I.1 (item number)	Albendazole, mebendazole and praziquantel for the indication of treatment of taeniid cestode cysts
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The larval stages of three taeniid cestode parasites, Echinococcus granulosus, Echinococcus multilocularis and Taenia solium, produce cysts in humans that are of medical relevance. The diseases caused by these parasitic cysts are called cystic echinococcosis (CE), alveolar echinococcosis (AE), and cysticercosis (being neurocysticercosis (NCC) the most common form) respectively, and they are recognised by WHO as neglected tropical diseases. NCC is mainly a disease of poverty that predominantly affects rural populations in Africa, Asia and Latin America. Access to diagnostic and treatment, to better manage epilepsy and other NCC is a challenge for the people affected in these communities due to the availability and costs of specialised diagnostic and care. Stigma and social discrimination also mean that many people try to "hide" the disease.
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.	The only real options for treatment of CE are albendazole (ALB) and Mebendazole (MEB). ALB is the drug of choice as it has better bioavailability. ALB is also preferred to MEB, because MEB requires a higher dose and a higher pill burden, for example, an adult patient would require 8 tablets/day of MEB compared with 2 tablets/day ALB. ALB and praziquantel (PZQ) are the only drugs used for the antiparasitic treatment of NCC. ALB is usually the first choice, due to costs and availability.
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). Summary of available data 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 Summary of available data AE Recommendation: Long-term benzimidazole treatment for several years is mandatory in all inoperable AE patients and following surgical resection of the parasite lesions. Since residual parasite tissue may remain undetected at radical surgery, including liver transplantation (LT), benzimidazole should be given for at least 2 years and these patients monitored for a minimum of 10 years for possible recurrence. Pre-surgical benzimidazoles administration is not recommended except in the case of LT. Comparative effectiveness – medicines for CE & AE : Benzimidazoles failure is rare, but non-compliance of treatment might result in non-resectable AE cysts growing again. ALB in AE patients can only be discontinued after several years of treatment in a small proportion of patients . No pharmacological drug resistance has ever been reported. However, individual toxicity to treatment may be observed, with transaminase consistently five times greater than normal value and/or severe leucopenia the most common reasons for treatment cessation. In such cases, therapeutic options are limited. A number of different drugs have been evaluated either in vitro (PZQ, amphotericin B, alpha-difluoromethylornithine, artemether, caspofungin, itraconazole, ivermectin, mefloquine, methiazole, miltefosine, nitazoxanide, rifampin, and trimethoprime sulfamethoxazole) or in vivo (nitazoxanide, amphotericin B). Some of them (itraconazole, methiazole and nitazoxanide) showed promising in vitro activity. Nitazoxanide, the most promising compound based on in vitro results, failed to exhibit a clinically meaningful effect in humans. Amphotericin B, has shown a parasitostatic effect both in vitro and in vivo. However, the number of patients treated thus far is limited. The drug also has significant side effects and must be administrated intravenously. Amphotericin B may be an option in the rare cases where benzimidazole treatment fails. Summary of available data NCC: Praziquantel was first used for NCC in 1979 (4) as the first specific cysticidal drug, followed by ALB in 1987. All studies reviewed conclude that the use of cysticidal drugs (albendazole and praziquantel) is beneficial for the patient. 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: Use of ALB and MEB for CE & AE: Benzimidazoles are well tolerated in 70-80% of cases, but more adverse side effects are seen in patients with immunosuppression (36). 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 (37). 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. Use of ALB and PZQ for NCC: The main side effects of ALB in patients treated with doses of 15 mg/kg/day (up to 1200 mg/day) or less for 28 days are due to the parasiticidal activity and treatment-induced inflammation, including headaches, seizures, and dizziness. Thus, there is a transient increase in the number of seizures after therapy. Hepatoxicity and leukopenia are known side effects of ALB and are relative contraindications to its continued use. In studies of chronic therapy, mainly for echinococcosis, elevated liver enzymes were seen in up to 16% of cases, requiring drug discontinuation in 3.8%. The elevated transaminases normalized in almost all cases when the drug is discontinued promptly. Leukopenia is also noted in up to 10% of cases receiving prolonged therapy, but only requires discontinuation in <1% of cases Both liver enzymes and complete blood counts should be monitored during the first month in patients receiving ALB alone or in combination with PZQ. The optimal frequency of monitoring is unknown, but our panel felt that monitoring laboratory test weekly is adequate. In those receiving prolonged duration of ALB, liver enzymes should continue to be monitored with the frequency based on clinical indications and tolerance. In the presence of absolute neutropenia or elevation of transaminase >5 times the upper limits of normal, ALB should be withheld until laboratory tests normalize and alternative approaches considered (eg, PZQ or no anthelminthics). This usually only an issue in prolonged courses of therapy such as those used for subarachnoid disease. The adverse effects noted with PZQ depend on the indication, dose, and duration of therapy. Most adverse effects in patients with NCC are due to its cysticidal activity, including headaches, dizziness, and seizures. Initial dose-ranging studies of PZQ did not note other significant adverse events with doses of to 50 mg/kg/day for up to 28 days. Doses of up to 100 mg/kg/day for up to 28 days have been used in NCC without additional adverse laboratory adverse events. However, >10% of those treated with PZQ develop gastrointestinal side effects such as nausea, vomiting, or abdominal pain. Allergic reactions including urticaria and other rashes are also noted in a small proportion of cases. Thus, patients should be advised about gastrointestinal and allergic reactions. In 2 trials of combination therapy using both ALB and PZQ in parenchymal NCC, there were no more or different adverse events with combination therapy than with ALB alone. Just as in monotherapy, liver enzymes and complete blood counts should be monitored.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: The required monitoring are summarised in the previous section above

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Risk to benefit ratio is favourable
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Quality of evidence is high
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: The treatment of taeniid cestode cysts requires specialised diagnostic or monitoring facilities, and/or specialised medical care, and/or specialised training, therefore the request in this application is to include the medicines in the Complementary list. Medicine
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: The medicines are already in the EDL
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: The medicines are already in the EDL
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	A review of access, cost and affordability across different settings has been provided. In general these medicines are accessible, relatively cheap and affordable in different settings
Any additional comments	None
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.	The application request for inclusion of these compounds in the complementary list of the EDL, since the treatment of taeniid cestode cysts requires specialised diagnostic or monitoring facilities, and/or specialised medical care, and/or specialised training. Given the limited options for management of this condition using available drugs, I recommend that the committee accepts this application .

References (if required)	