

Application for inclusion of albendazole, mebendazole and praziquantel on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the indication of treatment of taeniid cestode cysts.

Version: 29th November 2020

General items

1. Summary statement of the proposal for inclusion, change or deletion.

The WHO Model List of Essential Medicines (21st List – 2019) already includes albendazole (ALB), mebendazole (MEB) and praziquantel (PZQ) as intestinal anthelmintics (section 6.1.1). We would like to **expand the indication of ALB, MEB and PZQ to include the “Treatment of taeniid cestode cysts” in EML and EMLc** (as a new sub-section under 6.1). The use of these medicines for the treatment of taeniid cestode cysts **is already prescribed in the “WHO Model Prescribing Information – Drugs used in Parasitic Diseases” 2nd edition, Geneva, 1995.**

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. The ICD-11 code for Echinococcosis (both CE and AE) is 1F73, and for NCC is 1F70.0.

The medicines requested (as per table below) are relevant for the treatment of taeniid cestode cysts in **adults and children**. The target population are the individuals that have been diagnosed with the diseases, and anthelmintic treatment has been deemed necessary. These neglected diseases affect poor and marginalised populations, in which the cost of clinical management limits the patients’ treatment options.

Medicine	Albendazole	Mebendazole	Praziquantel
Disease	First choice for: <ul style="list-style-type: none">• Cystic Echinococcosis• Alveolar echinococcosis• Neurocysticercosis	Second choice for: <ul style="list-style-type: none">• Cystic Echinococcosis• Alveolar echinococcosis	<ul style="list-style-type: none">• Neurocysticercosis (alone or in combination with ALB)

The medicines requested for inclusion, are used to kill or suppress the parasites. ALB and MEB are members of a group of compounds referred to as benzimidazoles. They have been used for the treatment of AE since the mid-70s, and ALB has been used for CE since 1981 (1). The medicine of choice for CE and AE is ALB. MEB is used if ALB is not available or poorly tolerated (2). For CE, the medicines 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 and to prevent secondary echinococcosis. For AE, the drugs are used to suppress the parasite, after resection of the AE lesions, and for long term treatment in cases of inoperable AE, after liver transplantation (due to AE), and after incomplete lesion resection (3).

The medicines available for NCC are ALB and PZQ. For NCC, PZQ was first introduced in 1979 as the first specific cysticidal drug (4), followed by ALB in 1987 (5). ALB tends to be used more as it is cheaper and more available. In some instances (for example when there are more than 2 viable parenchymal cysts), it is recommended to use ALB combined with PZQ (6).

It is important to note that the requested medicines have been used for a very long time for the treatment of taeniid cestode cysts, they are the medicine of choice, and they are the only medicines being currently used or available. These drugs are essential for the Neglected Tropical Disease programmes covering management of patients with the above-mentioned conditions.

The treatment of taeniid cestode cysts requires specialised diagnostic or monitoring facilities, and/or specialised medical care, and/or specialised training, therefore the request is to include them in the **Complementary list**.

2. Relevant WHO technical department and focal point (if applicable).

The applicant is the WHO Department of the Control of Neglected Tropical Diseases.

3. Name of organization(s) consulted and/or supporting the application.

Not applicable.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Albendazole: ATC code: P02CA03

Mebendazole: ATC code: P02CA01

Praziquantel: ATC code: P02BA01

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

ALBENDAZOLE – CE, AE & NCC:

Presentation: Tablet (chewable) 400mg

Availability: Tablets 400 mg is the presentation used for preventive chemotherapy for lymphatic filariasis and soil-transmitted helminths. This presentation is usually available in the market. Some well-known brands are Eskazole and Zentel. There are also generic drugs.

MEBENDAZOLE - CE & AE:

Presentation: Tablet (chewable) 500mg

The dose required for treatment of echinococcosis (40-50mg/kg) is high compared to that required for treatment of other parasitic infections (100 or 200mg), hence the 500mg tablets are preferred for echinococcosis treatment. The 100mg tablets are likely to be preferred for intestinal parasites that require lower doses.

Availability: The presentation of tablets 500mg is the same presentation used for preventive chemotherapy for soil-transmitted helminths. WHO receives a donation of 500mg tablets from Johnson & Johnson (Vermox). It is not widely available in the market.

PRAZIQUANTEL - NCC:

Presentation: Tablets 500mg, tablets 600mg

A paediatric formulation of PZQ is not currently available. Treatment of clinical cases is recommended with available "adult" tablets because the risks of side effects are much lower than the ones linked to the infection.

The dose of praziquantel for cysticercosis is 50mg/kg, so the 500mg and 600mg tablets are preferred to the 150mg tablets.

Availability: Merck produces Cysticide (tablets 500mg) and also produces 600mg tablets for the schistosomiasis donation program. Biltricide (tablets 600mg) is produced by Bayer. Biltricide is donated to WHO by Bayer for the treatment of *T. solium* taeniasis. It is not widely available.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

The request is for individual medicines.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

ALBENDAZOLE - CE & AE (first choice):

Dose (adults & children): 10-15 mg/kg/day divided in two doses.

Treatment duration: CE: depends on the individual situation, stage and size of the CE cyst. Development of the cyst should be monitored by imaging. Current recommendations suggest continuous treatment for several months (minimum 3 months). AE: prolonged treatment that might last from 2 years (post-surgical treatment after curative resection) to life long (non-resectable AE lesion(s)).

References:

- WHO Model Prescribing Information – Drugs used in Parasitic Diseases (1995) (7).
- Expert consensus for the diagnosis and treatment of CE and AE in humans (2010) (2). The authors include the WHO Informal Working Group on Echinococcosis.
- Review: The echinococcoses: diagnosis, clinical management and burden of disease (2017) (3).

MEBENDAZOLE - CE & AE:

Dose (adults & children): 40-50 mg/kg daily divided in three doses.

Treatment duration: CE: depends on the individual situation, stage and size of the CE cyst. Development of the cyst should be monitored by imaging. Current recommendations suggest continuous treatment for several months (minimum 3 months). AE: prolonged treatment that might last from 2 years (post-surgical treatment after curative resection) to life long (non-resectable AE lesion(s)).

References:

- WHO Model Prescribing Information – Drugs used in Parasitic Diseases (1995) (7).
- Expert consensus for the diagnosis and treatment of CE and AE in humans (2010) (2). The authors include the WHO Informal Working Group on Echinococcosis.
- Review: The echinococcoses: diagnosis, clinical management and burden of disease (3)

ALBENDAZOLE – NCC:

Dose (adults & children): 15 mg/kg daily divided in two or three doses.

Treatment duration: 10-14 days.

References:

- WHO Model Prescribing Information – Drugs used in Parasitic Diseases (1995) (7).
- Clinical Practical Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) (2018) (6).
- WHO management guideline for *Taenia solium* neurocysticercosis (approved with revisions by the WHO Guideline Review Committee (GRC) - October 2020).

PRAZIQUANTEL - NCC:

Dose (adults & children): 50 mg/kg daily in three divided doses.

Treatment duration: 10- 14 days.

References:

- WHO Model Prescribing Information – Drugs used in Parasitic Diseases (1995) (7).
- Clinical Practical Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) (2018) (6).
- WHO management guideline for *Taenia solium* neurocysticercosis (approved with revisions by the WHO GRC – October 2020).

Additional requirements for CE, AE & NCC:

- Specialized diagnostic tests are required (imaging) before treatment and follow-up as treatment depends on the location, number, and stage of the cysts.
- Treatment should be conducted under specialized care.
- For CE and AE, the drug treatment will depend on the cyst stage, and any other treatments that might also be conducted (such as percutaneous treatment or surgery if indicated).
- For AE, because treatment involves prolonged periods (years or even lifelong), monitoring of blood drug levels is indicated to confirm adherence to treatment, to ensure adequate therapeutic drug levels and to avoid toxic reactions. Because benzimidazoles (BMZs) should be avoided in early pregnancy, contraceptive measures are necessary for women of reproductive age. As the treatment must be undertaken for years a decision to temporarily stop treatment (structured interruption) can be taken after months or years. In this case the absence of progressive disease needs to be verified (3).
- For NCC, anthelmintic therapy should be combined with corticosteroids because during the initial days of treatment, an increase in neurological symptoms occurs frequently, due to exacerbated inflammation around the dying larvae.

8. Information supporting the public health relevance.

Cystic echinococcosis:

Human infection with *E. granulosus* leads to the development of one or more cysts located most often in the liver and lungs, and less frequently in the bones, kidneys, spleen, muscles and central

nervous system. The asymptomatic incubation period of the disease can last many years until hydatid cysts grow to an extent that triggers clinical signs. The clinical signs vary depending on the number, location and size of the cysts and manifests commonly with pain and compromised organ function, worsening as the cysts enlarge. Infection is debilitating and fatal in some patients.

CE is globally distributed and exhibits the highest prevalence in communities where pastoral activities predominate, as the most common transmission cycle involves dogs and sheep (but can also involve other livestock species). These include regions in all countries bordering the Mediterranean, many regions and countries in central Asia, parts of China, Australia, and South America. In endemic regions, human incidence rates for CE can reach more than 50 per 100,000 person-years, and prevalence levels as high as 5%–10% may occur in parts of Argentina, Peru, East Africa, Central Asia and China.

Epidemiological information on disease burden:

(Summary of the review published by Kern et al (3)).

The first global estimate of the nonmonetary burden of CE was conducted in 2006 (8). Without adjusting for underreporting an estimated 285,400 DALYs were lost due to CE. However, after the value was adjusted for underreporting, the estimate increased to more than 1 million DALYs lost, which is similar to evaluations for diseases such as Chagas disease, dengue and onchocerciasis (8). The 2010 and 2013 GBD Studies included DALY estimates for echinococcosis and CE, respectively (9, 10). However, methodological decisions make interpretation of the 2010 GBD values problematic in that the study attempted to combine CE and AE into a single estimate (9). In parallel to the 2010 GBD Study the World Health Organization's Foodborne Disease Burden Epidemiology Reference Group (WHO-FERG) published a global CE burden estimate of 184,000 DALYs for the year 2010 (11), but it is considered to be largely underestimated and data gaps remain a problem.

The first study using the DALY to evaluate the burden of CE was conducted in a remote and highly endemic region of the Tibetan Plateau of Western China (12), showing a burden of 17,955 DALYs, and an average of approximately 0.81 DALY lost per person. This study helped to convey the magnitude of this chronic disease on populations who could not readily obtain medical treatment. Other studies have since been conducted in diverse geographic locations, including Peru, Sardinia, Nepal, and Xinjiang, China (13-16).

The monetary burden of CE has been estimated globally. Based on a 2006 estimate of the global burden of CE, monetary annual losses attributable to human CE were estimated to be \$193 million and increased to \$764 million when adjusted for underreporting (8). Although CE-associated monetary losses have been estimated for several countries, the lack of a standardized methodology makes comparisons difficult.

Assessment of current use:

CE is often expensive and complicated to treat, sometimes requiring extensive surgery and/or prolonged drug therapy. There are 4 options for the treatment of CE:

- 1) percutaneous treatment of the hydatid cysts with the PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique,
- 2) surgery,
- 3) antiparasitic drug treatment and
- 4) "watch and wait".

The choice is primarily based on the imaging characteristics of the cyst, following a stage-specific approach, and on the health care infrastructure and human resources available. For CE, there is an average of 2.2% post-operative death rate for surgical patients and about 6.5% of cases relapse after an intervention.

Sole treatment with benzimidazoles is more effective on young cysts and on liver cysts. It 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 (3).

Likely impact of treatment on the disease:

The impact of the treatment with benzimidazoles depends on the stage of the cyst and on the cyst's germinal layer integrity. As mentioned above, benzimidazoles are more effective on young cysts and on liver cysts. Approximately one third of patients treated with suitable CE cysts are cured by the treatment and thus avoid abdominal or other surgery.

Public health need:

The only real options for treatment of CE are ALB and 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.

The need for long term administration of ALB for CE, ranging from 3 months to over 12 months in particular cases, and the high costs of ALB in some areas (see Section 11), especially considering that the majority of patients come from poor pastoralist communities, mean that the cost of treatment prevents many patients having access to the required treatment.

The lack of availability of ALB even in countries such as Italy (17), where CE is endemic and highly endemic in certain areas, poses serious problems to patients and physicians.

Alveolar echinococcosis:

Infection in humans with *E. multilocularis* is characterized by an asymptomatic incubation period of 5–15 years, and the slow development of a primary tumour-like lesion which is usually located in the liver. Clinical signs include weight loss, abdominal pain, general malaise and signs of hepatic failure. Larval metastases may spread either to organs adjacent to the liver (for example, the spleen) or distant locations (such as the lungs, or the brain) following dissemination of the parasite via the blood and lymphatic system. If left untreated, AE is progressive and universally fatal.

AE is confined to the northern hemisphere, in particular to regions of China, the Russian Federation, Central Asia and countries in continental Europe. The transmission cycle usually involves foxes and other wild canids but might also involve domestic dogs. The intermediate hosts are several rodent species. Areas of highest endemicity in Central Asia and the Tibetan plateau involve domestic dogs as definitive hosts.

Epidemiological information on disease burden:

(Summary of the review published by Kern et al (3)). Assessment of the burden of AE faces many of the same challenges as for CE. The first global estimate of the burden of AE was published in 2010 (18). This study calculated that there were approximately 18,200 new cases of AE per year, with 91% of these cases occurring in China. Based on these values, a median of 666,434 DALYs lost per year was estimated. The WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) also published global AE burden estimates for the year 2010 (11), estimating a burden of 688,000 DALYs per year. In general, the global burden of CE appears to be greater than for AE due to higher overall disease frequency. However, on an individual patient level, burden tends to be higher for AE sufferers due to the clinical severity of the disease.

There have only been a few regional studies looking at the nonmonetary and monetary burden of AE. As with CE the first determination was conducted for a highly endemic pastoralist population located in western Sichuan Province, China (12). Since this initial study, there have been only a few attempts to evaluate the burden of AE in specific geographic locations, such as in Switzerland (19). Data gaps for estimating the burden of AE are similar to those encountered for CE and include a lack of frequency data and information on clinical course in areas with poor medical infrastructure.

Assessment of current use:

ALB and MEB are the only options for treatment. Prolonged treatment is necessary and might last from 2 years (post-surgical treatment after curative resection) to life long (non-resectable AE lesions). – More details are provided in section 9.

Likely impact of treatment on the disease:

For AE, early diagnosis and radical (tumour-like) surgery followed by anti-infective prophylaxis with ALB remain the key elements for a successful treatment. If the lesion is confined, radical surgery can be curative. Unfortunately, in many patients the disease is diagnosed at an advanced stage. As a result, if palliative surgery is carried out without complete and effective anti-infective treatment, frequent relapses will occur. Even with treatment, people often face reduced quality of life.

Public health need:

As for CE, the only real options for treatment of AE are ALB and 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. An adult patient would require 8 tablets/day of MEB compared with 2 tablets/day ALB and it is likely that compliance will be affected, especially in long term treatments

as required for AE.

The required prolonged treatment (from 2 years to life-long), and the cost of treatment and associated follow-up is an economic burden for patients in poor communities which limits their access to treatment.

Survival analyses of French and Swiss AE patients have shown that modern treatments such as resection of liver lesions followed by prolonged therapy with benzimidazoles can result in survival of AE patients similar to those of healthy populations (19). Where treatment options are available, the burden in terms of DALYs is modest because of the improved prognosis; for example, in Switzerland, there is a total burden of approximately 78 DALYs per annum due to AE, or 3.7 DALYs per case, 10 times less than the global estimate. However, many people affected in the poor communities of Central Asia and the Tibetan plateau, do not have access to early diagnosis or treatment, and the cost of a years-long or life-long treatment represents a barrier to adequate medical care that is largely restricted to patients in wealthy countries.

Neurocysticercosis:

NCC is produced by the larval stages of *T. solium* encysting in the central nervous system. In many cases NCC is asymptomatic, but the most common sign of symptomatic NCC are epileptic seizures. NCC is thought to be the leading cause of preventable epilepsy worldwide. NCC can also cause chronic headaches, blindness, focal deficits, and psychiatric symptoms. Clinical signs will vary depending on the number, location, and size of the cysts. Parenchymal brain cysts are associated with seizures and epilepsy and are more amenable to treatment, particularly in individuals with viable or degenerating cysts. Extraparenchymal NCC is associated with hydrocephalus, meningitis, focal neurologic deficits, and sometimes death, and are more difficult to treat.

T. solium is endemic in Latin America, South and South-East Asia, and parts of sub-Saharan Africa where pigs roam free (pigs are the intermediate host), and open defecation is practiced. It is a disease of poverty, principally affecting the most marginalized communities.

Epidemiological information on disease burden:

Limited data is available on the burden of *T. solium* induced disease. Two different research groups have estimated the number of NCC-associated epilepsy cases globally to be 370,710 in 2010 (11) and 1.93 million in 2015 (20), highlighting the need for more data on this disease. The burden of *T. solium* was estimated to be 2,788,426 DALYs by the WHO Estimates of the Global Burden of Foodborne Diseases (11).

In areas endemic for cysticercosis, approximately 30% of people with epilepsy show lesions of NCC on imaging (21). Epilepsy affects an estimated 23.4 million people worldwide (22) and can involve loss of consciousness, acute bowel or bladder dysfunction, injuries or sudden death. It is also associated with social stigma and discrimination in many countries, especially in women and girls in which might be associated to witchcraft. Between 60% to 70% of people with epilepsy respond to treatment however, approximately 80% of people with epilepsy live in low- and middle-income countries, and do not receive appropriate treatment.

Assessment of current use:

ALB and PZQ are the only drugs used for the antiparasitic treatment of NCC. ALB is usually the first choice, due to costs and availability. More details are provided in Section 9.

Likely impact of treatment on the disease:

Antiparasitic therapy results in better resolution of cysts, lower risk for recurrence of seizures, and improved seizure control. More details are provided in Section 9.

Importantly, it also has a social impact, as a better control of seizures and epilepsy might assist in managing social discrimination and stigma.

Public health need:

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.

NCC burdens health systems, economies, societies and individuals due to the impact of epilepsy on wages, health costs, and social stigmatization of sufferers and caretakers.

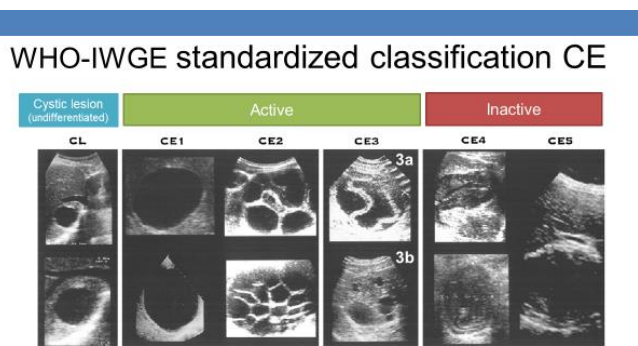
9. Review of benefits: summary of evidence of comparative effectiveness.

CE & AE:

The main reference document is the “Expert consensus for the diagnosis and treatment of CE and AE in humans” published in 2010 (2) by the WHO-Informal Working Group Echinococcosis (WHO-IWGE), which reviewed and updated the previous WHO-IWGE recommendations. An expert meeting of the WHO-IWGE aimed to reach a consensus on the clinical management of patients with CE and AE was organized in France, chaired by Prof. P. Craig (UK) Coordinator, WHO-IWGE, and by Dr. F.-X. Meslin, Division of Emerging Diseases, WHO. A final consensus was achieved in February 2009. Papers covering the subject were obtained by a Medline search of the literature published in English on this subject. Papers published from 1980 to 2008 were included. The authors’ files were used as well. Levels of recommendations followed the “Guide to Practice Guidelines” of the Infectious Diseases Society of America (23).

Summary of available data CE

A relatively recent narrative review has been published by Kern et al in 2017 (3). The information below is from the Expert Consensus from 2010. Any additional information from the narrative review has been clarified. The nomenclature of the CE cysts used in the text, is the one of the WHO-IWGE as per Table below:



Recommendation: 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.

Strength of recommendation: B (moderate evidence to support a recommendation for use)

Quality of Evidence: III (evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of committees).

Drugs: ALB is currently the drug of choice to treat CE, either alone or together with percutaneous treatment. Given orally, at a dosage of 10–15 mg/kg/day, in two divided doses, with a fat rich meal to increase its bioavailability, it should be administered continuously, without the monthly treatment interruptions recommended in the 1980s. Treatment interruptions were felt to be required because of the limited long-term toxicity data available in the early days of use. However, optimal dosage and optimal duration have never been formally assessed. Alternatively, MBZ may be used at a dosage of 40–50 mg/kg body weight daily, in three divided doses with fat-rich meals, if ALB is not available or not well tolerated.

Benefits: 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 (24, 25). ALB is more effective in young patients and for small CE1 and CE3a cysts. Benzimidazoles are less effective for CE2 and CE3b (24, 25). The importance of cyst stage and size in determining response to treatment was confirmed by a systematic review (26). Randomized controlled trials that compare standardized benzimidazole therapy on responsive cyst stages with the other treatment modalities are needed to draw reliable conclusions.

Additional information from Kern et al review (3): 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 with additional interventional procedures: 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.

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.

Strength of recommendation: B (moderate evidence to support a recommendation for use)

Quality of Evidence: III (evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of committees).

Drugs: 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.

Benefits: 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 (19, 27).

Additional information from Kern et al review (3): Treatment with benzimidazoles was introduced into clinical practice in 1975. 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 non-parasitocidal, 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.

Comparative effectiveness – medicines for CE & AE

Reviewed by Kern et al, 2017 (3)

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 (28). 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 (29). 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 trimethoprim 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 administered intravenously. Amphotericin B may be an option in the rare cases where benzimidazole treatment fails.

Neurocysticercosis:

Praziquantel was first used for NCC in 1979 (4) as the first specific cysticidal drug, followed by ALB in 1987 (5).

The first meta-analysis of cysticidal drugs for neurocysticercosis: albendazole and praziquantel was published by Del Brutto and colleagues in 2006 (30).

The IDSA and ASTMH used the GRADE methodology to evaluate the quality of the evidence and produce recommendations for their Clinical Practical Guidelines for the diagnosis and treatment of neurocysticercosis published in 2018 (6).

The WHO has also used the GRADE methodology for the recently submitted WHO management guideline for *Taenia solium* neurocysticercosis (approved with revisions by the WHO GRC – October 2020).

All of them conclude that the use of cysticidal drugs (albendazole and praziquantel) is beneficial for the patient.

Summary of available data NCC:

1- Meta-analysis ALB and PZQ for the treatment of NCC (Del Brutto et al, 2006):

Eleven studies met the inclusion criteria. 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.

2- Clinical Practical Guidelines for the diagnosis and treatment of neurocysticercosis (ISDA and ASTMH):

Recommendations related to antiparasitic treatment (the recommendation number as per original Guidelines):

11. In patients with untreated hydrocephalus or diffuse cerebral edema, we recommend management of elevated intracranial pressure alone and not antiparasitic treatment (strong, moderate).
12. In the absence of elevated intracranial pressure, we recommend use of antiparasitic drugs in all patients with viable parenchymal NCC (strong, moderate).
13. For patients with 1–2 viable parenchymal cysticerci, we recommend albendazole monotherapy for 10–14 days compared to either no antiparasitic therapy (strong, high) or combination antiparasitic therapy (weak, moderate).
14. We recommend albendazole (15 mg/kg/day) combined with praziquantel (50 mg/kg/day) for 10–14 days rather than albendazole monotherapy for patients with >2 viable parenchymal cysticerci (strong, moderate).
15. We suggest retreatment with antiparasitic therapy for parenchymal cystic lesions persisting for 6 months after the end of the initial course of therapy (weak, low).
21. We recommend that patients with multiple enhancing lesions and seizures be initially treated with antiepileptic drugs, antiparasitic therapy, and corticosteroids as outlined in the section on viable parenchymal cysticerci (*weak, moderate*).
25. We suggest albendazole therapy rather than no antiparasitic therapy for all patients with single enhancing lesions (weak, moderate).
29. We recommend symptomatic therapy alone instead of antiparasitic drugs in patients with calcified parenchymal lesions (*strong, moderate*).
38. We recommend that patients with subarachnoid cysts be treated with antiparasitic drugs

(strong, low).

39. (subarachnoid cysts) We suggest that antiparasitic therapy be continued until there is radiologic resolution of viable cysticerci on MRI and resolution of other evidence of cysticerci (weak, low). Responses often require prolonged therapy, which can last for more than a year.

45. We suggest that both medical (antiparasitic drugs plus anti-inflammatory drugs) and surgical approaches be considered for spinal NCC (weak, low).

47. There is no evidence that management of NCC in children should be different than in adults with the same form of disease (strong, moderate). Dosing should be weight based.

The summary of evidence for all these recommendations is included in the Guidelines document (6).

3- WHO management guideline for *Taenia solium* neurocysticercosis (approved with revisions by the WHO GRC – October 2020):

This submitted guideline includes two proposed recommendations related to antiparasitic treatment:

- Anthelmintic therapy in combination with corticosteroids should be provided to individuals with symptomatic NCC and **viable parenchymal brain cysts** for better outcomes in terms of cyst resolution, and potentially improved seizure control.

Strength: strong Quality of evidence: moderate

Rationale: Quality of evidence was moderate for the effect of anthelmintic therapy on cyst resolution, and moderate for the effect of anthelmintic therapy in improving seizure control. It was decided that this should be a strong recommendation because the potential benefit – cyst resolution and possibly improved seizure control – likely outweighs any potential harm associated with the use of anthelmintic therapy.

Important remarks:

- ALB, in combination with corticosteroids, has been shown to be superior to either corticosteroids only or no treatment at all.
 - Dual therapy with PZQ and ALB has been shown to be more effective than treatment with ALB alone in individuals with two or more parenchymal brain cysts.
 - Evidence on the use of ALB in pregnant women was not evaluated; pregnant women should seek expert advice before receiving treatment with ALB.
 - There is no evidence that anthelmintic therapy in children should be different to that of adults.
 - Although evidence is lacking, the clinical experience of experts indicates that anthelmintic drugs should not be used in patients with symptomatic NCC and encephalitis. If inflammation is pronounced in these cases, patients should be treated with corticosteroids alone.
 - Enhanced dosing schedules of corticosteroids (i.e. of 28 days duration) was associated with better clinical outcomes compared to shorter dosing schedules (e.g. of 10 days duration), however this may not be the optimal schedule.
- Anthelmintic therapy in combination with corticosteroids should be provided in individuals with symptomatic NCC and **single enhancing lesion** for better outcomes in terms of cyst resolution and potentially improved seizure control.

Strength: moderate Quality of evidence: moderate to very low

Rationale: Quality of evidence was viewed as low for the effect of anthelmintic therapy on cyst resolution, and very low for the effect of anthelmintic therapy in improving seizure control. It was decided that this should be a conditional recommendation because of the methodological heterogeneity between studies. However, all studies found the combination of ALB and corticosteroids to have a beneficial effect.

Important remarks:

- Quality of evidence was graded as low for the effect of anthelmintic therapy on cyst resolution, and very low for the effect of anthelmintic therapy on seizure control in individuals with symptomatic NCC with single enhancing lesion.
- Many studies were available on the use of anthelmintic therapy in combination with corticosteroids in individuals with single enhancing lesions, however significant limitations are present in the synthesis of this data in existing meta-analyses.

The summary of evidence for all these recommendations is included in Annex IV of the submitted Guideline. The table below is a summarised version. Only studies related to ALB are included in the table below, as the studies which included PZQ had methodological issues (31-33), but based on

expert opinion, plus the study on the combination of ALB and PZQ (34), PZQ was also included in the recommendation.

Question 2: In individuals with symptomatic NCC with viable parenchymal brain cysts , is the use of anthelmintic therapy associated with better clinical outcomes compared to symptomatic treatment alone?	
Factor	Explanation
Narrative summary of the evidence base	<p>Eight RCTs were found for PICO 2. Due to the high risk of bias in six studies, only two studies were included and due to the incomparability of several factors, synthesis of evidence from the different studies is impossible.</p> <p><u>Seizure control:</u> Based on Carpio et al. (2008) and Romo et al. (2014); the latter re-analysed data from the former, therefore it was not counted as a separate study. When the analysis was restricted to patients only with active parenchymal lesions (71) during months 1–12 the reduction in generalized seizures was significant (ALB n=36 vs placebo n=28; RR 0.07; 95% CI 0.01–0.78). Garcia et al. (2004) showed no difference in people free of seizures in different groups. The reduction of partial seizures was not significant, but the reduction of seizures with generalization was greater in the ALB group. Patients in the placebo group had increased tendency to present seizures with generalization (22/59 versus 13/57 in ALB group, RR 1.63, 95% CI: 0.91–2.92).</p> <p><u>Cysticidal effect:</u> Carpio et al. (2008) showed a greater statistically significant effect in the proportion of patients in whom cysts disappeared after anthelmintic treatment in the ALB group compared with placebo. Reduction of number of cysts was not provided. Garcia et al. (2004) showed significant difference in reduction of number of cysts both in noninflamed cysts and cysts with early signs of inflammation. The number of patients free of viable cysts was also higher in the ALB group.</p> <p><u>Adverse events:</u> Carpio et al. (2008) showed no significant difference. Garcia et al. (2004) showed only significant higher occurrence of abdominal pain in the ALB group.</p>
Summary of the quality of evidence	<p>Due to high risk of bias of the initial eight RCTs, only two were further considered. As to the comparison on seizure, the quality of evidence is moderate due to confounding factors.</p> <p>As to the comparison on cysticidal effect, the quality of evidence is moderate due to serious inconsistency and other confounding factors.</p>
Balance of benefit and harms	Benefit of treatment (ALB in combination with corticosteroids) of symptomatic people with active NCC outweighs the harm
<p>Clinical consideration(s)/regional consideration(s)</p> <p>Although there are no systematic reviews available, clinical experience of experts indicates that anthelmintic drugs must not be used in patients with massive numbers of cysts and NCC encephalitis. If inflammation is pronounced in these cases, patients should be treated with corticosteroids alone.</p>	
<p>Strength of recommendation(s)</p> <p>Strong</p>	

<p>Question 4: In individuals with symptomatic NCC with single enhancing lesion (SEL), is the use of anthelmintic therapy associated with better clinical outcomes compared to symptomatic treatment alone?</p> <p>Question 5: In individuals with symptomatic NCC with single enhancing lesion, is the use of anti-inflammatory therapy associated with better clinical outcomes compared to AED treatment alone?</p>	
Factor	Explanation
Narrative summary of the evidence base	<p>One meta-analysis was found including 14 studies.</p> <p>ALB and corticosteroids combined compared to symptomatic treatment significantly decreases the risk of seizure recurrence for individuals with SEL (OR 0.32, 95% CI 0.10–0.93). ALB alone did not significantly reduce this risk (albendazole alone: OR 0.66, 95% CI 0.22–2.17);</p> <p>ALB and corticosteroids compared to conservative treatment was as well the best option regarding lesion resolution (OR 3.05, 95% CI 1.24–7.95). However, ALB alone results also in better lesion resolution compared to symptomatic treatment (ALB alone: OR 2.63, 95% CI 1.61–6.34).</p> <p>An additional three studies were found (not included in the meta-analysis). These three studies support the results of the meta-analysis.</p> <p>Regarding the treatment with corticosteroids, a beneficial effect was found compared to no corticosteroid treatment (RR 0.44, 95% CI [0.23, 0.85]). Side effects of corticosteroids were not addressed.</p>
Summary of the quality of evidence	<p>Quality of evidence was graded as low for the effect of anthelmintic therapy on cyst resolution, and very low for the effect of anthelmintic therapy on seizure control in individuals with symptomatic NCC with SEL</p> <p>Regarding treatment with corticosteroids of individuals with symptomatic NCC with SEL, the evidence was graded as moderate due to downgrading on indirectness.</p>
Balance of benefit and harms	No statement can be made on whether benefit of treatment (ALB in combination with corticosteroids) of individuals with symptomatic NCC with SEL outweighs the harm based on expert opinion. Side effects were not analysed as not mentioned in the above studies.
<p>Clinical consideration(s)/regional consideration(s)</p> <p>Although there is no systematic review available, clinical experience of experts indicates that anthelmintic drug must not be used in patients with pronounced inflammation; in those cases, patients should be managed with corticosteroids alone.</p>	
<p>Strength of recommendation(s)</p> <p>Conditional - It was decided that this should be a conditional recommendation because of the heterogeneity between studies. However, all studies found the combination of ALB and corticosteroids to have a beneficial effect.</p>	

10. Review of harms and toxicity: summary of evidence of safety.

ALB, MEB and PZQ have been used as drug of choice for taeniid cestode cysts for over 30 years, so it is very difficult to estimate how many patients would have been treated to date.

Pregnancy: ALB has been proven teratogenic in rats and rabbits. Physiological exposure to ALB and its principal metabolite, ALB sulfoxide, in early human pregnancy is substantially lower than in the animal species in which teratogenic or embryotoxic effects have been recorded. Therefore, the risk of fetal exposure from the recommended therapeutic dose is probably very small. Despite the

fact that no abnormal birth outcome has been observed following ALB administration during pregnancy, treatment of gravid or potentially gravid females should be avoided, unless the benefit of treatment significantly outweighs the potential risk to the developing fetus (35).

Use of ALB and MEB for CE & AE:

The summary below is extracted from the "Expert consensus for the diagnosis and treatment of CE and AE in humans" published in 2010 (2) by the WHO-Informal Working Group Echinococcosis, with some small additions from the review published by Kern et al, 2018 (3):

Contraindications CE: Benzimidazoles are contraindicated in cysts at risk of rupture and in early pregnancy. Benzimidazoles must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression.

Contraindications AE: In view of the severity of AE, there are only a few contraindications for medical treatment, and they are mostly due to life-threatening side effects. In some instances (e.g. pregnant women) certain precautions are necessary.

Adverse events: 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.

Medical requirements CE: Hospitalization is not necessary but regular follow-up is required. Costs of BMZ and repeated examinations may be prohibitive in countries with limited resources.

Medical requirements AE: Hospitalization is not needed but regular medical and laboratory checks for adverse reactions and efficacy are necessary. The costs of anthelmintics and repeated medical examinations are high. Reference centres should be used to monitor drug levels and specific antibodies, and for specialised imaging techniques (such as PET/CT or MR scans).

Monitoring/Pharmacovigilance CE: Follow-up visits, including ultrasound examination should be done every 3–6 months initially, and every year once the situation is stable. Leukocyte counts and aminotransferase measurements are necessary at monthly intervals to detect adverse reactions. Oral drug doses can be adapted to individual patients in order to achieve adequate serum levels but only a few laboratories have the capability to determine ALB sulfoxide or MBZ plasma drug levels.

Expert opinion (Dr John Horton, medical practitioner and pharmaceutical consultant): *'The ideal would be to have the ability to monitor drug levels, especially when there is evidence of lack of effect. Since we do not know what an effective plasma level would be, largely because while one can measure plasma levels, one cannot do the same for tissue or cyst levels. It is likely that, for any given plasma level, the cyst concentrations will vary between patients, cysts in individual patients and from one day to the next. Penetration will be a function of blood flow and cyst wall thickness if it is dependent on passive diffusion as seems likely. Thus, measurement of plasma levels will only tell you whether the drug is being absorbed and whether, on a particular day and time, there is adequate drug present. As a result of relatively few centres having the capability to routinely monitor drug levels, there are no studies that confirm that regular monitoring actually improves outcome by permitting dose adjustment. Similarly, there are no studies that look at the reverse - not measuring - although in reality most of the published work has been based on the observation that the current dose regimen 'works to some extent, in most patients, most of the time'.*

Expert opinion (Dr Leonardo Uchiumi, medical practitioner in rural Patagonia and expert in CE, Argentina): *'We never have measured serum levels of ALB in clinical situations. It is because of practical and economic reasons (it is only available in just a few centres and in the context of research, it is not feasible in a clinical context, and it is not cost-effective monitoring ALB levels in patients) and I think that we do not need to do it in clinical practice. We try to be pragmatic. We have a protocol for the use of ALB and we analyse the response to ALB based on images using a maximum of 2 cycles of 120 continuous days in the period of one year. If the patient has not any sign of improvement by images, we go to the next stage of treatment by surgery (usually) or percutaneous treatment. We cannot just wait for that patient to become symptomatic or complicated. We avoid to chronify a patient with a latent cyst and try to offer some invasiveness options.*

The monitoring of patients is focused on the side effects of ALB, rather than its levels. We indicate tests of liver enzymes (hepatotoxicity) and hemogram (leukopenia, is rare, I have never seen any case with leukopenia and much less for agranulocytosis as described in the literature). Other side effects are clinical as gastrointestinal intolerance (may be the more common side effect) and alopecia (I have never seen such side effects of ALB but are described in the literature). If side effects arise, stopping ALB should be enough to overcome this situation.

In the real world, even if we could check for the levels of ALB in serum, this would not indicate the levels of ALB inside the cyst as it depends on the nature and structure of the cyst. In our experience, with small cysts (up to 5-7 cm) of CE1 type and in children, ALB has a 90-95% efficacy'.

Monitoring/Pharmacovigilance AE: 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 µmol/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 $1.0 \times 10^9/L$ indicates benzimidazoles toxicity and warrants treatment withdrawal.

Expert opinion on the monitoring frequency for plasma levels (Dr John Horton): 'The elimination half-life of ALB sulphoxide is between 7 and 10 hours so that steady-state concentrations in the plasma are likely to be achieved within 3-4 days allowing for the variable absorption. Similarly, the majority of the drug in the plasma will be cleared over a similar time, although there will be small amounts remaining due to clearance from deep compartments for 1-2 weeks. Thus, if one is going to detect any significant changes in concentration one should probably monitor at no less than 5-7-day intervals since one needs this time for drug levels to reach steady-state again.

What happens in the real world if this is not done? 'I am not aware of any such study. Indeed, most of what happens in the real world is in the absence of any plasma data.'

Use of ALB and PZQ for NCC:

1- Information extracted from the Clinical Practical Guidelines for the diagnosis and treatment of neurocysticercosis (ISDA and ASTMH) (6):

Recommendations related to monitoring antiparasitic treatment (the recommendation number as per original Guidelines):

9. We recommend that patients treated with albendazole for >14 days be monitored for hepatotoxicity and leukopenia (strong, moderate).

The consensus of the panel was that patients who will receive ALB or ALB plus PZQ for >14 days should be monitored with complete blood counts and liver enzymes during the first month. 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 ULN, ALB should be withheld until laboratory tests normalize and alternative approaches considered (e.g. praziquantel or no anthelmintics). This is usually only an issue in prolonged courses of therapy such as those used for subarachnoid disease.

10. No additional monitoring is needed for patients receiving combination therapy with albendazole and praziquantel beyond that recommended for albendazole monotherapy (strong, moderate).

Summary of evidence (references included in the original document):

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 parasitocidal activity and treatment-induced inflammation, including headaches, seizures, and dizziness. Thus, there is a transient increase in the number of seizures after therapy. Hepatotoxicity 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. Reversible alopecia may also occur in up to 10% of cases. Most patients tolerate continuous therapy without interruption. Higher doses (30 mg/kg/day) have been used in some case of subarachnoid cysticercosis, but there are limited data on safety. Few adverse events were noted with duration of up to 4 weeks. Thus, prolonged or high-dose ALB can be used when needed (eg, subarachnoid NCC or giant cysticerci).

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 anthelmintics). 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.

Antiparasitic drugs can worsen symptoms of NCC by inducing an inflammatory response. Evidence from large case series suggests fewer adverse events in patients treated with antiparasitic drugs and steroids compared to antiparasitic drugs alone. Based on this fact, most authorities recommend using corticosteroids whenever antiparasitic therapy is planned. The doses and duration vary with different forms of NCC.

2- Information extracted from WHO management guideline for *Taenia solium* neurocysticercosis (approved with revisions by the WHO GRC – October 2020):

A significant proportion of patients with NCC develop symptoms at the time of the death of at least one of their brain parasites. Thus, when specific anthelmintic agents (initially PZQ and later ALB) were introduced, some authors hypothesized that there was no need to hasten the natural inflammation that accompanied the death of the parasite by using these agents. This led to debate in the literature regarding whether anthelmintic treatment or natural involution of a cyst leads to less scarring and thus a better prognosis in terms of epilepsy evolution. Currently, most of experts affirm there is consensus that the use of anthelmintic drugs is of benefit in most cases with viable parasites, despite having an efficacy of less than 100%.

During the initial days of treatment, an increase in neurological symptoms occurs frequently, due to exacerbated inflammation around the dying larvae. Most symptoms are limited to seizures. Other symptoms such as headaches, focal neurological signs, dizziness, and vomiting are most often reported in the days following anthelmintic treatment, however, the literature is very limited in reporting symptoms other than seizures.

The evidence search identified two studies that included information about adverse events for ALB. There were no studies found related to adverse events and PZQ.

Carpio et al. 2008 (38) showed no significant difference between the ALB group and the placebo group. The summary of patients with possible adverse events can be seen in the table below:

Table 3 Number of patients with possible adverse events by treatment (% of valid responses to question)

Symptom	No (valid %) with symptom in albendazole group	No (valid %) with symptom in placebo group	p Value for χ^2 test
During 8 days of treatment			
Seizures	2 (2.4)	3 (3.5)	1.00*
Headache	59 (70.2)	53 (61.6)	0.236
Stomach problems (nausea, pain or vomiting)	38 (45.2)	40 (46.5)	0.868
Intracranial hypertension	0 (0)	3 (0.5)	0.246*
During first month following treatment			
Seizures	8 (9.8)	10 (12.0)	0.637
Headache	50 (61.0)	51 (61.4)	0.951
Stomach problems (nausea, pain or vomiting)	9 (11.0)	13 (15.7)	0.376
Intracranial hypertension	0 (0)	0 (0)	NA

*Fisher's exact test.

The most common problems reported were headache, seizures and stomach problems. However, seven people died during the study period (two in the treatment group, and five in the placebo group). Most of these patients had extra-parenchymal NCC.

Garcia et al. 2004 (39) observed the same proportion of side effects (e.g. seizures, headaches or other neurological symptoms) during treatment in both study groups (treatment and placebo). However, there was a significant higher occurrence of abdominal pain in the ALB group:

Table 2. Side Effects in the Two Study Groups.			
Side Effect	Albendazole (N=57) no. of patients	Placebo (N=59) no. of patients	P Value
Neurologic			
Partial seizures	8	5	0.51
Seizures with generalization	2	1	0.62
Headache	32	31	0.84
Paresthesia	1	3	0.62
Paresis	1	0	0.49
Dizziness	9	4	0.21
Non-neurologic			
Abdominal pain	8	0	0.006
Nausea	5	2	0.27
Diarrhea	2	0	0.24
Rash	0	1*	1.00
Other	2	1	0.62

* The rash remitted immediately after phenytoin treatment was suspended.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Information on the price of ALB has been collated by Dr Leonardo Uchiumi on behalf of the WHO-IWGE. Dr Uchiumi undertook a survey during 2019. The table below shows the prices of a 400mg tablet in USD, and the cost of a 3-month and 4-month treatment (as used for CE).

Country	Cost (400 mg pill)	3 months (adult 800 mg/day)	4 months (adult 800 mg/day)	% difference	Brand name	Manufact. company
Iran	0.02	3.6	4.8		Bendex	Cipla Ltd.
Bangladesh	0.06	10.8	14.4	200	Albizole	Opsonin
Argentina	0.38	68.4	91.2	1800	Generic	PROFARSE
Hungary	0.8	144	192	3900	Eskazol	GSK
Argentina	1.67	300.6	400.8	8250	Nematel	Elea Phoenix
Spain	1.75	315	420	8650	Eskazole	GSK
Bulgaria	2.09	376.2	501.6	10350	Zentel	GSK
Italy*	2.4	432	576	11900	Zentel	GSK
Uruguay	4.4	792	1056	21900	Helmiben	CELSIUS
Poland	4.5	810	1080	22400	Zentel	GSK
Germany	11.36	2044.8	2726.4	56700	Eskazole	GSK
Switzerland	15	2700	3600	74900	Zentel	GSK

Source: Global access to benzimidazoles: preliminary results of an ongoing survey (unpublished data). Leonardo Uchiumi on behalf of WHO-IWGE. Presented at the World Congress in Echinococcosis, Lima, Peru, 2019.

Additional ALB and PZQ costs have been obtained for this application to complement the above information:

Chile: (information provided by Dr Gerardo Acosta – October 2020)

- Zentel (ALB): 22879–25990 CLP for 3 tablets, 7626–8663 CLP per tablet (9.69 -11 USD/tablet)
- Locally produced ALB: 2 tablets 200mg 4047–4590 CLP (5.14–5.83 USD)

Colombia: (information provided by Dr Liliana Tovar – October 2020)

- Zentel (ALB) 400mg tablet: \$13520 (3.60 USD)
- Various generics ALB 400mg tablets: \$1900 (0.55 USD), \$2350 (0.70 USD), \$2500 (0.75 USD)
- Praziquantel: not available

Ethiopia: (Information provided by Dr Veronica Nwankpe – October 2020)

- Generic ALB: 400mg tablet 33 Birr (0.88 USD)

India: (Information provided by Dr Hameed Nuru – October 2020)

- Locally produced ALB 18-20 Rupees (0.30 USD) per 400 mg tablet.

Kenya: (Information provided by Dr Eberhard Zeyhle – October 2020)

- Zentel (ALB) costs Ksh175/= (USD 1.75) per 400mg tablet
- Alben a generic ALB, costs between Ksh 87/= and 97/= (USD 0.87 and 0.97) per 400mg tablet

Kyrgyzstan: (Information provided by Dr Kuban Abdykerimov and Dr Siezdbek Aitbaev – October 2020)

- Local manufacturer ALB: 30 KGS (0.38 USD) per 400mg tablet
- Indian manufacturer ALB: 55 KGS (0.69 USD) per 400mg tablet
- Turkish manufacturer ALB: 100 KGS (1.26 USD) per 400mg tablet

Mexico: (Information provided by Dr Agnes Fleury – October 2020)

- Branded ALB: 30-40 Mexican pesos (1.4 – 1.9 USD) per 400mg tablet. That represents for NCC a cost of 60-160 Mexican pesos/day (2.8 – 7.4 USD/day).
- Generic ALB: 10 Mexican pesos (0.5 USD) per 400mg tablet.
- Praziquantel: the cost of the treatment is 200 Mexican pesos/day (9.3 USD/day). It is

difficult to find in Mexico.

Morocco: (Information provided by Fatima Amarir – October 2020)

- Zentel (ALB) 400mg tablet: 400 DH (4.3 USD). It is sold in hospitals at 23.20 (2.5 USD).
- Generic ALB brands are sold at 20-22 DH (2.25-2.47 USD).

Mongolia: (Information provided by Dr Bayar Tserendovdon – October 2020)

- Zentel (ALB) 400mg tablet: 4.7 USD. This represents 846 USD for a 3-month treatment.
- Endaril (ALB) 400mg tablet: 1.8 USD per tablet
- Generic ALB can cost 0.13 per 400mg tablet.

Nigeria: (Information provided by Dr Veronica Nwankpe – October 2020)

- Generic ALB 400mg tablets: 300 Naira (0.78 USD)

Sudan: (Information provided by Dr Hameed Nuru – October 2020)

- Locally produced ALB: 50 SD pounds (0.90 USD) per 400mg tablet.
- Imported ALB: 250 SD pounds (4.5 USD) per 400 mg tablet.

Tanzania: (Information provided by Dr Bernard Ngowi and Dr Rogers Mosha – October 2020)

- Zentel (ALB) 400mg tablet: 5000 -7000 TZS (2.20-3 USD)
- ALB 400mg tablets from India: 1000 TZS (0.43 USD)
- Praziquantel from India, 600mg tablet: 1500 - 5000 TZS (0.65-2.20 USD)

Turkey: (Information provided by Dr Nazmiye Altintas – October 2020)

- Locally produced ALB (Biofarma İlaç San. ve Tic. A.Ş):
 - 3 tablets 400mg 9.25 TL (1.17 USD) = 0.39 USD/tablet
 - 60 tablets 400 mg 105.50 TL (13.39 USD) = 0.22 USD/tablet

Uganda: (Information provided by Dr Fred Musisi – October 2020)

- Zentel (ALB) 400mg tablet: 8000 – 10000 UGX (2.15 – 2.69 USD)
- Albendazole 400mg tablet produced in India: 2000 – 5000 UGX (0.54 – 1.34 USD)
- Praziquantel 500mg tablet: 1500 UGX (0.40 USD)

Zambia: (Information provided by Dr Victor Mbao – October 2020)

Prices from a government hospital's pharmacy (subsidised prices):

- Albendazole from India: K5 per 400 mg tablet (USD 0.25/tablet)
- Praziquantel K10 per 600mg tablet (USD 0.5/tablet)

Summary of ALB costs provided in 2020, and costs for the minimum 3-month treatment period for CE in countries with endemic areas:

Country	Cost (USD)		Generic or locally produced	
	400mg tablet	3-month treatment	400mg tablet	3-month treatment
Chile	10.35	1,862.1	5.49	987.3
Ethiopia		-	0.88	158.4
Kenya	1.75	315.0	0.92	165.6
Kyrgyzstan		-	0.78	139.8
Morocco	4.30	774.0	2.36	424.8
Mongolia	4.70	846.0	0.97	173.7
Sudan	4.50	810.0	0.90	162.0
Turkey		-	0.22	39.6
Uganda	2.42	435.6	0.94	169.2

When more than one price has been provided for a type of drug, the average price has been used.

Summary of ALB and PZQ costs provided in 2020, and costs for the minimum 14-day treatment period for NCC in countries with endemic areas:

Country	ALBENDAZOLE				Praziquantel	
	Branded		Generic or locally produced		500mg tablet	14-day treatment
Cost (USD)	400mg tablet	14-day treatment	400mg tablet	14-day treatment		
Colombia	3.6	151.2	0.7	28.0		-
India		-	0.30	12.6		-
Kenya	1.75	73.5		-		-
Mexico	1.90	79.8	0.50	21.0	3.15	132.3
Nigeria		-	0.78	32.8		-
Tanzania	2.6	109.2	0.43	18.1	1.43	59.9
Uganda	2.42	101.6	0.94	39.5	0.4	16.8
Zambia		-	0.25	10.5	0.5	21.0

When more than one price has been provided for a type of drug, the average price has been used.

Cost-effectiveness is not being provided, as there are no real alternatives.

Regulatory information

12.Summary of regulatory status and market availability of the medicine.

N/A: ALB, MEB and PZQ are already included in the EML. This is an expansion of indication.

13.Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia).

The 3 medicines, ALB, MEB and PZQ are already included in the EML and EMLc.

The 3 medicines are included in the International Pharmacopoeia and the United States Pharmacopoeia. ALB and MEB are included in the British Pharmacopoeia.

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