DELAMANID

DELTYBA ®

50 mg Film-coated tablets
Anti-tuberculosis (Multi-Drug Resistant Tuberculosis)

Formulation:

Each film-coated tablet contains 50 mg delamanid.
Excipient with known effect: each film-coated tablet contains 100 mg lactose (as monohydrate).

Product Description:

Round, yellow, film-coated tablet, 11.7 mm in diameter.

INDICATIONS:

Delamanid (Deltyba) is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, 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.

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

DOSAGE AND ADMINISTRATION:

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

Delamanid (Deltyba) must always be administered as part of an appropriate combination regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB). 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 (Deltyba) is administered by directly observed therapy (DOT).

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.

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.

Use in Specific Populations

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 (Deltyba) in patients with severe renal impairment and its use is not recommended *(see Pharmacokinetics).*

Hepatic impairment
No dose adjustment is considered necessary in patients with mild hepatic impairment. Delamanid (Deltyba) is not recommended in patients with moderate to severe hepatic impairment *(see Warnings and Precautions and Pharmacokinetics).*

Elderly patients (> 65 years of age)
No data are available in the elderly.

Method of Administration
For oral use.
Delamanid should be taken with food.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients (see Important Precautions).

Serum albumin < 2.8 g/dL (see Warnings and Precautions regarding use in patients with serum albumin ≥2.8 g/dL)

Taking medicinal products that are strong inducers of CYP3A4 (e.g. carbamazepine).

WARNINGS AND PRECAUTIONS:

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.

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 therafter. 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 Important Precautions 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, are obtained at baseline and corrected if abnormal.

Important Precautions

Cardiac risk factors
Treatment with delamanid should not be initiated in patients with the following risk factors unless the possible benefit of delamanid is considerd 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 Important Precautions regarding use with other fluoroquinolones)*
  - bedaquiline
  - triazole antifungal agents
  - 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
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 Contraindications). 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 coadministration 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 coadministration is considered to be unavoidable in order to construct an adequate treatment regimen for MDRTB it is recommended that there is very frequent monitoring of ECGs throughout the full delamanid treatment period.

Hepatic impairment
Delamanid (Deltyba) is not recommended in patients with moderate to severe hepatic impairment (*see Special Populations and Pharmacokinetics).*

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

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
Delamanid (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.

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).

DRUG INTERACTIONS:

The complete metabolic profile and mode of elimination of delamanid has not yet been fully elucidated *(see Important Precautions and Pharmacokinetics).*

Effects of other medicinal products on Delamanid (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 Delamanid (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(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 delamanid to have an effect on these transporters.

Anti-Tuberculosis medicines
In a clinical drug-drug interaction study in healthy subjects, delamanid was administred 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 administred 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 Warnings and Precautions)*. 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.

ADVERSE REACTIONS:

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%).

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.

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* Hypoaesthesia	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	ElectrocardiogramQT prolonged

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

Other 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 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.

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.

USE IN SPECIFIC POPULATION:

Pregnancy
There are very limited data from the use of delamanid in pregnant women. Studies in animals have shown reproductive toxicity *(see Preclinical Safety data).*
Delamanid (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 breastfeeding infant cannot be ruled out, it is recommended that women should not breastfeed during treatment with Delamanid (Deltyba).

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

OVERDOSAGE:

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.

CLINICAL PHARMACOLOGY:

Mechanism 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 antimycobacterial activity.

Pharmacodynamics

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

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 Warnings and Precautions). Delamanid does not show cross-resistance with any of the currently used anti-tuberculosis drugs.

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.

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).
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.

PHARMACOKINETICS:

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.

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).

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 antimycobacterial 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.

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

Special Populations

Paediatric population

During treatment with the recommended delamanid doses to adolescents and children with a body weight of at least 30 kg, 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 (50 mL/min < CrCLN < 80 mL/min) does not appear to affect delamanid exposure. Therefore no dose adjustment is needed for patients with mild or moderate renal impairment. It is not known whether delamanid and metabolites will be significantly removed by haemodialysis or peritoneal dialysis.

Patients with hepatic impairment

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

Elderly patients (≥ 65 years)

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

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 repeatdose 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 Kdependent 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 Cmax for delamanid in breast milk was 4-fold higher than that of the blood. In juvenile toxicity studies in rats, all delamanid treatment-related findings were consistent with those noted in adult animals.

PHYSICOCHEMISTRY:

Non-proprietary name:
Delamanid

Chemical name:

r-INN: (2*R*)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1- yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole

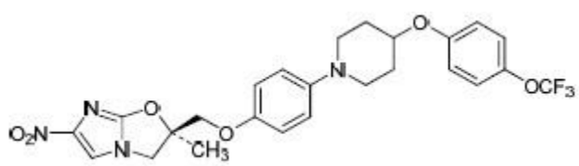
USAN, JAN: (2*R*)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1- yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*]oxazole

Molecular formula:
$C_{25}H_{25}F_3N_4O_6$

Molecular weight:
534.48

Structural formula:

r-INN, USAN:



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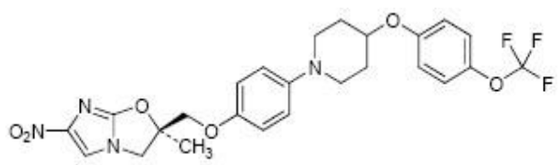

PACKAGING/AVAILABILITY:
Blister pack (Box of 48's)

STORAGE AND HANDLING:
Store at temperatures not exceeding 30°C.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

FDA REGISTRATION NO.
DR-XY46031

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