthy subjects, DELTYBA 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). DELTYBA exposure remained unchanged (< 25 % difference) with anti-HIV medicines tenofovir disoproxil and efavirenz but was slightly increased with the combination anti-HIV medicines containing lopinavir/ritonavir.

Effects of DELTYBA on other medicines:

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

In-vitro studies showed that DELTYBA and metabolites did not have any effect on the transporters MDR1(pgp), 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}, there is a potential for DELTYBA to have an effect on these transporters.

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- *Anti-Tuberculosis medicines*

In a clinical interaction study in healthy subjects, DELTYBA was administered alone (200 mg daily) and with rifampicin/isoniazid/pyrazinamide (300/720/1800 mg daily) or ethambutol (1100 mg daily) for 15 days. Exposure of concomitant anti-TB medicines (rifampicin/isoniazid/pyrazinamide) was not affected. Co-administration with DELTYBA significantly increased steady state plasma concentrations of ethambutol by approximately 25 %, the clinical relevance is unknown.

- *Anti-HIV medicines*

In a clinical 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 anti-HIV-medicines, tenofovir disoproxil, lopinavir/ritonavir and efavirenz, did not affect the exposure to these medicines.

- *Medicines with the potential to prolong QTc*

Care must be taken in using DELTYBA in patients already receiving medicines associated with QT interval prolongation. Co-administration of moxifloxacin and DELTYBA in MDR-TB patients has not been studied. Moxifloxacin is not recommended for use in patients treated with DELTYBA *(see section 4.3).*

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

DELTYBA should not be used in pregnant women.

There are no or a limited amount of data from the use of DELTYBA in pregnant women.

Studies in animals have shown reproductive toxicity.

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Deltyba is not recommended in pregnancy and in women of childbearing potential not using contraception.

Lactation

It is unknown whether delamanid/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of delamanid and/or its metabolites in milk. A risk to the newborns/infants cannot be excluded.

It is recommended that women should not breastfeed during treatment with DELTYBA.

Fertility

DELTYBA had no effect on male or female fertility in animals. There are no clinical data on the effects of delamanid on fertility in humans.

4.7 Effects on ability to drive and use machines

DELTYBA may cause adverse reactions such as headaches and tremors and may have no or negligible effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

Patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that DELTYBA does not adversely affect their ability to do so *(see section 4.8).*

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4.8 Undesirable effects

a. Summary of the safety profile

The most frequently observed adverse drug reactions in patients treated with delamanid + Optimised Background Regimen (OBR) (i.e. incidence > 10 %) are nausea (32,9 %), vomiting (29,9 %), headache (27,6 %), insomnia (27,3 %), dizziness (22.4 %), tinnitus (16,5 %), hypokalaemia (16,2 %), gastritis (15,0 %), decreased appetite (13,1 %), and asthenia (11,3 %).

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.

Tabulated list of adverse reactions

System Organ Class	**Frequency very common**	**Frequency common**	**Frequency uncommon**
Infections and infestations			Herpes zoster Oropharyngeal candidiasis Tinea versicolor*
Blood and lymphatic	Reticulocytosis	Anaemia* Eosinophilia*	Leukopenia Thrombocytopenia

system disorders			
Endocrine disorders		Hypothyroidism (hypothyroidism, primary hypothyroidism)	
Metabolism and nutrition disorders	Hypokalaemia Decreased appetite Hyperuricaemia*	Hypertriglyceridaemia	Dehydration Hypocalcaemia Hypercholesterolaemia
Psychiatric disorders	Insomnia	Psychotic disorder Agitation Anxiety and anxiety disorder Depression and depressed mood Restlessness Hallucinations	Aggression Persecutory type delusional disorder Panic disorder Adjustment disorder with depressed mood Neurosis Dysphoria Mental disorder Sleep disorder Increased libido*
Nervous system disorders	Dizziness* Headache Paraesthesia Tremor	Peripheral neuropathy Somnolence* Hypoaesthesia	Lethargy Balance disorder Radicular pain Poor quality sleep
Eye disorders		Dry eye* Photophobia	Allergic conjunctivitis *

Ear and labyrinth disorders	Tinnitus	Ear pain	
Cardiac disorders	Palpitations		First degree atrioventricular block Ventricular extrasystoles* Supraventricular extrasystoles
Vascular disorders		Hypertension Hypotension Haematoma* Hot flushes*	
Respiratory, thoracic and mediastinal disorders	Haemoptysis	Dyspnoea Cough Oropharyngeal pain Throat irritation Dry throat* Rhinorrhoea*	
Gastro-intestinal disorders	Vomiting Diarrhoea* Nausea Upper abdominal pain	Gastritis* Constipation* Abdominal pain Lower abdominal pain Dyspepsia Abdominal discomfort	Dysphagia Oral paraesthesia Abdominal tenderness*
Hepatobiliary disorders			Abnormal hepatic function

Skin and sub-cutaneous tissue disorders		Dermatitis Urticaria Pruritic rash * Pruritus* Maculopapular rash* Rash* Acne Hyperhidrosis	Alopecia* Eosinophilic pustular folliculitis* Generalised pruritus * Erythematous rash
Musculoskeletal and connective tissue disorders	Arthralgia* Myalgia*	Osteochondrosis Muscular weakness Musculoskeletal pain* Flank pain Pain in extremity Muscle spasms	
Renal and urinary disorders		Haematuria*	Urinary retention Dysuria* Nocturia
General disorders and admin-istration site conditions	Asthenia	Pyrexia* Chest pain Malaise Chest discomfort* Peripheral oedema *	Feeling hot
Investigations	Electrocardiogram QT prolonged	Increased blood cortisol	Electrocardiogram ST segment depression Increased transaminases*

			Prolonged activated partial thromboplastin time * Increased gammaglutamyltransferase * Decreased blood cortisol Increased blood pressure

* The frequency for these events was lower for the combined DELTYBA plus OBR group in comparison to the placebo plus OBR group

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, while the incidence of QTcF change from baseline > 60ms ranged from 3,1 % (5/161) – 10,3 % (35/341) in patients receiving delamanid 200 mg total daily dose.

Palpitations

For patients receiving 100 mg DELTYBA + OBR twice daily, the frequency was 8,1 % (frequency category common).

Paediatric population

Based on a study in 13 children and adolescents aged 6 – 17 years, the frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Clinical study safety data are not available for children under 6 years.

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Hallucinations have been reported predominantly in paediatric patients during post-marketing studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

- An overdose may precipitate side effects and may increase the severity thereof (see section 4.8).
- Treatment of overdose should involve immediate measures to remove DELTYBA from the gastrointestinal tract and symptomatic and supportive care as required.
- Frequent ECG monitoring should be performed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

Pharmacotherapeutic group and ATC code:

A 20.2.3 Tuberculostatics

Pharmacotherapeutic group: Antimycobacterials, antibiotics, ATC code: J04AK06

Mechanism of action:

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Delamanid inhibits the synthesis of mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. The identified metabolites of delamanid do not show anti-mycobacterial activity.

Pharmacodynamic effects:

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 medicines.

Susceptibility testing interpretive criteria

When 7H11 agar medium is used for drug susceptibility testing, the recommended epidemiological cut-off (ECOFF) and susceptibility testing interpretive criteria for delamanid are:

ECOFF: 0,016 mg/L

Clinical breakpoint: S ≤ 0,016 mg/L; R > 0,016 mg/L

S = susceptible; R = resistant

5.2 Pharmacokinetic properties

Absorption:

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Oral bioavailability of delamanid improves when administered with a standard meal, by about 2.7-fold compared to fasting conditions. Delamanid plasma exposure increases less than proportionally with increasing dose.

Distribution:

Delamanid highly binds to all plasma proteins with a binding to total proteins of ≥ 99,5 %. Delamanid has a large apparent volume of distribution (Vz/F of 2,100 L).

Biotransformation/Metabolism:

Delamanid is primarily metabolized in plasma by albumin and to a lesser extent by CYP3A4. The complete metabolic profile of delamanid has not yet been elucidated, and there is a potential for drug interactions with other co-administered medications. The identified metabolites do not show anti-mycobacterial activity, but some contribute to QTc prolongation, mainly DM-6705. Concentrations of the identified metabolites progressively increase to steady state after 6 to 10 weeks.

Elimination:

Delamanid disappears from plasma with a $t_{1/2}$ of 30-38 hours. Delamanid is not excreted in urine.

Special populations:

Renal impairment

Less than 5 % of an oral dose of delamanid is recovered from urine. Mild renal impairment (50 mL/min < CrCL< 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.

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 *(*see section 4.3*)*.

Elderly patients (≥ 65 years)

No dose adjustment is considered necessary for patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment (see section 4.3*)*.

Paediatric patients

During treatment with the recommended delamanid doses to adolescents and children with a body weight of at least 10 kg (see section 4.2), similar plasma exposure was obtained as in adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Carmellose calcium, cellulose microcrystalline, hypromellose phthalate, magnesium stearate, povidone (K-25), silica colloidal hydrated, sodium starch glycolate (type A).

Film-coating:

Hypromellose, iron oxide yellow (E172), macrogol 8000, titanium dioxide, talc.

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 30 ºC.

Store in the original package to protect from moisture.

Do not remove the tablets from the blister strips until required for use.

6.5 Nature and contents of container

The tablets are packaged in silver aluminum/aluminum foil blisters. Each blister strip contains 8 separately blistered tablets.

6 blister strips are placed into a carton.

Pack size 48's.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd.

4 Brewery Street,

Isando, Gauteng,

1601

8 REGISTRATION NUMBER(S)

52/20.2.3/0460

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 March 2019

10 DATE OF REVISION OF TEXT

27 September 2024