The 20th Expert Committee on the Selection and Use of Essential Medicines
Department of Essential Medicines and Health Products
World Health Organization 20 Avenue Appia CH
1211 Geneva 27, Switzerland

11 February 2015

Re: Otsuka Public Comment on the Submission by WHO for the Inclusion of Delamanid in the WHO Model List of Essential Medicines

As the developer, manufacturer, and patent holder of delamanid, Otsuka would like to comment on the WHO submission for inclusion of delamanid in the WHO Model List of Essential Medicines.

We are providing in our response additional information pertinent to relevant sections of the submission, including updated data regarding efficacy, safety, and cost-effectiveness and updated information regarding registration and pricing.

If you have questions or would like to discuss further, please contact us.

Best regards,

[Signature]

Eric Adam
Strategic Alliances Director

cadam@otsuka.ch
Multidrug-resistant tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, is an important obstacle to TB control. In 2013, MDR-TB represented 480,000 incident TB cases worldwide and, as denoted by global experts including the World Health Organization, reflected a critical, global need to develop new anti-TB drugs. Delamanid is a novel nitro-dihydro-imidazooxazole anti-TB drug and one of two newly-approved drugs in the last 40 years for the management of MDR-TB patients. Delamanid’s novel mechanism of action involves inhibition of mycolic acid synthesis and delamanid has demonstrated early bactericidal activity comparable to rifampicin, one of the most potent anti-TB drugs. Delamanid represents a critical advancement in the treatment of MDR-TB patients for two overarching reasons:

- The mechanism of action is novel and the compound represents a new class of anti-TB drugs (nitro-dihydro-imidazooxazole), a critical need in combination therapy for MDR-TB where resistance to individual drugs can lead to within-class resistance.

- Clinical studies involving treatment with delamanid provide evidence of a significant improvement in short and long-term treatment outcomes (including a reduction in mortality) while offering a favorable safety profile and no relevant anti-MDR-TB or anti-retroviral drug-drug interactions.

In the WHO interim policy guidance for the use of delamanid in MDR-TB patients, “WHO recommends that delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB” and there is not a restriction of the recommendation of delamanid for any subset of MDR-TB patients. As the policy guidance notes, “Delamanid is intended to be introduced alongside other anti-TB drugs in composing an effective second-line regimen based on WHO guidelines; further highlighting its importance in the essential management of the estimated close to one-half million patients developing MDR-TB each year.” The evidence base for delamanid includes – to date – the largest completed randomized, placebo-controlled trial in MDR-TB patients.

Delamanid is recommended for the treatment of adult MDR-TB patients in 50mg tablets to be administered as 100mg twice daily for six months.
Section 6: International availability - sources, of possible manufacturers and trade names

Delamanid is registered under the trade name Deltyba®, and is available through Otsuka in the EU, Japan, Republic of Korea, and in individual countries under compassionate use where local regulations allow and proper treatment protocols are in place.
Section 8: Information supporting the public health relevance

• **Assessment of current use**

Delamanid has been evaluated in a total of 887 individuals (healthy subjects, drug susceptible TB patients, and MDR-TB patients) from completed trials for safety including 481 MDR-TB patients for efficacy.

• **Target population**

Delamanid is intended for use in adult pulmonary MDR-TB patients.
**Section 10: Summary of comparative effectiveness in a variety of clinical settings**

- **Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)**

To identify and summarize the available data, information contained in regulatory filings and clinical study reports, unpublished data, and the following references (including not-yet-available references in review and in press) were utilized:


Section 10: Summary of comparative effectiveness in a variety of clinical settings

• Summary of available data (appraisal of quality, outcome measures, summary of results)

Description of clinical development program

The clinical development program for delamanid was sponsored by Otsuka Pharmaceutical and Development Commercialization, Inc., conducted in partnership with national tuberculosis programs (NTPs) and non-governmental organizations (NGOs), and was comprised of three connected clinical trials (see Table 1). In summary, Trial 204 was a three-month randomized, placebo controlled trial to assess patients assigned to treatment for two months with either delamanid plus an optimized background regimen (OBR) designed based on WHO guidelines or a placebo plus OBR or; hospitalization was required for the two-month treatment period of the trial. Trial 208 was an open-label extension [of Trial 204], to allow for any patient completing Trial 204 (i.e. whether initially assigned to placebo or delamanid) to continue treatment with delamanid plus OBR for an additional six months. Trial 116 followed all patients enrolled in Trial 204 (irrespective of participation in Trial 208) for long-term treatment outcomes through 24 months. The trials were conducted from May 2008 through May 2012 at 17 sites in nine countries (China, Egypt, Estonia, Japan, Korea, Latvia, Peru, Philippines and the USA) with 481 patients completing Trial 204 and 421 continuing through Trial 116.
Table 1: Clinical Trials Forming the Basis of Clinical Efficacy

<table>
<thead>
<tr>
<th>Protocol No., Trial Type, and Phase</th>
<th>No. of Sites &amp; Location</th>
<th>Total Start/End Dates</th>
<th>Total Objectives</th>
<th>Trial Design and Type of Control</th>
<th>Test Product(s), Dose, Route, and Regimen</th>
<th>No. of Patients Per Arm Entered/Treated</th>
<th>Treatment Duration</th>
<th>Gender (%) Mean Age (Range), Race (%)</th>
<th>Healthy Patients or Main Inclusion Criteria</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Trial (MDR-TB)</td>
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<tr>
<td>242.67-204 (safety, efficacy)</td>
<td>17/Multinational</td>
<td>May 2009 - Jun 2010</td>
<td>411</td>
<td>Determine safety, efficacy, and PK of two delamanid doses regimens in combination with OBR</td>
<td>Double-blind, randomized (1:1:1) stratified by disease severity, placebo-controlled parallel group trial</td>
<td>Delamanid tablet (SPD) PO (given under fed conditions) 100 mg BID + OBR Placebo BID + OBR Total: 481</td>
<td>56 days</td>
<td>All Patients: 67.4% M; 32.6% F; 38.2 yrs (18-61 yrs); 57.9% Asian; 26.6% Other; 19.9% White; 0.2% Black; Spontaneous culture-positive, multidrug-resistant polycylogenous bacteriologic proportion of patients achieving culture conversion within 56 days; ECG evaluation, and PK parameters for delamanid and metabolites</td>
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<tr>
<td>Uncontrolled Studies (MDR-TB)</td>
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<tr>
<td>242-60-200 (safety, efficacy)</td>
<td>14/Multinational</td>
<td>Mar 2009 - Oct 2011</td>
<td>213</td>
<td>Obtain extended safety data and to evaluate efficacy for an additional 6 months beyond exposure in Trial 242-67-204</td>
<td>Open-label extension trial for patients in Trial 242-67-204</td>
<td>Delamanid 50 mg tablets (SPD) PO 100 mg BID + OBR with optional treatment to 200 mg BID + OBR Total: 213</td>
<td>6 months</td>
<td>All Patients: 75.4% M; 24.6% F; 36.9 yrs (18-61 yrs); 57.9% Asian; 23.3% White; 18.3% Other; Patients who completed Trial 242-67-204, maintained susceptibility to delamanid, and benefited from long-term exposure</td>
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<tr>
<td>242-10-116 (safety, efficacy)</td>
<td>18/Multinational</td>
<td>Feb 2011 - Mar 2012</td>
<td>425</td>
<td>Capture comprehensive long-term data on microbiologic and clinical responses as well as final treatment outcomes from 24-month MDR-TB treatment for patients previously enrolled in Otsuka trials evaluating the effects of delamanid on sputum conversion during the earlier course of MDR-TB treatment</td>
<td>Open-label observational trial to capture final treatment outcomes. Patients with MDR-TB or refractory MDR-TB who have previously received delamanid in a clinical trial or who receive delamanid during post-marketing</td>
<td>NA/OBR only; no delamanid exposure Total: 425 421 from Trial 242-67-204 and 4 from Trial 242-60-200 13</td>
<td>N/A</td>
<td>All Patients: 66.4% M, 33.6% F; 56 yrs (18-63); 53.6% Asian; 20.4% White; 26.4% Other; Patients with MDR-TB previously enrolled in Otsuka trials evaluating the effects of delamanid on sputum conversion during the earlier course of MDR-TB treatment</td>
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**Trial 204**

Trial 204 (N=481) was a randomized double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of 100 mg (N=161) and 200 mg (N=160) delamanid twice daily versus placebo (N=160) when added to OBR. Patients were randomized to receive either delamanid or placebo in combination with an OBR for 8 weeks, and sputum culture status on liquid broth [mycobacterial growth indicator tube (MGIT) system (Becton Dickinson)] and solid medium was assessed weekly for 12 weeks to allow for confirmation of SCC occurring during the 8-week treatment period with delamanid or placebo plus OBR. The primary efficacy outcome was the proportion of patients achieving 2-month SCC. The trial included an additional month of data.
collection under blinded, controlled conditions to allow for confirmation of 2-month SCC and to assess for sustained benefit.

**Trial 208**

Trial 208 (N=213) was an open-label, extension trial for patients who completed Trial 204, and provided 6 months of treatment with delamanid, at either 100mg (n=137) or 200mg (n=76) twice daily for consenting patients. The trial was conducted at the same trial sites that participated in Trial 204, however, investigators remained blinded to patients’ Trial 204 treatment assignments. Sputum cultures were monitored using MGIT and solid media at weeks 1, 2, 4, 6, 10, 14, 18, 22, and 26 (week 1 being the start of Trial 208).

Overall, patients with more severe disease tended to be enrolled in Trial 208 (N=213) compared to those who were not enrolled in the trial (N=268). A higher proportion of patients who participated in Trial 208 versus those who did not participate in the trial had bilateral cavitation on chest radiograph at baseline (29.6% versus 19.4%), a high degree of baseline resistance (pre-XDR-TB and XDR-TB at 38.0% versus 21.0%), and previous treatment with second-line & third-line anti-TB drugs (51.2% versus 28.7%).

**Trial 116**

Trial 116 was a non-interventional trial designed to collect microbiological data and final treatment outcomes for patients who had previously participated in Trial 204 including those who did and did not take part in Trial 208. Patients continued OBR throughout their full treatment period including during participation in this trial. Microbiological data, including results from periodic sputum culture assessments on solid media (as per standard of care for longer-term treatment outcomes during the time frame of when the trial was conducted), was collected from patient visits occurring in the intervals specified on a local basis until 24 months after receiving the first dose of trial medication in Trial 204 (delamanid or placebo), or until the completion of their treatment, whichever occurred first.

**Assessment of Vital Status at 24 Months**

Vital status assessment at 24 months was conducted for nearly all patients (N=464 (96.5%) out of 481 patients randomized in Trial 204, including those who did not participate in Trial 116.

**Results from Clinical Development Program**

The primary endpoint of Trial 204 was the proportion of patients with sputum culture conversion at Day 57 (i.e. two-month SCC) as assessed by the more sensitive mycobacterial growth indicator tube (MGIT, Becton Dickinson) system. The stringent definition used for SCC was five or more consecutive weekly cultures that were negative for growth of M. tuberculosis (without subsequent positive cultures). Early
SCC is a recognized biomarker in tuberculosis and endorsed by Stringent Regulatory Authorities.

Of 481 patients who underwent randomization, 402 (83.6%) had cultures that were positive for multidrug-resistant tuberculosis with the use of MGIT at baseline (the modified intention-to-treat population) and were included in the primary efficacy analysis. Of these 402 patients, the proportion who had sputum-culture conversion with MGIT by 2 months in the group of patients who received delamanid at a dose of 100 mg twice daily was 45.4%, as compared with 29.6% in the placebo group; this represented a statistically significant increase (53%; 95% CI, 11 to 112; P = 0.008) (Figure 1). The proportion who had SCC in the 200-mg group was similar (41.9%) and was significantly higher than that in the placebo group (p=0.03).

**Figure 1: Proportion of Patients with Sputum-Culture Conversion by Day 57**

![Graph showing sputum culture conversion by day 57](image)

An additional key secondary analysis assessed differences among the groups with respect to time to sputum-culture conversion (Figure 2). For this analysis, Kaplan–Meier curves representing the time to conversion according to culture medium type showed 10% separation between the delamanid groups and the placebo group by day 36 with MGIT. By the end of the 2-month treatment period, the difference in sputum-culture conversion between the delamanid groups and the placebo group was significant (p = 0.001 for the comparisons of the 100-mg and 200-mg doses of delamanid with placebo).
Figure 2: Survival Analysis of Days to Sputum-Culture Conversion

Trial 116 evaluated treatment outcomes, as assessed by clinicians and defined by the World Health Organization, were categorised as favourable (cure and treatment completed) and unfavourable (death, defaulter, failure) (Table 2). Delamanid treatment groups were combined for analysis, based on their duration of treatment by virtue of participation in Trial 208. In total, 421 (87.5%) out of 481 patients from Trial 204 participated in Trial 116. Favourable outcomes were observed in 143 (74.5%) out of 192 patients who received delamanid for >=6 months, compared to 126 (55%) out of 229 patients who received delamanid for <=2 months (p<0.001) (Table 2). Mortality was reduced to 1.0% among those receiving long-term delamanid versus short-term/no delamanid (8.3%; p<0.001).

Table 2: Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimized background treatment regimen among patients originally randomized in Trial 242-07-204.

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Long-term treatment</th>
<th>Short-term treatment</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>143 (74.5: 67.7-80.3)</td>
<td>126 (55.0: 48.3-61.6)</td>
<td>269 (63.9: 59.1-68.5)</td>
</tr>
<tr>
<td>Cured</td>
<td>110 (73.3: 50.0-64.4)</td>
<td>111 (48.5: 41.8-55.1)</td>
<td>221 (52.5: 47.6-57.4)</td>
</tr>
<tr>
<td>Completed</td>
<td>33 (17.2: 12.1-23.3)</td>
<td>15 (6.6: 3.7-10.6)</td>
<td>48 (11.4: 8.5-14.8)</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>49 (25.0: 19.5-32.3)</td>
<td>103 (45.0: 36.4-51.7)</td>
<td>152 (36.1: 31.5-40.9)</td>
</tr>
<tr>
<td>Died</td>
<td>2 (1.0: 0.1-3.7)</td>
<td>19 (8.3: 5.1-12.7)</td>
<td>21 (5.0: 3.1-7.5)</td>
</tr>
<tr>
<td>Failed</td>
<td>32 (16.7: 11.7-22.7)</td>
<td>26 (11.4: 7.6-16.2)</td>
<td>58 (13.8: 10.6-17.4)</td>
</tr>
<tr>
<td>Defaulted</td>
<td>15 (7.6: 4.4-12.9)</td>
<td>58 (25.3: 19.8-31.5)</td>
<td>73 (17.2: 13.8-21.3)</td>
</tr>
</tbody>
</table>

Data are presented as n (%; 95% CI). MDR: multidrug-resistant; TB: tuberculosis; XDR: extensively drug-resistant. *: 192 patients received delamanid (100 mg and/or 200 mg twice a day) for at least 6 months; #: 229 patients received delamanid (100 mg or 200 mg twice a day) or placebo for 2 months; n=421. Differences between the long-term and the short-term treatment groups for the corresponding treatment outcome were statistically significant (p<0.001), all other differences did not reach statistical significance (p>0.05).
The assessment of vital status at ≥ 24 months was conducted on 464 (96.5%) of the patients originally enrolled in Trial 204, including 43 patients who did not participate in Trial 116 and were not reflected in the previously reported data (Table 3). From this data, patients treated ≥6 months with delamanid showed a significantly lower proportion of mortality compared to patients received <=2months (12.0% vs 2.9%, p=0.001).

**Table 3: Mortality among MDR-TB Patients Participating in the Delamanid Clinical Development Program**

<table>
<thead>
<tr>
<th>Delamanid Treatment Duration</th>
<th>N</th>
<th>Mortality (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6months</td>
<td>205</td>
<td>6 (2.9%)</td>
<td>0.22 (0.09-0.54)†</td>
</tr>
<tr>
<td>≤2months</td>
<td>259</td>
<td>31 (12.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Total</td>
<td>464</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

# p = 0.001

To assess variation among patients who enrolled in Trial 208 versus those who did not, baseline characteristics generally associated with negative treatment outcomes in MDR-TB patients were assessed for the 44.3% (213/481) of Trial 204 patients who participated in Trial 208 versus the 55.7% (268/481) of Trial 204 patients not entering Trial 208. Bilateral cavitation was present in 29.6% (63/213) of Trial 208 patients compared to 19.4% (52/268) not entering Trial 208. Extensively drug-resistant (were in greater proportion among Trial 208 participants (81/213, 38.0%) compared to non-participants (54/268, 20.1%). Additionally, more patients in Trial 208 were previously treated with second and third-line anti-TB drugs compared to patients not entering Trial 208 (109/213 or 51.2% versus 77/268 or 28.7%). Taken together, the distribution of these factors suggests that patients with more severe disease entered Trial 208 than did not.

The results across Trials 204/208/116 for the larger MDR-TB population also extend to the more difficult to treat extensively drug resistant (XDR-TB) patients (defined as MDR-TB patients additionally resistant to a fluoroquinolone and a second-line injectable agent). Treatment with delamanid (at either dose) in combination with an optimized background regimen (OBR) for 2 months improved 2-month SCC over placebo in combination with OBR (N=37) 26.1% vs. 0.0% (unpublished data). For long-term outcomes (N=36), patients receiving ≥6months treatment with delamanid in combination with an OBR achieved a higher proportion of sustained SCC and lower mortality compared to those receiving ≤2months treatment with delamanid: 65.2% vs. 30.8% and 12.5% vs. 33.3%, respectively (unpublished data).
In conclusion, delamanid administered for 2 months significantly improves 2-month SCC. Treatment with delamanid for at least 6 months significantly improves treatment outcomes, including a reduction in mortality. While there is potential for selection bias, an analysis of this bias supports the notion that sicker patients (i.e. those with higher bilateral cavitation, higher degree of XDR-TB, and higher degree of previous treatment episodes) were enrolled into the delamanid treatment arms. Overall, these results reflect programmatic conditions given the diverse range of populations enrolled in various resource-limited settings and the results span to the more difficult to treat XDR-TB population.
Section 10: Summary of comparative effectiveness in a variety of clinical settings

• Summary of available estimates of comparative effectiveness

Overall treatment outcomes for patients with MDR-TB are generally poor. Rates of morbidity and mortality are high, due in part to limited treatment options and the demographic characteristics of MDR-TB patients. In addition, global data from WHO have provided an estimate that fewer than half (48%) of patients with MDR-TB complete their treatment regimens. The poor outcomes seen among MDR-TB patients with current treatment regimens suggest that despite treatment, many MDR-TB patients will likely develop chronic, highly resistant forms of TB associated with high mortality and high transmission rates.

The results from the largest meta-analysis of MDR-TB treatment outcomes yet reported showed favorable outcomes for 4,934 of 9,898 (54%) patients while 732 (8%) had failed or relapsed, 1,392 (15%) had died, and 2,095 (23%) had defaulted (i.e., left therapy before therapy had been completed). In addition, 1,932 (21%) patients experienced adverse drug reactions requiring changes in therapy. Furthermore, high mortality rates occur among XDR-TB patients (as high as 98% in a cohort with HIV co-infection) and favorable treatment outcomes for these patients are low (< 20% in some reports).

The data from the delamanid clinical development program highlight that the outcomes in the non-delamanid receiving comparison groups reflect consistently with previously published data regarding baseline standard of care (i.e., optimized background regimens), and that the addition of delamanid to standard of care improved treatment outcomes and reduced mortality in those diverse settings. In addition, the improvement in patients receiving delamanid extended to the XDR-TB population, thereby reflecting the generalizability of the data to all MDR-TB patients.
Section 11: Summary of comparative evidence on safety

• **Estimate of total patient exposure to date**

887 patients represent the total exposed patients used in delamanid regulatory filings, including healthy patients, patients with drug-susceptible TB, and patients with MDR-TB. 511 total patients (in a 2:1 ratio of delamanid patients: placebo patients) are enrolled in the current Phase III study.

A total of 395 MDR-TB patients were exposed to delamanid in Trials 204 and 208 (Table 1). In these trials, nearly half of the patients received delamanid for ≥6 months.

Table 1: Duration of Exposure to Delamanid and Cumulative Delamanid Dose – MDR-TB Patients, Safety Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trial 204</th>
<th>Trial 208</th>
<th>All Delamanid (N = 213)</th>
<th>All Delamanid (N = 395)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration, days</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>10.19 (2.576)</td>
<td>21.66 (4.456)</td>
<td>9.74 (2.706)</td>
<td>17.43 (3.825)</td>
</tr>
<tr>
<td>Range</td>
<td>0.5 – 19.2</td>
<td>0.6 – 32.4</td>
<td>0.0 – 100</td>
<td>0.2 – 72.6</td>
</tr>
<tr>
<td><strong>Cumulative delamanid dose, g</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>161 (100.0)</td>
<td>160 (100.0)</td>
<td>6 (3.5)</td>
<td>166 (26.8)</td>
</tr>
<tr>
<td>Range</td>
<td>0 – 22.4</td>
<td>0 – 32.4</td>
<td>0 – 100 (25.0)</td>
<td>0 – 72.6</td>
</tr>
<tr>
<td><strong>Cumulative dose categories</strong></td>
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<tr>
<td>≤ 11.2</td>
<td>161 (100.0)</td>
<td>160 (100.0)</td>
<td>6 (3.5)</td>
<td>166 (26.8)</td>
</tr>
<tr>
<td>&gt; 11.2 and ≤ 22.4</td>
<td>0</td>
<td>0</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
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<tr>
<td>&gt; 22.4 and ≤ 36.6</td>
<td>0</td>
<td>0</td>
<td>105 (49.3)</td>
<td>38 (9.6)</td>
</tr>
<tr>
<td>&gt; 36.6 and ≤ 50.0</td>
<td>0</td>
<td>0</td>
<td>26 (12.2)</td>
<td>4 (10.2)</td>
</tr>
<tr>
<td>&gt; 50.0 and ≤ 65.0</td>
<td>0</td>
<td>0</td>
<td>6 (2.8)</td>
<td>50 (12.7)</td>
</tr>
<tr>
<td>&gt; 65.0</td>
<td>0</td>
<td>0</td>
<td>65 (30.5)</td>
<td>60 (15.2)</td>
</tr>
</tbody>
</table>

*BID = twice daily, OBR = optimized background treatment regimen, SD = standard deviation, Trial 204 = Trial 243-07-204, Trial 208 = Trial 243-07-208.*

*Duration of exposure is number of days on study medication (delamanid or placebo). Duration of exposure = (treatment start date – treatment start date) + 1.

*Total cumulative delamanid dose was calculated as sum of treatment duration (days) x total dose per day (300 mg (100 mg BID) or 400 mg (150 mg BID)) in Trials 204 or 208.*

*For patients switched during Trial 208, the total cumulative delamanid dose was adjusted accordingly. Trial gap for patients converted to continue into Trial 208 was not included in the calculation.
Section 11: Summary of comparative evidence on safety

• **Description of the adverse effects/reactions and estimates of their frequency**

For Trial 204, the incidence of Treatment Emergent Adverse Events was examined using a more stringent criteria of a difference of at least 3 percentage points between the delamanid 100 mg BID + OBR group and the placebo + OBR group and higher in the delamanid + OBR group than in the placebo + OBR group, the level to be reported as adverse drug reactions (ADRs) for delamanid (Table 2). QT interval prolongation meets these criteria and is a clinically significant event. Headache also meets these criteria, and the clinical significance of this is supported by the observation of headache as a frequent finding in clinical trials of delamanid performed prior to those performed in MDR-TB patients. In addition, abdominal pain meets the criteria; however, the clinical relevance of this event is questionable, as abdominal pain is a common toxicity of medications included in OBR. When considering the medical concept of abdominal pain (including the terms abdominal pain, abdominal pain upper, and abdominal pain lower), abdominal pain was very consistent. A 3 percentage point difference in a very common clinical finding in treated MDR-TB patients is of questionable clinical importance. In addition, paresthesia and tremor are commonly associated with OBR in clinical practice; their association with delamanid is less clear. Musculoskeletal chest pain, the chest pain captured under the SOC General Disorders and Administration Site Conditions, and throat irritation are characteristic of tuberculosis, where chronic cough causes chest pain and sputum expectoration causes throat irritation and even infection of adjacent organs, particularly the larynx. Therefore, it is clinically unlikely that differences in these last two disease-associated adverse events are due to a delamanid effect.

### Table 2: Treatment-Emergent Adverse Events Occurring in at Least 3% of Patients in the Trial 204 Delamanid 100 mg BID + OBR Group and With an Incidence of at Least 3% Percentage Points Higher Than in the Placebo + OBR Group

<table>
<thead>
<tr>
<th>System Organ Class and MedDRA Preferred Term</th>
<th>Number (%) of Patients</th>
<th>Delamanid 100 mg BID + OBR (N = 161)</th>
<th>Placebo + OBR (N = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16 (9.9)</td>
<td>11 (6.9)</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
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<tr>
<td>Chest pain</td>
<td>16 (9.9)</td>
<td>7 (4.4)</td>
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<tr>
<td>Investigations</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Electrocardiogram QT interval prolonged</td>
<td>16 (9.9)</td>
<td>6 (3.8)</td>
<td></td>
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<tr>
<td>Nervous System Disorders</td>
<td></td>
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<tr>
<td>Headache</td>
<td>38 (23.6)</td>
<td>30 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>17 (10.6)</td>
<td>12 (7.5)</td>
<td></td>
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<tr>
<td>Tremor</td>
<td>19 (11.8)</td>
<td>13 (8.1)</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
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<tr>
<td>Throat irritation</td>
<td>5 (3.1)</td>
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</table>

**BID** = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; optimized background treatment regimen; OBR = optimized background treatment regimen.
No additional safety concerns beyond those identified in Trial 204 were identified in Trial 208.

Two deaths were reported in patients enrolled in the MDR-TB trials during the time of active participation: 1 death in Trial 204 and 1 death in Trial 208. Both patients were treated with delamanid and both deaths were due to TEAEs assessed overall as unrelated to delamanid. Cause of death for the patient in Trial 204 was respiratory failure (Treatment Period Day 9) and for the patient in Trial 208 was right ventricular failure (Trial Day 71, 62 days after discontinuation of delamanid on Treatment Period Day 9). No other deaths in Trials 204 and 208 were reported.

Although the current Phase III trial is blinded, the independent Data Safety and Monitoring Committee has not raised any additional safety concerns not already observed in the Phase II program.
Section 11: Summary of comparative evidence on safety

• **Summary of comparative safety against comparators**

It is essential to consider the spectrum of toxicities often associated with OBR when assessing the safety profile of delamanid (1-3).

Of the Category 1 medications, the most recent WHO Guidelines recommend the use of pyrazinamide, but many patients were taking a regimen that also included ethambutol. Pyrazinamide is associated with hyperuricemia, hepatotoxicity, arthralgias, nausea, and vomiting. Ethambutol can cause optic neuritis, color blindness, and decreased visual acuity. In a recent publication of a retrospective cohort study of toxicities associated with OBR in 1027 MDR-TB patients, hyperuricemia was observed in 2.8% of patients, hepatotoxicity in 8.9%, arthralgias in 13.4%, nausea in 58.2%, vomiting in 39.1%, and visual disturbances in 3.2% of patients.

Category 2 comprises the injectable agents including amikacin, kanamycin, capreomycin, and streptomycin. Most MDR-TB patients will receive at least 1 medication from this group. The injectable medications have been associated with hearing loss and vestibular disturbances, including vertigo, dizziness, and tinnitus, neurotoxicity, and renal toxicity. All Category 2 medications are known to cause electrolyte abnormalities; however, Capreomycin, a peptide, is frequently associated with electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia. Retrospective cohort data show hearing loss was observed in 19.0% of patients, tinnitus in 12.1%, dizziness in 23.5%, other vestibular disorders in 9.0%, peripheral neuropathy in 8.2%, renal toxicity in 4.3%, and electrolyte disturbances in 2.8% of patients.

The fluoroquinolones comprise the Category 3 anti-TB medications which include levofloxacin, moxifloxacin, gatifloxacin, and ofloxacin. The quinolones have been associated with gastrointestinal intolerance including nausea, vomiting, diarrhea, and abdominal discomfort, CNS disorders such as headache, insomnia, nightmares, dizziness, and skin disorders, such as erythema, pruritus, and rash. Moxifloxacin is known to cause QT interval prolongation and was a prohibited medication in all delamanid trials conducted to date. However, 96% of patients who were on trials 204 and 208 received a fluoroquinolone with delamanid and most received it throughout the trials; 60% received levofloxacin (Table 2.7.4.1.3.2.3.2-1). A recent rigorously conducted study indicated that levofloxacin 1000 mg and 1500 mg cause a 4.4 to 7.4 msec increase in QT at peak daily effect compared to a 13.2 msec increase caused by 400 mg of moxifloxacin, the recommended dose for tuberculosis. Most of our patients received 750 mg levofloxacin QD, the recommended dose for tuberculosis, and did not have clinical manifestations associated with prolonged QT interval. Retrospective cohort data show diarrhea was observed in 20.4% of patients, abdominal pain in 23.9%, headache in 9.5%, rash in 8.6%, and itching in 8.7% of patients.

Category 4, the second-line oral bacteriostatic agents includes para-aminosalicylic acid, cycloserine or terizidone, and ethionamide or prothionamide. Para-aminosalicylic
acid (PAS), ethionamide, and prothionamide are commonly associated with gastrointestinal toxicities such as taste perversion, excessive salivation, nausea, vomiting, loss of appetite, abdominal pain, and gastritis. When PAS is used in combination with ethionamide, patients should be monitored closely for hypothyroidism. Cycloserine has been shown to cause psychiatric symptoms including psychosis, paranoia, depression, aggression, seizures, suicidal ideation, and peripheral neuropathy. Retrospective cohort data show psychiatric symptoms were observed in 13.2% and seizures in 4.9% of MDR-TB patients treated with OBR.

Category 5 anti-TB medications have limited use as part of OBR in MDR-TB, and very few patients in delamanid clinical trials were treated with medications from this group. As suggested by the retrospective cohort data, OBR medications can cause a wide range of side effects, and it is important to consider the potential contribution from OBR when evaluating the safety and tolerability of delamanid in patients with MDR-TB.

In summary, against the existing second-line anti-TB drugs, delamanid’s safety profile is favorable and many of the toxicities observed with other second-line drugs are not present in delamanid. QT prolongation is a small, well-quantified risk that has not resulted in clinical safety concerns.

**References**


Section 12: Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

Otsuka is committed to providing affordable and responsible access to delamanid. To this end, Otsuka is developing a differential pricing strategy that distinguishes between resource-limited and resource-rich settings. In all cases, affordable access will be coupled with strong pharmacovigilance systems to minimize the potential for developing resistance to delamanid and ensure it remains a viable treatment option for patients now and in the future.

Two economic studies are available: one in low and middle income countries and one in high income countries.

The economic study in low and middle income countries (conducted on behalf of WHO) focused on China, Estonia, Nepal, Peru, Philippines, and Russia (of note, the delamanid clinical development program was conducted in 4 of these countries). Using a uniquely constructed and conservative model, this analysis concluded “Delamanid is highly likely to be cost-effective in most environments – for a wide range of assumptions about the translation of trial results to current practice.” Under nearly all scenarios in all countries, the Incremental Cost-Effectiveness Ratios (ICERs) for each of the 4 scenarios assessed (exploring the impact of delamanid in an additive, proportional, or maximum limit approach and relative to mortality) for each country were well below the per capita Gross National Incomes for each country (China was US$4920; Estonia, US$15260; Nepal, US$540; Peru, US$5150; Philippines, US$2210; and Russia, US$10730) that were used as the Willingness to Pay threshold in the analysis (Figure 1). Moreover, “the absolute values in terms of ICERs may substantially under-represent the true cost-effectiveness of delamanid. This is particularly important to note in the case of the results for XDR-TB.”

Figure 1: Incremental Cost-Effectiveness Ratios (in USD)
The economic study in high income countries focused on Germany. The study determined “The results of our analysis show that treatment with Deltyba™ for 24 weeks added on to a five-drug BR [background MDR-TB regimen] is cost-saving in 73% of all probabilistic assumptions from a societal perspective compared to BR alone, even with a 20% increase of its current market price. Under conditions prevalent in Germany, Deltyba™ added to a five drug BR regimen is likely to be cost-saving compared to BR alone under a wide range of assumptions. Adding delamanid remained cost-effective when costs due to loss of productivity were excluded as the QALYs gained by lower lethality and a higher proportion of successfully treated patients outweighed the delamanid drug costs. These results strongly support the application of Deltyba™ in treating MDR-TB patients.”

**References**


Section 13: Summary of regulatory status of the medicine (in various countries)

Regulatory submissions are pending in the People’s Republic of China, Indonesia and the United States. Future filings and other access strategies will be prioritized in countries where Otsuka has conducted clinical trials, in high-burden MDR-TB countries and resource-limited settings and in countries where requests for delamanid have been initiated by National Tuberculosis Control Programs.