

## REVIEW ARTICLE

# Delamanid- A Relatively New Anti-Tuberculosis Drug

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## Abstract

**Background:** Tuberculosis (TB) is a global health problem which occurs in every part of the world. It is a curable and preventable bacterial infectious disease caused by *Mycobacterium tuberculosis*, still it is prevalent. Emergence of MDR and XDR-TB made the picture more complicated. Hence search for new drugs are going on to address the problem. Delamanid is a relatively new drug developed to tackle the situation. **Methods:** Medline database was searched using the keywords like Delamanid, Tuberculosis, New anti TB drugs, Multi drug resistant tuberculosis (MDR-TB), XDR-TB to find out the articles related with Delamanid. **Results:** The literature indicates that Delamanid is a good drug along with other appropriate anti TB drugs for the management of multi drug resistant tuberculosis. **Conclusion:** Delamanid in the dose of 100mg twice daily along with other appropriate anti TB drugs is recommended for the management of pulmonary multi drug resistant tuberculosis. It is relatively safe drug as have less adverse drug reactions and drug interactions.

**Keywords:** Delamanid, MDR-TB, XDR-TB, Tuberculosis.

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## Introduction

Tuberculosis (TB) is a global health problem which occurs in every part of the world. It is a curable and preventable bacterial infectious disease caused by *Mycobacterium tuberculosis*. Most commonly lungs are affected with Tuberculosis although other organs can also be affected by it.<sup>1</sup>

Among the top 10 leading causes of death all over the world, it is one of them with more than 95% deaths occurs in low to middle income developing countries. In the year of 2016, around 10.4 million people globally affected with it and 1.7 million death occurred in that year with it. Among the category of children, 1 million children fell ill with it and 250000 died in that year of 2016.<sup>1</sup>

Although more than 85% cases of susceptible TB can be treated successfully with the use of WHO recommended 1<sup>st</sup> line drugs- Rifampicin, Isoniazid, Ethambutol and Pyrazinamide but still multidrug resistant TB (MDR-TB) is emerging. There are many causes behind the emergence of MDR-TB, amongst them improper use of

effective anti TB therapy, incorrect prescription by health care provider, poor quality of drugs and premature stoppage of therapy are few.<sup>1,2</sup>

MDR-TB is treatable and curable with the use of second line anti TB drugs although it is difficult to treat with main 1<sup>st</sup> line drugs particularly it has resistant against most important drugs Isoniazid and Rifampicin.<sup>1,2</sup> According to WHO it is a serious threat to public health. In the year of 2016, around 600000 new cases of Rifampicin resistant were estimated amongst them 490000 were diagnosed as MDR-TB cases.<sup>1</sup>

Extensively drug-resistant TB (XDR-TB) is a more serious form of MDR-TB caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options. About 6.2% of MDR-TB cases had XDR-TB in 2016.<sup>1</sup> There are very few options are available to treat XDR-TB amongst them some cases cannot be treated.<sup>3</sup>

To eradicate TB, new strategies should be adopted. In the strategies, development of new drugs is essential. Research is going on for development of new anti TB drugs.<sup>4</sup> Delamanid

a relatively new drug, which have the property of early bactericidal activity.<sup>5</sup> In this paper we have tried to review the properties of Delamanid, a relatively new anti TB drug.

### Delamanid History

Otsuka Pharmaceutical Co., Ltd. was involved in anti TB drug development program since early 1990s. They developed Delamanid which is a bicyclic nitroimidazole and 1<sup>st</sup> in its class. It was approved by the European Medicines Agency (EMA) in 2014 for the treatment of adult pulmonary multi-drug resistant (MDR)-TB. Since then several other countries approved it for the management of multidrug resistant TB along with other anti TB drugs.<sup>6</sup>

### Delamanid Structure

Delamanid is a dihydro-nitroimidazooxazole derivative. The chemical name of Delamanid 681492-22-8; OPC-67683; UNII-800T6M1PC7; 800T6M1PC7; MMV688262. It has molecular weight of 534.492 g/mol. The molecular formula is C<sub>25</sub>H<sub>25</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub>.<sup>7</sup>

### Absorption

It has poor water solubility. Usual 100mg dose of Delamanid in adult patient achieve peak plasma concentration upto 135ng/mL.<sup>6</sup> In animal studies involving rat, peak blood and all tissues concentration was achieved by 8 or 24 hours post dose.<sup>8</sup> After 10-14 days steady-state plasma concentration is achieved. Absolute oral bioavailability in human being is in between 35% to 60%. Oral bioavailability increases when taken with meals.<sup>6</sup>

### Distribution

It is widely distributed in various tissues, including the breast milk, lungs, central nervous system, eyeball, placenta and fetus. 2100 L is found to be its apparent volume of distribution. It's C<sub>max</sub> in breast milk is 4 times higher than that of blood.<sup>6,8</sup> It is a drug of highly plasma protein binding ability (around 99.5%).<sup>6,8,9</sup>

### Metabolism and Elimination

It is primarily metabolized by serum albumin and by lesser extent in liver by CYP3A4. After metabolism 4 major metabolites are formed which are without significant pharmacological activities. But the main metabolite may cause prolongation of QT interval. It has biological half life of 30 to 38 hours. The main route of

elimination is biliary route. Approximately 95% drug is eliminated by this route while around 5% is eliminated by kidneys.<sup>6,8</sup>

### Mechanism of action

Delamanid is a prodrug which is converted into active form with the help of mycobacterial F420 coenzyme system. It has mycobacteriocidal activity against both growing and nongrowing mycobacteria. Active intermediate formed is responsible for inhibition of methoxy-mycolic and keto-mycolic acid synthesis. It leads to deficient mycobacterial cell wall components which is ultimately responsible for destruction of mycobacteria. Delamanid has 0.006 to 0.024 g/mL minimum inhibitory concentration. Mutations in coenzyme F420 genes can be responsible for drug resistance.<sup>6</sup>

### Adverse Drug Reactions

Delamanid may cause prolongation of QT interval with repeated dosing. This reaction is usually observed with 200mg twice daily dose rather than 100mg dosing. The main metabolite can inhibit cardiac potassium channel (hERG) which is responsible for QT interval prolongation. It is with mild to moderate severity without any episode of syncope and arrhythmia.<sup>6,10,11</sup> Animal study data suggests that Delamanid may cause decrease in vitamin K-dependent blood clotting, increase prothrombin time (PT), and activated partial thromboplastin time (APTT).<sup>6</sup>

### Drug Interactions

Other 2<sup>nd</sup> line anti TB drugs like fluoroquinolones and clofazimine, may increase the chances of cardiotoxicity. Research data also suggest prolongation of QT interval when levofloxacin is concomitantly administered. But there is no study suggesting drug interaction when moxifloxacin and/or clofazimine when concomitantly administered. There is no data available to suggest QT interval prolongation with the use of antiretroviral drugs such as ritonavir etc. along with Delamanid. But co-administration of Delamanid with drugs which are strong inhibitor of CYP3A4 such as lopinavir/ritonavir have 30% higher exposure risk to the Delamanid metabolite DM-6705, which has been associated with QTc prolongation.<sup>12,13,14</sup>

### Contraindications and precautions

Hypersensitivity to Delamanid is contraindication for its use. Use of Delamanid in hypoalbuminaemia is also another contraindication. Use during lactation and pregnancy is not recommended. There is no data available for its use in elderly patient and in children and adolescents below 18 years. Mild to moderate renal impairment and mild hepatic impairment doesn't suggest Delamanid dose adjustment. But in severe renal impairment and moderate to severe hepatic impairment, Delamanid is not recommended.<sup>14</sup>

### Indications

It is indicated for use as a part of an appropriate combination regimen for pulmonary MDR-TB in adult patients in whom the current approved regimen cannot be used because of resistance or intolerance.<sup>15</sup>

### Dosage

WHO recommended 100mg twice daily dose of Delamanid irrespective of body weight for a period of six months. It should be given along with meal as food increases bioavailability while other anti TB drugs are taken empty stomach as their absorption is better without food. Moreover, 200mg dose doesn't provide any advantages rather than it may increase the chances of QT interval prolongation. As far as dosing supervision (treatment monitoring) is concerned, it should be adapted twice daily.<sup>12</sup>

### Conclusion

Delamanid is a relatively new anti TB drug. In the dose of 100mg twice daily along with other appropriate anti TB drugs, it is recommended for the management of pulmonary multi drug resistant tuberculosis. It is relatively safe drug as have minimum adverse drug reaction profile and least kind of drug interactions. Delamanid provides important weapon against not only multi drug resistant tuberculosis but also provide better hope against XDR-TB and tuberculosis in HIV patients.

**Conflict of Interest:** None declared

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