C.6	Delamanid – removal of age restriction – EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: A new strength formulation for delamanid (25 mg dispersible tablet) was added to the 2021 EMLc complementary list for the treatment of multidrug resistant tuberculosis with an age restriction of over 3 years. The application is to remove the age restriction. A WHO Guideline Development Group reviewed the emerging PK and safety evidence on the use of delamanid in children under 3 years of age. This included the 0-2 years cohort in the completed paediatric delamanid Otsuka 232 trial (unpublished, 37 children recruited across all cohorts) and further observational cohort data on 7 children. Limited information is available. Observational and trial data from older children has identified hallucinations as a particular safety concern, as part of the well-recognised CNS toxicity associated with the use of delamanid. In the 232 trial age based dosing was used, with lower drug exposures noted. The WHO subsequently developed weight/age based dosing guidance for children below 2 years of age. Specific concerns of CNS toxicity on the developing brain in young children were noted. Delaminid was recommended in the updated 2022 WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents for the treatment of children with MDR/RR-TB aged below 3 years as part of longer treatment regimens (*conditional recommendation, very low certainty of evidence*). It was noted that there were limited oral options to treat MDR-RR TB in young children.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: MDR TB is a major health problem with as estimated 450,000 cases in 2021, with around 30,000 cases occurring in children. Many thousands of children are treated for multidrug resistant or rifampicin resistant (MDR/RR-TB) each year. Delamanid is an established component of oral drug resistant TB guidelines in adults and children. There are a limited number of oral antibiotics available to treat MDR/RR-TB in younger children. Prolonged treatment courses of injectable antibiotics are associated with significant toxicity as well as complex practicality issues in young children.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: A Guideline Development Group (GDG). Reviewed the emerging evidence of the use of delamanid in younger children in 2021. In 2022 updated WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents were published. The Otsuka 232 trial was an open label safety, tolerability and pharmacokinetic study of delamanid in children with drug resistant tuberculosis. The study recruited 37 children from birth to 18 years of age from 2013-2020 with the younger cohort age bands receiving the delamanid paediatric formulation. The PK data informed the new weight/age band based dosing tables in the 2022 WHO treatment guidelines. Observational data from a further 7 children aged under 3 years was available.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: In the very limited data available, the GDG noted no cardiac safety signals were reported distinct from those reported in adults (prolonged QT), although drug exposure was low in children aged under 2 years with the dosing regimen used in the 232 trial. Central nervous system toxicity is a well recognised side effect of delamanid treatment in adults and older children, including tremors, anxiety, depression and insomnia. Hallucination has more recently been noted as a concern in children aged 2-16 years treated with delamanid for MDR TB. The effects of delamanid on the developing brain in children under 2 years of age was noted as a concern by the GDG.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Where possible an ECG should be obtained before treatment. Monitoring for the emergence of neuro-psychiatric effects should be in place, which in younger children may be more difficult to detect.
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: See above

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: In the 2021 EMLc it was noted that Delamanid was potentially being submitted to the Global Fund Expert Review Panel. No new information is provided.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☐ No ☐ Not applicable Comments: In the 2021 EMLc it was noted that Delamanid 25 mg tablet was being submitted to the EMA CHMP. No update is provided in the application.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☐ No ☐ Not applicable Comments: Delamanid is recommended in the updated 2022 WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents for the treatment of children with MDR/RR-TB aged below 3 years as part of longer regimens (*conditional recommendation, very low certainty of evidence*).