

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Deltyba 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg delamanid.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Round, yellow, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4.2, 4.4 and 5.1).

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

4.2 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 4.4 and 5.1). 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).

Posology

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

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 4.4 and 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 (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of delamanid in children and adolescents below 18 years has not yet been established.

No data are available.

Method of administration

For oral use.

Delamanid should be taken with food.

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 \geq 2.8 g/dL)
- Taking medicinal products that are strong inducers of CYP3A4 (e.g. carbamazepine).

4.4 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*.

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.

Resistance to delamanid has occurred during treatment. The risk of selecting for resistance to delamanid appears to be increased when it is used with few agents predicted to be active and/or when these additional agents were not among those deemed to be most effective against *M. tuberculosis*. In addition, limited clinical data indicate that the addition of delamanid to regimens for treating MDR-TB that were resistant to rifampicin and isoniazid but otherwise susceptible, gave the highest efficacy whereas use of delamanid as part of the best available regimens that could be constructed for treating XDR-TB was associated with the lowest efficacy.

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).

Magnitude of QT interval prolongation effect

In a placebo controlled study in MDR-TB patients receiving 100 mg delamanid twice daily the mean placebo corrected increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months. 3% of patients experienced an increase of 60 ms or greater at some point during the trial and 1 patient exhibited a QTcF

interval > 500 ms (see section 4.8). No cases of Torsades de Pointes or temporally related events suggestive of proarrhythmias occurred.

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, 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 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 or QTc > 500 ms.
- 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 hypokalaemia, hypocalcaemia or hypomagnesaemia.
- 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 4.4 regarding use with other fluoroquinolones)
 - triazole antifungal agents
 - pentamidine
 - saquinavir
 - Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
- Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

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 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 4.2 and 5.2).

HIV-infected patients

There is no experience of the use of delamanid in patients receiving concomitant therapy against HIV (see section 4.5).

Limitation of data on the efficacy of delamanid

Current evidence is derived from one randomised controlled trial of 2 months duration and an open extension trial of 6 month duration in addition to long-term outcome collected after end of MDR-TB treatment (see section 5.1).

Biotransformation and elimination

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.

Excipients

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

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 Deltyba

Cytochrome P450 3A4 inducers

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.

Anti-HIV medicines

In clinical drug-drug interaction studies in healthy subjects, delamanid was administered alone (100 mg twice daily) and with tenofovir (300 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 and efavirenz but was slightly increased with the combination anti-HIV medicine containing lopinavir/ritonavir.

Effects of Deltyba 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 (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 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.

Anti-HIV medicines

In a clinical drug-drug interaction study in healthy subjects, delamanid was administered alone (100 mg twice daily) and tenofovir (300 mg), lopinavir/ritonavir (400/100 mg) for 14 days and with efavirenz for 10 days (600 mg daily). Delamanid given in combination with the anti-HIV-medicines, tenofovir, lopinavir/ritonavir and efavirenz, did not affect the exposure 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 4.4). 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

4.6 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 5.3).

Deltyba is not recommended in pregnant women or in women of childbearing potential unless they are using a reliable form of 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 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

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 and tremor are very common).

4.8 Undesirable effects

Summary of the safety profile

The frequency of the adverse drug reactions described below is based on data of one double blind controlled clinical trial involving 481 patients with MDR-TB, in which 321 patients received delamanid in combination with an Optimised Background Regimen (OBR). Due to the limited size of this dataset it is currently not possible to clearly differentiate between OBR therapy and delamanid as cause for the adverse reactions mentioned below.

Electrocardiogram QTc interval prolongation has been identified as the most prominent safety concern of treatment with delamanid (see also section 4.4). A major factor contributing to QTc interval prolongation is

hypoalbuminaemia (particularly below 2.8 g/dl). Other important adverse drug reactions are anxiety, paraesthesia, and tremor.

The most frequently observed adverse drug reactions in patients treated with delamanid (i.e. incidence > 10%) are nausea (38.3%), vomiting (33%), and dizziness (30.2%).

Tabulated list of adverse reactions

The adverse reactions listed in the table below were reported in at least one of the 321 patients receiving delamanid in the double blind placebo controlled clinical trial mentioned above. 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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 drug reactions to delamanid

System Organ Class	Frequency uncommon	Frequency common	Frequency very common
Infections and infestations	Herpes zoster Oropharyngeal candidiasis Tinea versicolor*		
Blood and lymphatic system disorders	Leukopenia Thrombocytopaenia	Anaemia* Eosinophilia*	Reticulocytosis
Metabolism and nutrition disorders	Dehydration Hypocalcaemia Hypercholesterolaemia	Hypertriglyceridaemia	Hypokalaemia Decreased appetite Hyperuricaemia*
Psychiatric disorders	Aggression Delusional disorder, persecutory type Panic disorder Adjustment disorder with depressed mood Neurosis Dysphoria Mental disorder Sleep disorder Libido increased*	Psychotic disorder Agitation Anxiety and anxiety disorder Depression and depressed mood Restlessness	Insomnia
Nervous system disorders	Lethargy Balance disorder Radicular pain Poor quality sleep	Neuropathy peripheral Somnolence* Hypoesthesia	Dizziness* Headache Paraesthesia Tremor
Eye disorders	Conjunctivitis allergic*	Dry eye* Photophobia	
Ear and labyrinth disorders		Ear pain	Tinnitus
Cardiac disorders	Atrioventricular block first degree Ventricular extrasystoles* Supraventricular extrasystoles		Palpitations
Vascular disorders		Hypertension Hypotension	

		Haematoma* Hot flush*	
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough Oropharyngeal pain Throat irritation Dry throat* Rhinorrhoea*	Haemoptysis
Gastrointestinal disorders	Dysphagia Paraesthesia oral Abdominal tenderness*	Gastritis* Constipation* Abdominal pain Abdominal pain lower Dyspepsia Abdominal discomfort	Vomiting Diarrhoea* Nausea Abdominal pain upper
Hepatobiliary disorders	Hepatic function abnormal		
Skin and subcutaneous tissue disorders	Alopecia* Eosinophilic pustular folliculitis* Pruritus generalised* Rash erythematous	Dermatitis Urticaria Rash pruritic* Pruritus* Rash maculo-papular* Rash* Acne Hyperhidrosis	
Musculoskeletal and connective tissue disorders		Osteochondrosis Muscular weakness Musculoskeletal pain* Flank pain Pain in extremity	Arthralgia* Myalgia*
Renal and urinary disorders	Urinary retention Dysuria* Nocturia	Haematuria*	
General disorders and administration site conditions	Feeling hot	Pyrexia* Chest pain Malaise Chest discomfort* Oedema peripheral*	Asthenia
Investigations	Electrocardiogram ST segment depression Transaminases increased* Activated partial thromboplastin time prolonged* Gamma-glutamyltransferase increased* Blood cortisol decreased Blood pressure increased	Blood cortisol increased	Electrocardiogram QT prolonged

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

Description of selected adverse reactions

ECG QT interval prolongation

Electrocardiogram QT prolonged was reported in 9.9% of patients receiving delamanid as 100 mg twice daily (frequency category common) compared to 3.8% of patients receiving placebo + OBR. This ADR was not accompanied by clinical symptoms. The incidence of a QTcF interval >500 msec was uncommon and

observed in one patient (1/321 patients). There were no accompanying clinical symptoms and the event resolved. A total of 12/321 patients in the total delamanid twice daily + OBR group had a change in QTcF of >60 ms versus 0% on placebo + OBR. The presence of hypoalbuminaemia was associated with an increased risk of prolongation of the QTc interval (see section 4.4). QTc interval prolongation has been identified as the most prominent safety concern of treatment with delamanid. This results in the contraindication described in section 4.3 and in the warnings in section 4.4. Major factors contributing to QTc interval prolongation are hypoalbuminaemia (particularly below 2.8 g/dL) and hypokalaemia. Therefore very frequent monitoring of albumin levels, serum electrolytes and ECG is recommended.

Palpitations

For patients receiving 100 mg delamanid + OBR twice daily, the frequency was 8.1% (frequency category common) in comparison to a frequency of 6.3% in patients receiving placebo + OBR twice daily.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

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. 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.

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 (see section 4.4). 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

In a single, double blind, placebo controlled study, 161 MDR-TB patients received 8 weeks treatment with delamanid 100 mg twice daily in combination with WHO recommended individualised OBR. Two-month sputum conversion (SCC) (i.e. growth of *Mycobacterium tuberculosis* to no growth over the first 2 months) observed among those patients who were sputum culture positive at baseline is tabulated below for the delamanid plus OBR and placebo plus OBR treatment groups:

	Patients randomised to 100 mg BID + OBR	Patients randomised to Placebo + OBR
SCC in MGIT [®] n/N (%)	64/141 (45.4%)	37/125 (29.6%)
SCC on solid media n/N (%)	64/119 (53.8%)	38/113 (33.6%)

MGIT[®] Mycobacterium growth indicator tube liquid media system
n= subjects with SCC at 2 months

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Delyba in one or more subsets of the paediatric population in {treatment in multi-drug resistant tuberculosis} (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

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 $\geq 99.5\%$. Delamanid has a large apparent volume of distribution (V_z/F of 2,100 L).

Biotransformation

Delamanid is primarily metabolised 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.

Elimination

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

Special populations

Paediatric population

No studies have been performed in paediatric patients.

Patients with renal impairment

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

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 that of the blood.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose phthalate

Povidone

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)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister:
48 tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Novel Products GmbH
Erika-Mann-Straße 21
80636 München
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/875/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 April 2014
Date of latest renewal: 3 March 2017

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Otsuka Novel Products GmbH
Erika-Mann-Straße 21
80636 München
Germany

AndersonBrecon (UK) Ltd.
Wye Valley Business Park
Brecon Road
Hay-on-Wye
Hereford
HR3 5PG
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH should agree the educational material with the Member States, prior to launch.

In each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority and implement it prior to launch.

The MAH shall ensure that all healthcare professionals involved in the prescribing, dispensing, handling or administration of Deltyba are provided with educational material.

1. The Educational material for Healthcare Providers (HCPs) shall address the following key elements:

- SmPC
- Drug- resistance
- Risk of QT interval prolongation
- Drug use during pregnancy
- Drug use during breast feeding.

2. The educational material for Patients to be provided via the HCPs to reinforce and supplement the information provided in the patient information leaflet. It shall address the following key elements:

- Drug use during pregnancy
- Drug use during breast feeding.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To complete a confirmatory trial examining delamanid added to optimal background regimen in licensed indication: Phase 3 trial comparing delamanid 100 mg BID for 2 months + 200 mg QD for 4 months plus OBR for 18-24 months versus OBR for 18-24 months with placebo for the first 6 months.	Submission of final report: By 2Q2017
To resolve the uncertainties around exposure and antimicrobial activity, by conducting a further study exploring the relationship between different doses with respect to 2 months SCC and longer term outcome : to perform a controlled study of the efficacy, safety and pharmacokinetics of delamanid 100 mg twice daily for 2 months followed by delamanid 200 mg in a single daily dose for 4 months or delamanid 400 mg single daily dose for 6 months in adult patients with pulmonary multidrug-resistant tuberculosis, based on a CHMP-agreed protocol.	Submission of final report: By 4Q2021

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR BLISTER PACKS

1. NAME OF THE MEDICINAL PRODUCT

Deltyba 50 mg film-coated tablets
delamanid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: 50 mg delamanid

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

48 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

None

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Novel Products GmbH
Erika-Mann-Straße 21, 80636 München
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/875/004

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Deltyba 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Aluminium/Aluminium

1. NAME OF THE MEDICINAL PRODUCT

Deltyba 50 mg film-coated tablets
delamanid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Short title: OTSUKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

LOT

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Deltyba 50 mg film-coated tablets delamanid

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Deltyba is and what it is used for
2. What you need to know before you take Deltyba
3. How to take Deltyba
4. Possible side effects
5. How to store Deltyba
6. Contents of the pack and other information

1. What Deltyba is and what it is used for

Deltyba contains the active substance delamanid, an antibiotic for the treatment of tuberculosis in the lung caused by bacteria that are not killed by the most commonly used antibiotics to treat tuberculosis.

2. What you need to know before you take Deltyba

Do not take Deltyba:

- if you are allergic to delamanid or any of the other ingredients of this medicine (listed in section 6).
- if you have very low levels of albumin, in the blood.
- if you are taking medicines that strongly induce a certain liver enzyme called “CYP450 3A4” (e.g. carbamazepine).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Deltyba.

Before you start taking Deltyba, and during the treatment, your doctor may check your heart's electrical activity using an ECG (electrocardiogram) machine (electrical recording of the heart). Your doctor may also perform a blood test to check the concentration of some minerals and proteins which are important for the function of your heart.

Tell your doctor if you have one of the following conditions:

- you have reduced levels of albumin, potassium, magnesium or calcium in the blood
- you have been told that you have heart problems, for example a slow heart rhythm (bradycardia) or have a history of heart attack (myocardial infarction)
- if you have a condition called congenital long QT syndrome or have a serious heart disease or problems with heart rhythm.
- you have liver disease or kidney disease.
- you have HIV.

Children

Deltyba is not suitable for children under age 18.

Other medicines and Deltyba

Tell your doctor...

- if you are taking, have recently taken or might take any other medicines, including medicines or herbal remedies obtained without prescription,
- if you are taking medicines to treat an abnormal heart rhythm (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
- if you are taking medicines to treat psychoses (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine) or depression
- if you are taking certain antimicrobial medicines (e.g. erythromycin, clarithromycin, moxifloxacin, sparfloracin, pentamidine, or saquinavir).
- if you are taking triazole antifungal medicines (e.g. fluconazole, itraconazole, voriconazole).
- if you are taking certain medicines to treat allergic reactions (e.g. terfenadine, astemizole, mizolastine).
- if you are taking any of the following: cisapride (used to treat stomach disorders), droperidol (used against vomiting and migraine), domperidone (used against nausea and vomiting), diphemanil (used to treat stomach disorders or excessive sweating), probucol (lowers the level of cholesterol in the bloodstream), levomethadyl or methadone (used for the treatment of opiate addiction), vinca alkaloids (anti-cancer medicines), or arsenic trioxide (used to treat certain types of leukaemia).
- if you are taking HIV-medicines containing lopinavir/ritonavir.

You may be more at risk for dangerous changes of the heart rhythm.

Pregnancy and breast-feeding

Deltyba may cause harm to an unborn baby. It is not usually recommended for use during pregnancy.

It is important to tell your doctor if you are pregnant, think you may be pregnant, or are planning to get pregnant. Your doctor will weigh up the benefits to you against the risks to your baby of taking Deltyba whilst you are pregnant.

It is not known if delamanid passes into breast milk in humans. Breast-feeding is not recommended during treatment with Deltyba.

Driving and using machines

Deltyba is not expected to have an influence on your ability to drive and use machines. If you experience side effects that might affect your ability to concentrate and react, do not drive or use machines.

Deltyba contains lactose monohydrate.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Deltyba

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is two 50 mg tablets taken twice a day (morning and evening) as advised by your doctor. The tablets should be taken during or just after a meal. Swallow the tablets with water.

If you take more Deltyba than you should

If you have taken more tablets than your prescribed dose, contact your doctor or your local hospital. Remember to take the pack with you so that it is clear what medicine you have taken.

If you forget to take Deltyba

If you forget a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, just skip the missed dose.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Delyba

DO NOT stop taking the tablets unless your doctor tells you to. Stopping too early could allow the bacteria to recover and to become resistant to delamanid.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The frequency of the side effects listed below is defined using the following definitions:

Very common: may affect more than 1 in 10 people

Common: may affect up to 1 in 10 people

Uncommon: may affect up to 1 in 100 people

Side effects very commonly reported in clinical studies with Delyba were:

- Sensations of irregular and/or forceful beating of the heart
- Vomiting
- Nausea
- Diarrhoea
- Stomach pain
- Headache
- A tingling, burning or pricking sensation or numbness of the skin (paresthesia)
- Shaking (tremor)
- Decreased appetite
- Dizziness
- Hearing a persistent sound in your ear when no sound exists (tinnitus)
- Intense lack of energy
- Joint or muscle pain
- Difficulties with falling or staying asleep
- Increase in immature red blood cells
- Low blood potassium level
- Increased blood uric acid level
- Coughing up blood
- Changes found in investigations (electrocardiogram, ECG) of the heart

Side effects commonly reported in clinical studies with Delyba were:

- Anaemia
- Increase of certain white blood cells (eosinophilia)
- Increased blood tryglycerides
- Psychotic disorder
- Agitation
- Anxiety
- Depression
- Restlessness
- Nerve damage causing numbness or pain (burning) or tingling feeling in hands or feet
- Drowsiness
- Reduced sensation
- Dry eye
- Decreased tolerability of the eyes for bright light
- Ear pain
- Increase of blood pressure (hypertension)

- Decrease of blood pressure (hypotension)
- Bruising
- Hot flushes
- Shortness of breath
- Cough
- Pain in the mouth or throat
- Throat irritation
- Dry throat
- Runny nose
- Chest pain
- Gastritis
- Constipation
- Indigestion
- Dermatitis
- Hives
- Itching
- Papules (small skin elevations)
- Rash
- Acne
- Increased sweating
- A bone disease called osteochondrosis
- Muscular weakness
- Pain in bones
- Flank pain
- Pain in arms or legs
- Blood in urine
- Fever
- Chest pain
- Feeling unwell
- Chest discomfort
- Foot, leg or ankle swelling
- Increased values for blood investigations for the hormone cortisol

Side effects uncommonly reported in clinical studies with Delyba were:

- Shingles
- Oral thrush
- Yeast infection of the skin (tinea versicolor)
- Low white blood cell count (leukopenia)
- Low blood platelets count (thrombocytopaenia)
- Dehydration
- Low blood calcium level
- High blood cholesterol level
- Aggression
- Paranoia
- Panic attacks
- Adjustment disorder with depressed mood
- Neurosis
- Feeling of emotional and mental discomfort
- Mental aberration
- Problems with sleeping
- Increase of libido
- Lethargy
- Balance disorder
- Regional pain

- Allergic conjunctivitis
- Heart rhythm problems
- Swallowing problems
- Abnormal feeling in the mouth
- Tenderness in the abdomen
- Hair loss
- Itchy or red skin including around the hair roots.
- Urine retention
- Painful urination
- Increased need to urinate at night
- Feeling hot
- Abnormal values for blood investigations related to coagulation (prolonged APPT)
- Abnormal blood values related to the function of the liver, biliary system or pancreas
- Decreased values for blood investigations for the hormone cortisol
- Increased blood pressure

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Delyba

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or bottle after “EXP:”. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Delyba contains

- One film-coated tablet contains 50 mg of the active substance delamanid.
- The other ingredients are hypromellose phthalate, povidone, all-rac- α -tocopherol, microcrystalline cellulose, sodium starch glycolate, carmellose calcium, colloidal hydrated silica, magnesium stearate, lactose monohydrate, hypromellose, macrogol 8000, titanium dioxide, talc, iron oxide (E172).

What Delyba looks like and contents of the pack

Delyba 50 mg film-coated tablets are round, and yellow.

Delyba is supplied in packs of 48 film-coated tablets in aluminium/aluminium blisters.

Marketing Authorisation Holder and Manufacturer

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Manufacturer
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This leaflet was last revised in <{MM/YYYY}>.

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.