I.1	Albendazole – mebendazole - praziquantel
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The application seeks to include agents (albendazole ALB, mebendazole MEB, and praziquantel PZQ) for treatment of Cystic Echinococcosis (CE), Alveolar Echinococcosis (AE), and Neurocysticercosis (NCC). CE, AE, and NCC have substantial global disease burden and is a priority for many countries especially in LMICs and communities with predominant pastoral practice. The GBD for these conditions have been well articulated in application citing trust worthy research evidence.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Albendazole (ALB) for CE: This is the treatment of choice for CE, especially because of its good bioavailability compared to mebendazole and lower pill burden. Albendazole (ALB) for AE: This is the treatment of choice for AE, especially because of its good bioavailability compared to mebendazole and lower pill burden. Albendazole (ALB) for NCC: ALB is one of the only drugs used in antiparasitic treatment of NCC – the other being PZQ. ALB treatment is usually long for the above conditions ranging from 3 months to livelong treatments. It is also not readily available in some regions. ALB is also expensive and not readily affordable to the groups most at risk of conditions requiring its use. Mebendazole (MEB) for CE: This is the second line treatment of choice for CE, has less bioavailability compared to albendazole and higher pill burden. Mebendazole (MEB) for AE: This is the second line treatment of choice for AE, has less bioavailability compared to albendazole and higher pill burden. MEB is not used for NCC Praziquantel (PZQ) for NCC: PZQ is used in the treatment of NCC and recommended to be used in combination with ALB. PZQ is not used for CE and AE. The WHO Model List of Essential Medicines (21st List – 2019) already includes albendazole (ALB), mebendazole (MEB) and praziquantel (PZQ) as intestinal anthelminthics (section 6.1.1). The application seeks to expand the indication to include “Treatment of taeniid cestode cysts” in EML and EMLc (as a new sub-section under 6.1).
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). **Cystic Echinococcosis (CE)** Benzimidazoles are indicated for inoperable patients with liver or lung CE; patients with multiple cysts in two or more organs, or peritoneal cysts. Small (<5 cm) CE1 and CE3a cysts in the liver and lung respond favourably to benzimidazole alone. Benzimidazoles should be used to prevent recurrence following surgery or PAIR. Benzimidazoles can be used in patients of any age. However, there is little experience with children under-6 years old; it is less limited by the patient's status than surgery. Standard dosage of ALB for 3–6 months produces an average of 30% cure. The number of patients with clinical or ultrasound improvement increases with longer durations of treatment while the proportion of patients with cure does not significantly change. ALB is more effective in young patients and for small CE1 and CE3a cysts. Benzimidazoles are less effective for CE2 and CE3b. The importance of cyst stage and size in determining response to treatment was confirmed by a systematic review. Randomized controlled trials that compare standardized benzimidazole therapy on responsive cyst stages with the other treatment modalities are needed to draw reliable conclusions. The impact of the treatment with Benzimidazoles depends on the stage of the cyst and on the cyst's germinal layer integrity. They are more effective on young cysts (e.g. CE1) and on liver cysts; effectiveness on CE2 cysts is less than 50%. Small cysts (<5 to 6 cm) CE1 and CE3a cysts located in the liver and lungs may respond favourably to sole treatment with a benzimidazole. Drugs alone are not effective against giant cysts (>10 cm in diameter). Sole treatment with a benzimidazole is also indicated for patients with inoperable liver or lung CE; patients with multiple cysts in two or more organs and patients with peritoneal cysts. Benzimidazoles are also used as an adjunct to surgery or interventional procedures to reduce the cyst's internal tension, to complement the mechanical removal of the cyst or the chemical sterilization of the parasite and to prevent secondary echinococcosis. A prospective study demonstrated that a protocol that combines ALB and PAIR (Puncture, Aspiration, Injection, Re-aspiration) reduces the chance of cyst recurrence. CE treatment centres recommend combined pre- and postoperative ALB use between one and four months. At present, surgeons tend to administer ALB from one week to one day before and from one to three months after intervention. Actual duration of treatment is dependent on surgical factors such as whether or not the cyst is opened. ALB treatment is typically administered for one month after surgery in patients who have successfully undergone complete surgical resection of the cyst (radical procedure) or PAIR. The recommended treatment time extends to 3-6 months in patients with incompletely resected cysts (nonradical procedures), or when spillage has occurred during surgery or PAIR. **Alveolar Echinococcosis (AE)** ALB is the drug of choice, and is given orally at a dosage of 10–15 mg/kg/day, in 2 divided doses, with fat-rich meals. In practice, a daily dose of 800mg is given to adults, divided in two doses. Continuous ALB treatment of AE is well tolerated and has been used for more than 20 years in some patients. Intermittent treatment should no

	longer be used. Occasionally, ALB has been given in higher doses of 20 mg/kg/day for up to 4.5 years. Alternatively, if ALB is not available or not well tolerated, MBZ may be given at daily doses of 40–50 mg/kg/day split into three divided doses with fat-rich meals. Controlled, but non-randomized studies showed that long-term benzimidazole improved the 10-year survival rate in non-radically operated AE patients compared to untreated historical control patients from 6–25% to 80–83%, respectively, and prevented recurrences after radical surgery. Unlike for CE, benzimidazoles only suppress *E. multilocularis* growth, therefore necessitating long-term treatment. It is difficult to assess the effectiveness of long term benzimidazole treatment. Most commonly, effectiveness is assessed by using CT or other imaging method to measure the larval mass. Since benzimidazoles treatment is largely considered nonparasitocidal, regression and non-progression are usually considered treatment success. Whether long-term benzimidazole treatment eventually exerts an effect on parasite viability is still under debate, although the evidence for such an effect is mounting. Whether the long-term efficacy of benzimidazoles, in some patients with AE, is related to direct parasitocidal activity or an indirect effect through immune stimulation is unknown. **Neurocysticercosis (NCC)** Six trials randomly assigned 464 patients with cystic lesions (vesicular cysticerci), and 5 trials randomly assigned 478 patients with enhancing lesions (colloidal cysticerci). Parasites were located in the brain parenchyma or subarachnoid space at the convexity of the cerebral hemispheres. Cysticidal drug therapy was associated with complete resolution of cystic lesions (44% vs. 19%; P=0.025). Trials on enhancing lesions showed a trend toward lesion resolution favoring the use of cysticidal drugs (72% vs. 63%; P=0.38) that became statistically significant when an outlier trial was excluded from the analysis (69% vs. 55%; P = 0.006). Risk for seizure recurrence was lower after cysticidal treatment in patients with enhancing lesions (14% vs. 37%; P=0.001). The single trial evaluating the frequency of seizures in patients with cystic lesions showed a 67% reduction in the rate of generalized seizures with treatment (P = 0.006). Conclusion: Cysticidal drug therapy results in better resolution of colloidal and vesicular cysticerci, lower risk for recurrence of seizures in patients with colloidal cysticerci, and a reduction in the rate of generalized seizures in patients with vesicular cysticerci compared with no specific therapy. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Yes.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Benzimidazoles are well tolerated in 70-80% of cases, but more adverse side effects are seen in patients with immunosuppression. The most common side effects are hepatotoxicity, elevation of transaminases, proteinuria, transient hair loss, gastrointestinal disturbances, leukopenia, thrombocytopenia and neurologic symptoms, including sleeplessness and vertigo. Alopecia is a recognized side effect in patients with chronic cholestasis and/or portal hypertension. Increase in aminotransferase levels may be due to drug-related efficacy or to real drug-related toxicity. Although no systematic evaluation has been performed, long-term administration does not seem to increase such risks or to generate resistance

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Examinations for adverse reactions (liver enzymes and complete blood cell counts) are necessary initially every 2 weeks (first 3 months), then monthly (first year), then every 3 months. As benzimidazole administration is crucial in all cases of AE, if an increase above 5 times the upper limit of normal (ULN) of aminotransferases is observed, the following steps are recommended: (1) check for other causes of the increase (other medication, viral hepatitis, AE-related biliary obstruction or liver abscess), (2) monitor drug levels, (3) if ALB sulfoxide plasma levels are higher than the recommended range of concentrations (1–3_mol/L, 4 h after morning drug intake), decrease ALB dosage and shift to the alternative benzimidazoles (MBZ if ALB and vice versa) and (4) if an increase over 5× ULN persists, consult a reference centre. Decrease of leukocyte count under 1.0× 109/L indicates benzimidazoles toxicity and warrants treatment withdrawal.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable: ALB, MEB, and PZQ are the only treatments currently available for CE, AE, and NCC which are neglected tropical diseases of medical significance.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	High: several systematic reviews have synthesised evidence on efficacy and safety of these agents. Several guidelines and expert consensus have also concluded on the agents.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Yes, the treatment of taeniid cestode cysts requires specialised diagnostic or monitoring facilities, and/or specialised medical care, and/or specialised training. This application also proposes addition of the above in the complementary list.
Are you aware of 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:

Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: several guidelines already mention the use of the agent in their recommendations: 1. WHO management guideline for Taenia solium neurocysticercosis (approved with revisions by the WHO GRC – October 2020) 2. "Expert consensus for the diagnosis and treatment of CE and AE in humans" published in 2010 (2) by the WHO-Informal Working Group Echinococcosis 3. Clinical Practical Guidelines for the diagnosis and treatment of neurocysticercosis (Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH))
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	These drugs are not readily available and are also expensive for the target population most at risk of these diseases. The WHO receives donations of these agents which facilitates access. Inclusion (expansion of indication to CE, AE, and NCC) in the EML will enable governments to procure, stock, and subsidize therefore further increasing access for these indications and allow clinicians to easily prescribe for these conditions.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Considering the body of evidence in support of efficacy of ALB as first choice for CE, AE, and NCC; MEB as second choice for CE and AE; and PZQ in a combined therapy in NCC I will recommend these agents for the for expansion in the EML for conditions cited.
References (if required)	