# - ANTI-TUBERCULOSIS AGENT –
# DELTYBA® 50 mg film- coated tablets
# < Delamanid >

## 1. COMPOSITION

Each film-coated tablet contains 50mg delamanid.

Excipient with known effect: each film-coated contains 100mg lactose (as monohydrate).

| Brand Name | Active Ingredient |
|---|---|
| DELTYBA 50 mg film-coated tablets | 50 mg of delamanid per tablet |

## 2. PRODUCT DESCRIPTION

Deltyba 50 mg Film-coated tablet

Round, yellow, film-coated tablets, debossed with “DLM” and “50” on one side.

## 3. Therapeutic indications

Deltyba is indicated for use as part of an appropriate combination regimen for low risk pulmonary multi-drug resistant tuberculosis (MDR-TB) longer regimen in adult, adolescents and children with a body weight of at least 30 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4, 6 and 11.1)

Consideration should be given to official guidance on the appropriate use antibacterial agents.

## 4. Posology and method of administration

Treatment with delamanid should be initiated and monitored by a physician experienced in the management of multidrug-resistant *Mycobacterium tuberculosis*.

Delamanid must always be administered as part of an appropriate combination regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB) (see sections 6 and 11.1). Treatment with an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to WHO guidelines.
It is recommended that delamanid is administered by directly observed therapy (DOT).

### 4.1 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.



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– 30 kg or above and less than 50 kg: the recommended dose is 50 mg twice daily for 24 weeks.

The safety and efficacy of delamanid in children with a body weight of less than 30 kg has not yet been established. No data are available.

*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 sections 6 and 11.2).

*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 (see sections 6 and 11.2).

**4.2 Method of administration**

For oral use.
Delamanid should be taken with food.

**5. Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- Serum albumin <2.8 g/dL. (see section 6 regarding use in patients with serum albumin ≥2.8g/dL)
- Taking medicinal products that are strong inducers of CYP3A4 (e.g. carbamazepine).

**6. Special warnings and precautions for use**

There are no data on treatment with delamanid for more than 24 consecutive weeks.

There are no clinical data on the use of delamanid to treat
- Extra pulmonary 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 treatment as recommended by WHO to prevent development of resistance to delamanid.



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Resistance to delamanid has occurred during treatment. The risk of selecting for resistance to delamanid appears to be increased when it is used with less than the number and type of recommended agents for an appropriate combination regimen.

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 Consideration 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 be administered more frequent ECG monitoring. It is also recommended that serum electrolytes, e.g. potassium, calcium and magnesium 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 risk. Such patients should receive very 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 of QTc > 500ms.
- History of symptomatic cardiac arrhythmias or with 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 hypokalemia, hypocalcemia, hypomagnesaemia or hypoalbuminaemia.
- Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
  - Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
  - Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.
  - Certain antimicrobial agents, including:
    - macrolides (e.g. erythromycin, clarithromycin)
    - moxifloxacin, sparfloxacin (see section 6 regarding use with other fluoroquinolones)
    - triazole antifungal agents
    - pentamidine
    - saquinavir
  - Certain non-sedating anthihistamines (e.q. terfenadine, astemizole, mizolastine).
  - Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.



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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 5). Patients who commence delamanid 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 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.

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 to severe hepatic impairment (see sections 4 and 11.2).

*Biotransformation and elimination*
The complete metabolic profile of delamanid in man has not yet been fully elucidated (see sections 8 and 11.2). 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.

Excipients
Deltyba film-coated tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised not to drive or use machines if they experience any adverse reaction with a potential impact on the ability to perform these activities (e.g. headache is very common and tremor is common).

## 7. Undesirable effects

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%),



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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. The adverse 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 (≥1/1000 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.

Table: Adverse reactions to delamanid

| **System Organ Class** | **Frequency very common** | **Frequency common** | **Frequency Uncommon** |
|---|---|---|---|
| Endocrine disorders | - | Hypothyroidism[a] | - |
| Metabolism and nutrition disorders | Decreased appetite | - | - |
| Psychiatric disorders | Sleep disorders and disturbances[b] | Psychotic disorder[c]<br>Anxiety[d]<br>Depression[e]<br>Hallucination[f] | - |
| Nervous system disorders | Dizziness<br>Headache[g] | Hypoaesthesia<br>Tremor | Lethargy |
| Cardiac disorders | - | Atrioventricular block first degree<br>Ventricular extrasystoles<br>Palpitations | - |
| Respiratory, thoracic and mediastinal disorders | - | Throat irritation | - |
| Gastrointestinal disorders | Nausea<br>Vomiting<br>Gastritis[h] | Dyspepsia | - |
| Musculoskeletal and connective tissue disorders | - | Muscular weakness<br>Muscle spasms | - |
| General disorders and administration site conditions | - | Chest pain<br>Drug resistance | - |
| Investigations | - | Cortisol increased[i] | - |



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| System Organ Class | Frequency very common | Frequency common | Frequency Uncommon |
|---|---|---|---|
| | | Electrocardiogram QT prolonged | |

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in Table 'Adverse drug reactions to delamanid'. Preferred terms actually reported in the double-blind clinical trials and contributing to the relevant adverse drug reaction are indicated in parentheses, as listed below:

a. Hypothyroidism (hypothyroidism, primary hypothyroidism)
b. Sleep disorders and disturbances (initial insomnia, insomnia, sleep disorder)
c. Psychotic disorder (acute psychosis, psychotic disorder, reactive psychosis, substance-induced psychotic disorder)
d. Anxiety (anxiety, anxiety disorder, generalised anxiety disorder)
e. Depression (adjustment disorder with depressed mood, depressed mood, depression, major depression, mixed anxiety and depressive disorder, persistent depressive disorder, schizoaffective disorder depressive type)
f. Hallucination (hallucination; hallucination, auditory; hallucination, visual; hallucination tactile; hallucination mixed; hypnopompic hallucination; hypnagogic hallucination)
g. Headache (head discomfort, headache, migraine, sinus headache, tension headache, vascular headache)
h. Gastritis (chronic gastritis, gastritis, gastritis erosive)
i. Cortisol increased (Cushing's syndrome, hyperadrenocorticism, cortisol increased)

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 > 60ms 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*
For patients receiving delamanid + OBR in the phase 2 and 3 trials, the frequency was 8.1% (frequency category common) in comparison to a frequency of 6.3% in patients receiving placebo + OBR.

*Drug resistance*
Drug resistance against delamanid has been confirmed by validated drug susceptibility testing in a single case in post-marketing experience and occurred in four patients during the 6 months double-blind, placebo-controlled clinical trial. In all cases for which resistance developed during therapy, the OBR regimen was difficult to construct due to multi-drug resistance and the presence of resistant isolates was potentially confounded by nosocomial transmission.

*Paediatric population*
Based on a study (see section 11.1) 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.



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Clinical study safety data are not available for children under 6 years.
Cases of hallucination have been reported predominantly in the paediatric population during post-marketing. The incidence of hallucination in clinical trials was common for children (5.4%) and adults (1%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

## 8. 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 6 and 11.2).

Effects of other medicinal products on delamanid

*Cytochrome P450 3A4 inducers*

Clinical drug-drug interaction 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 300mg daily) with delamanid (200mg daily). No clinically relevant reduction in delamanid exposure was observed with the weak inducer efavirenz when administered at a dose of 600mg daily for 10 days in combination with delamanid 100mg twice daily.

*Anti-HIV medicines*

In clinical drug-drug interaction studies in healthy subjects, delamanid was administered alone (100mg twice daily) and with tenofovir (300mg daily) or lopinavir/ritonavir (400/100mg daily) for 14 days and with efavirenz for 10 days (600mg daily). Delamanid exposure remained unchanged (<25% difference) with anti-HIV medicine tenofovir and efavirenz but was slightly increased with the combination anti-HIV medicine containing lopinavir/ritonavir.

Effects of delamanid 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 $C_{max}$, there is a potential for delamanid to have an effect on these transporters.

*Anti-Tuberculosis medicines*

In a clinical drug-drug interaction study in healthy subjects, delamanid was administered alone (200mg daily) and with rifampicin/Isoniazid/pyrazinamide (300/720/1800mg daily) or ethambutol (1100mg 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



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steady state plasma concentrations of ethambutol by approximately 25%, the clinical relevance is unknown.

*Anti-HIV medicines*
In a clinical drug-drug interaction study in healthy subjects, delamanid was administered alone (100mg twice daily) and tenofovir (300mg), lopinavir/ritonavir (400/100mg) for 14 days and with efavirenz for 10 days (600mg daily). Delamanid given in combination with the anti-HIV-medicines, tenofovir, lopinavir/ritonavir and efavirenz, did not affect the expose to these medicinal products.

*Medicinal products with the potential to prolong QTc*
Care must be taken in using delamanid in patients already receiving medicines associated with QT prolongation (see section 6). Co-administration of moxifloxacin and delamanid in MDR-TB patients has not been studied. Moxifloxacin is not recommended for use in patients treated with delamanid.

## 9. FERTILITY, PREGNANCY AND LACTATION

Pregnancy
There are very limited data from the use of delamanid in pregnant women. Studies in animals have shown reproductive toxicity (see section 11.3).
Deltyba is not recommended during pregnant women or in women of childbearing potential unless they are using a reliable form or contraception.

Breast-feeding
It is unknown whether this medicinal product or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of delamanid and/or its metabolites in milk. Because a potential risk to the breast-feeding infant cannot be ruled out, it is recommended that women should not breastfeed during treatment with Deltyba.

Fertility
Deltyba had no effect on male or female in animals (see section 11.3). There are no clinical data on the effects of delamanid on fertility in humans.

## 10. 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. Albeit, some reactions were observed at a higher frequency and the rate of QT prolongation increased in a dose-related manner. Treatment of overdose should involve immediate measures to remove delamanid from the gastrointestinal tract and supportive care as required. Frequent ECG monitoring should be performed.

## 11. PHARMACOLOGICAL PROPERTIES

### 11.1 Pharmacodynamic properties

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



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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 (see section 6). Delamanid does not show cross-resistance with any of the currently used anti-tuberculosis medicinal product except pretomanid. *In vitro* studies have shown cross-resistance with pretomanid. This is likely to be due to delamanid and pretomanid being activated via the same pathway.

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 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 BID + 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 BID 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 BID as 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).



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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) has been 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.

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 13 patients who had a median age of 13 years (range 7-17), weighed 16-45 kg; 11/13 were Asian and 7/13 females. 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. Adolescents aged 12 years and older received the adult dose, 100 mg delamanid twice daily, and children aged 6 to 11 years 50 mg delamanid twice daily. This administered dose was higher than the currently recommended weight-based dosage in the paediatric population.

**11.2 Pharmacokinetic properties**

Absorption

Oral bioavailability of delamanid improves when administered with a standard meal, by about 2.7 fold compared to fasting conditions.

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 2,100L).

Biotransformation

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, if significant unknown metabolites are discovered. 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.



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Elimination

Delamanid disappears from plasma with a t1/2 of 30 to 38 hours. Delamanid is not excreted in urine.

Linearity/non-linearity

Delamanid plasma exposure increases less than proportionally with increasing dose.

Special populations

*Paediatric population*

During treatment with the recommended delamanid doses to adolescents and children with a body weight of at least 30 kg (see section 4.1), similar plasma exposure were obtained as in adults.

*Patients with renal impairment*

Less than 5% of an oral dose of delamanid is recovered from urine. Mild renal impairment (50mL/min < CrCLN < 80mL/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.

### 11.3 Preclinical safety data

Non-clinical data reveal no specific hazard for humans based on conventional studies for genotoxicity and carcinogenic potential. 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. In rabbits reproductive studies, embryo-fetal toxicity was observed at maternally toxic dosages. Pharmacokinetic data in animals have shown excretion of delamanid/metabolites into breast milk. In lactating rats, the $C_{max}$ for delamanid in breast milk was 4-fold higher than of the blood.

## 12. PHARMACEUTICAL PARTICULARS

### 12.1 List of excipients

Tablet core

Hypromellose phthalate



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Povidone (K-25)
all-rac-α-Tocopherol
Cellulose, microcrystalline
Sodium starch glycolate (type A)
Carmellose calcium
Silica, colloidal hydrated
Magnesium stearate
Lactose monohydrate

Film coating
Hypromellose
Macrogol 8000
Titanium dioxide
Talc
Iron oxide yellow (E172)

**12.2 Incompatibilities**
Not applicable

**12.3 Shelf life**
5 years

**12.4 Storage**
Store below 30°C

**12.5 Special precautions for storage**
Store in the original package in order to protect from moisture.

**12.6 Special precautions for disposal**

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

**12.7 Packaging**
Box, 6 blisters @ 10 film coated tablets
Reg. No.: DKI1956102017A1

**HARUS DENGAN RESEP DOKTER**

**Manufactured by:**
Otsuka Pharmaceutical Co., Ltd.,
Tokushima Itano Factory
13 Minami, Shishitoki, Matsutani, Itano-cho, Itano-gun
Tokushima 779-0195, Japan

**Imported and Repacked by:**
PT Otsuka Indonesia



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Jl. Sumber Waras No. 25
Lawang, Malang 65216, Indonesia

**Under License of:**
Otsuka Pharmaceutical Co., Ltd., Japan



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**INFORMASI PRODUK UNTUK PASIEN**
**DELTYBA®**
(Delamanid)

**Nama Obat** **: DELTYBA®**
**Bentuk sediaan** **:** Tablet salut selaput
**Deskripsi** **:** Tablet salut selaput berwarna kuning dengan emboss "DLM" dan "50" pada sisi yang lain

**Apa yang terkandung dalam DELTYBA?**
Zat aktif : Delamanid
Zat tambahan : Hypromellose phthalate, Povidone (K-25), all-rac-α-Tocopherol, Microcrystalline cellulose, Sodium starch glycolate (tipe A), Carmellose calcium, Colloidal hydrated silica, Magnesium stearate, Lactose monohydrate, Hypromellose, Macrogol 8000, Titanium dioxide, Talc, and Iron oxide yellow (E172)
Kekuatan **:** 50 mg

**Apakah DELTYBA?**
Deltyba mengandung zat aktif delamanid, yang diindikasikan sebagai bagian dari rejimen kombinasi yang sesuai untuk rejimen jangka panjang pada *multi-drug resistant tuberculosis* (MDR-TB) yang berisiko rendah pada pasien dewasa, remaja dan anak-anak dengan berat badan minimal 30 kg ketika rejimen pengobatan yang efektif tidak dapat diberikan dengan alasan resistensi atau tolerabilitas.

Pertimbangan sebaiknya diberikan berdasarkan pada panduan resmi tentang penggunaan agen antibakteri yang tepat.

**Bagaimana saya harus mengonsumsi DELTYBA?**
Selalu konsumsi obat ini sesuai petunjuk dokter. Bila Anda ragu, konsultasi dengan dokter atau apoteker.
Dosis yang dianjurkan oleh dokter adalah:
Dewasa, remaja dan anak-anak dengan berat badan 50 kg atau lebih: dua kali sehari dua tablet 50 mg (pagi dan sore)
Anak-anak dengan berat badan 30 kg atau lebih dan kurang dari 50 kg: dua kali sehari satu tablet 50 mg setiap hari selama 24 minggu.
Tablet harus dikonsumsi pada saat atau setelah makan. Telan tablet dengan air.

**Jika Anda mengonsumsi Deltyba lebih dari yang seharusnya**
Jika Anda mengonsumsi tablet lebih dari dosis yang ditentukan, hubungi dokter atau rumah sakit setempat. Ingatlah untuk membawa kemasan obat, sehingga jelas obat apa yang telah Anda konsumsi.

**Jika Anda lupa untuk mengonsumsi Deltyba**
Jika Anda lupa mengonsumsi satu dosis, konsumsi segera obat setelah Anda mengingatnya. Namun jika mendekati waktu untuk dosis berikutnya, lewatkan saja dosis yang terlupa tersebut.
Jangan konsumsi dua kali takaran dosis untuk menggantikan tablet yang terlupakan.

**Jika Anda berhenti mengonsumsi Deltyba**
**Jangan berhenti** mengonsumsi tablet kecuali atas saran dokter. Menghentikan konsumsi obat lebih awal dapat menyebabkan bakteri berkembang kembali dan menjadi resisten terhadap delamanid.
Jika Anda mempunyai pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker.


DISETUJUI OLEH BPOM: 30/05/2023 EREG10021412300058

**Siapa yang tidak boleh mengonsumsi DELTYBA?**
**Jangan mengonsumsi Deltyba:**
- Jika Anda alergi terhadap delamanid atau salah satu bahan lain dari obat ini (tercantum pada bagian **Apa yang terkandung dalam DELTYBA**).
- Jika Anda memiliki kadar albumin yang sangat rendah dalam darah.
- Jika Anda mengonsumsi obat yang secara kuat menginduksi enzim hati tertentu yaitu "CYP450 3A4" (misalnya carbamazepine).

**Anak-anak**
Deltyba tidak boleh dikonsumsi untuk anak dengan berat badan kurang dari 30 kg.

**Apa informasi paling penting yang harus saya ketahui tentang DELTYBA?**
**Peringatan dan Perhatian**
Bicarakan dengan dokter, apoteker atau perawat sebelum mengonsumsi Deltyba.
Sebelum mulai mengonsumsi Deltyba, dan selama pengobatan, dokter Anda dapat memeriksa aktifitas listrik jantung Anda dengan menggunakan mesin EKG (elektrokardiogram) atau (perekam jantung elektrik). Dokter Anda juga dapat melakukan tes darah untuk memeriksa konsentrasi beberapa mineral dan protein yang penting untuk fungsi jantung.

**Apa yang harus saya katakan pada dokter sebelum mengonsumsi DELTYBA?**

Beritahu dokter Anda jika Anda memiliki salah satu dari kondisi berikut:
- Anda mengalami penurunan kadar albumin, kalium, magnesium atau kalsium dalam darah
- Anda mempunyai masalah pada jantung, irama jantung yang lambat (bradikardia) atau memiliki riwayat serangan jantung (infark miokard)
- jika Anda mempunyai kondisi yang disebut Sindroma QT memanjang bawaan atau mempunyai masalah jantung yang serius atau gangguan irama jantung.
- Anda memiliki penyakit hati atau penyakit ginjal
- Anda memiliki HIV

**Deltyba dan obat-obat lainnya**
Katakan pada dokter Anda
- Jika Anda sedang mengonsumsi pengobatan lain, termasuk obat-obatan atau obat herbal yang diperoleh tanpa resep.
- Jika Anda mengonsumsi obat untuk mengobati irama jantung yang abnormal (misalnya amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
- Jika Anda mengonsumsi obat untuk mengobati psikosis (misalnya phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, atau thioridazine) atau depresi.
- Jika Anda mengonsumsi obat antimikroba tertentu (misalnya erythromycin, clarithromycin, moxifloxacin, sparfloxacin, pentamidine, atau saquinavir).
- Jika Anda mengonsumsi obat antijamur triazole (misalnya fluconazole, itraconazole, voriconazole).
- Jika Anda mengonsumsi obat tertentu untuk mengobati reaksi alergi (misalnya terfenadine, astemizole, mizolastine).
- Jika Anda mengonsumsi obat salah satu dari ini: cisapride (dikonsumsi untuk mengobati gangguan perut), droperidol (dikonsumsi untuk mengobati muntah dan migrain), domperidone (dikonsumsi untuk mengatasi mual dan muntah), diphemanil (dikonsumsi untuk mengobati gangguan perut atau keringat berlebihan), probucol (menurunkan kadar kolesterol dalam aliran darah), levomethadyl atau methadone (dikonsumsi untuk pengobatan kecanduan opiate), alkaloid vinca (obat anti kanker), atau arsenic trioksida (dikonsumsi untuk mengobati leukemia jenis tertentu ).
- Jika Anda mengonsumsi obat HIV mengandung lopinavir/ritonavir.
  Anda mungkin lebih berisiko mengalami perubahan ritme jantung yang berbahaya.

**Deltyba mengandung lactose monohydrate.**
Jika Anda diinformasikan dokter Anda bahwa Anda mempunyai intoleransi pada beberapa jenis gula, hubungi dokter sebelum mengonsumsi produk ini.

**Apakah memungkinkan obat ini dikonsumsi selama masa kehamilan dan menyusui?**

**Kehamilan dan masa menyusui**
Deltyba dapat membahayakan bayi yang belum lahir. Umumnya tidak direkomendasikan untuk dikonsumsi selama masa kehamilan. Penting untuk diinformasikan kepada dokter bila Anda sedang hamil atau ada kemungkinan hamil atau sedang merencanakan untuk hamil. Dokter Anda akan mempertimbangkan antara manfaat untuk Anda dibandingkan dengan resiko untuk bayi Anda dengan mengonsumsi Deltyba saat Anda hamil.
Saat ini tidak diketahui apakah delamanid melewati ASI. Menyusui tidak direkomendasikan selama pengobatan dengan Deltyba.

**Apa yang harus saya hindari saat menerima DELTYBA?**
**Mengemudi dan menggunakan mesin**
Deltyba diharapkan tidak memengaruhi kemampuan Anda untuk mengemudi dan menggunakan mesin. Jika Anda mengalami efek samping yang mungkin memengaruhi kemampuan Anda untuk berkonsentrasi dan bereaksi, jangan mengemudi atau menggunakan mesin.

**Apa efek samping yang mungkin dari DELTYBA?**
Seperti semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.
Frekuensi efek samping yang tercantum di bawah ini dapat didefinisikan menggunakan definisi sebagai berikut:
Sangat umum: dapat memengaruhi lebih dari 1 dari 10 orang
Umum: dapat memengaruhi 1 dari 10 orang
Jarang: dapat memengaruhi 1 dari 100 orang

**Efek samping yang sangat umum dilaporkan** dalam studi klinik dengan Deltyba adalah:
- Penurunan nafsu makan
- Gangguan tidur
- Merasa pusing
- Merasa mual
- Sakit kepala
- Iritasi lambung (gastritis)
- Muntah

**Efek samping yang umumnya dilaporkan** dalam studi klinik dengan Deltyba adalah:
- Nyeri dada
- Penurunan aktivitas kelenjar tiroid (hipotiroid)
- Gangguan irama jantung yang berakibat pingsan, pusing dan jantung berdebar (perpanjangan QT pada elektrokardiogram)
- Depresi
- Merasa cemas (ansietas)
- Halusinasi (melihat, mendengar atau merasa sesuatu yang tidak ada)*
- Gangguan irama jantung (atrioventrikular blok derajat 1)
- Gangguan pencernaan (dispepsia)
- Detak jantung tidak beraturan (extrasistol ventrikular)
- Lemah otot

- Kejang otot
- Kebas, penurunan sensasi rasa di tangan dan/atau kaki (hipoestesia)
- Jantung berdebar (palpitasi)
- Peningkatan kadar kortisol darah
- Gemetar (sering pada tangan) (tremor)
- Gangguan kejiwaan: hilangnya kontak dengan realitas, seperti mendengar suara atau melihat sesuatu yang tidak ada
- Iritasi tenggorokan
- Resistensi obat

*Kasus paling banyak dilaporkan pada anak-anak

**Efek samping yang jarang dilaporkan** dalam studi klinik dengan Deltyba adalah:
• Kelesuan (letargi)

**Pelaporan Efek Samping**
Jika Anda mengalami efek samping, bicarakan pada dokter, apoteker atau perawat. Ini termasuk efek samping yang mungkin tidak tercantum dalam selebaran ini. Dengan melaporkan efek samping kepada dokter, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

**Bagaimana menyimpan obat ini?**
Simpan obat ini jauh dari pandangan dan jangkauan anak-anak.
Jangan mengonsumsi obat ini setelah tanggal kadaluarsa yang tercantum pada dus atau blister setelah "EXP". Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.
Simpan dalam kemasan asli untuk melindungi dari kelembaban.
Jangan membuang obat apapun melalui air buangan atau limbah rumah tangga.
Tanyakan apoteker Anda bagaimana cara membuang obat yang sudah tidak dikonsumsi.
Tindakan-tindakan ini akan membantu melindungi lingkungan.
Simpan dibawah temperatur 30 °C [86 °F]. Jangan dibekukan.

**Kemasan**
Dus, 6 blister @ 10 tablet salut film

**Reg Number DKI1956102017A1**

**HARUS DENGAN RESEP DOKTER**

Otsuka

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