Praziquantel

Section: 6. Anti-infective medicines > 6.1. Anthelminthics > 6.1.3. Antischistosomals and other antitrematode medicines

EMLc | Codes ATC: P02BA01

Indication	Schistosomiasis Code ICD11: 1F86
INN	Praziquantel
Type de médicament	Chemical agent
Type de liste	Liste de base
Additional notes	The square box applies only to the listing of praziquantel on the EMLc for schistosomiasis
Formulations	**Oral > Solid > tablet:** 600 mg (scored) ; 500 mg ; 150 mg
Historique des statuts LME	Ajouté pour la première fois en 1982 (TRS 685) Modifié en 2007 (TRS 950) Modifié en 2023 (TRS 1049) Modifié en 2025 (TRS 1064)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	arpraziquantel (Codes ATC: P02BA03) Oral > Solid > dispersible tablet: 150 mg
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Praziquantel
DrugBank	Praziquantel

Recommandation du comité d'experts

The Expert Committee recognized the public health importance of effective treatments, in age-appropriate dosage forms, for the control and elimination schistosomiasis in children. The Committee noted that more than 50 million preschool-aged children are currently at risk of schistosomiasis in sub-Saharan Africa. The Committee noted that arpraziquantel is the biologically active enantiomer of racemic praziquantel, the medicine currently included on the Model Lists (and recommended in WHO guidelines) for the treatment of schistosomiasis. For administration to preschool-aged children, praziquantel tablets need to be divided, crushed and given with water. The resultant solution has an unpalatable, bitter taste which may cause children to gag or vomit, thereby negatively affecting accurate dosing and treatment compliance. In terms of benefits and harms, based on the evidence presented, the Committee noted that arpraziquantel was associated with high cure rates across age groups, with a similar cure rate to praziquantel. Adverse effects were consistent with the known adverse effects of praziquantel. The Committee considered that the proposed formulation was age-appropriate for the target population, allowing precise dosing of children and infants of different body weights and with better palatability and acceptability than praziquantel for the target age group. However, the Committee also noted the high pill burden to achieve the required weight-based doses. The Committee expressed concern that the application reported that the product was not yet available and that marketing authorization applications were planned in early adopter countries in 2025. However, the Committee also noted that the European Medicines Agency gave a positive scientific opinion

of the product in 2023 in accordance with Article 58 for markets outside of the European Union and it was prequalified by WHO in 2024. The Committee also expressed concern about the financial implications of arpraziquantel use, given it would need to be procured, whereas praziquantel is currently donated. The Committee considered the input from the WHO Department of Neglected Tropical Diseases, which considered the inclusion of arpraziquantel 150 mg dispersible tablets in the EMLc at this time to be premature, given that it is not currently available, and expressed a preference to wait for 300 mg dispersible tablets to become available. Overall, the Committee considered that making an effective, safe, age-appropriate and palatable dosage form of arpraziquantel available should be prioritized, and that its inclusion on the EMLc could serve as an important signal to highlight this priority. Therefore, the Expert Committee recommended the inclusion of arpraziquantel 150 mg dispersible tablets on the EMLc for treatment of schistosomiasis in preschool-aged children based on evidence of similar efficacy and safety with praziquantel, and better palatability and acceptability. Listing is recommended for arpraziquantel as a therapeutic alternative to praziquantel under a square box listing.

Contexte

Arpraziquantel has not been previously evaluated for inclusion on the Model Lists. Praziquantel (40 mg/kg, single dose) is recommended by WHO for the treatment of schistosomiasis in adults and school-aged children (1) and is currently included in the EML and EMLc as 150 mg, 500 mg and 600 mg conventional tablets for this indication. Arpraziquantel contains the biologically active enantiomer (R-(-)-praziquantel) of praziquantel and shares the same mechanism of action.

Pertinence pour la santé publique

Schistosomiasis, caused by parasitic flatworms (blood flukes), is one of the most neglected tropical diseases and is endemic in 78 countries, with moderate to high transmission kinetics in 51 of these countries. WHO estimates that 779 million people are at risk of acquiring a Schistosoma infection with more than 236 million people in 51 countries requiring preventive chemotherapy for schistosomiasis. Over 50% of infections in endemic countries are in children younger than 14 years (1). Schistosomiasis in preschool-aged children has been linked to anaemia (2, 3), decreased immune responses to vaccines (4), co-morbidities due to schistosomiasis egg trapping and subsequent inflammatory local responses (4–6), reduced quality of life, cognitive impairment and educational loss (7–13). The WHO road map for neglected tropical diseases 2021–2030 targets the elimination of schistosomiasis as a public health problem globally by 2030 (14). Praziquantel is well established as the standard treatment for schistosomiasis. However, praziquantel tablets need to be divided, crushed and given with water for dosing in young children. Furthermore, the bitter taste of the solution triggers gagging or vomiting and has negative implications for treatment compliance (15). Additionally, using the relationship between height and weight to predict bodyweight in children increases the risk of under- or over-dosing from dose adjustments when crushing and dividing praziquantel tablets, with a variance of up to 30% of the optimal dose (16).

Bénéfices

The application reported that the efficacy of arpraziquantel has been demonstrated in phase II and III clinical studies. In the clinical development programme for arpraziquantel, 442 children aged 3 months to 6 years were treated with arpraziquantel. The cure rates achieved with arpraziquantel 50 mg/kg in S. mansoni infection and 60 mg/kg in S. haematobium infection were high (> 85% and 95%, respectively). The egg reduction rates were > 90% in both species. An open-label, partly randomized phase III study evaluated the efficacy, safety, palatability and pharmacokinetics of arpraziquantel dispersible tablets in 288 children aged 3 months to 6 years infected with S. mansoni or S haematobium in Côte d'Ivoire and Kenya (17). Participants were divided into four cohorts. In cohort 1, participants aged 4–6 years with S. mansoni infection were randomly assigned (2:1) to receive a single dose of oral arpraziquantel 50 mg/kg (cohort 1a) or oral praziquantel 40 mg/kg (cohort 1b). Participants with S mansoni infection in cohorts 2 (aged 2–3 years) and 3 (aged 3 months to 2 years), received a single dose of oral praziquantel 50 mg/kg. The first 30 participants in cohort 4a (aged 3 months to 6 years) infected with S. haematobium received a single dose of oral arpraziquantel 50 mg/kg. After follow-up assessments, the dose was

increased to 60 mg/kg (cohort 4b). For participants with S. mansoni infection in cohorts 1a, 2 and 3, cure rates with arpraziquantel 50 mg/kg were 87.8% (95% confidence interval (CI) 79.6% to 93.5%), 93.1% (95% CI 77.2% to 99.2%) and 94.4% (95% CI 72.7% to 99.9%), respectively. The cure rate in cohort 1b for participants receiving praziquantel was similar (81.3%, 95% CI 67.4% to 91.1%). For participants with S. haematobium infection in cohorts 4a and 4b, the cure rates at week 3 were 58.6% (95% CI 35.9% to 76.5%) and 86.2% (95% CI 74.6% to 93.9%). Subgroup analyses indicated that cure rates were independent of sex and were similar between countries. Higher cure rates were seen in participants with light infection intensity than in those with moderate or heavy infection intensity (17). Group geometric mean egg reduction rates ranged from 98.8% (95% CI 97.5% −99.7%) to 99.7% (99.5% to 99.9%) in all cohorts. Palatability was assessed in participants aged 5–6 years from cohorts 1 and 4, using a modified 100 mm visual analogue scale. The median palatability score of arpraziquantel was greater than praziquantel (84 mm (interquartile range (IQR) 54 mm to 91 mm) versus 50 mm (IQR 26 mm to 87 mm) (17).

Torts

Arpraziquantel is the biologically active enantiomer of racemic praziquantel. Thus, the safety profile of arpraziquantel is expected to be consistent with that of the well characterized formulations of racemic praziquantel (18–20). In the above-mentioned phase III partly randomized trial, treatment-emergent adverse events occurred in 168/288 (58%) participants, including serious treatment-emergent adverse events in four participants. The most frequently reported such events considered to be treatment-related were abdominal pain (14%), diarrhoea (9%), somnolence (7%) and vomiting (6%). The incidence rates of any treatment-emergent adverse event and treatment-related adverse events were comparable between children aged 4–6 years receiving arpraziquantel 50 mg/kg and praziquantel 40 mg/kg: 66/100 (66%) versus 31/50 (62%) and 31/100 (31%) versus 14/50 (28%), respectively (17). The application reported the following safety data from the clinical development programme of arpraziquantel to show that the safety profile of single doses of arpraziquantel in children aged 3 months to 6 years was consistent with the known safety profile of racemic praziquantel. • Analysis of a pooled safety analysis dataset that included data from paediatric participants in phase II and III studies showed the frequency of treatment-emergent adverse events was reported as 59.4%, 62.5% and 62.2% of participants treated with praziquantel tablets, praziquantel dispersible tablets and arpraziquantel, respectively. The incidence of arpraziquantel-related treatment-emergent adverse events or serious treatment-emergent adverse events was low (< 20% overall) and was generally similar across treatment groups. No treatment-emergent adverse events leading to death or discontinuation on the study were reported. • The most frequently reported treatment-emergent adverse event was anaemia, which was reported in 24.7% of participants in the praziquantel tablet group, 37.5% in the praziquantel dispersible tablet group and 19.0% in the arpraziquantel group. Other reported treatment-emergent adverse events, including abdominal pain, diarrhoea, malaria and vomiting were observed with incidences that were consistent with the population under study and with concomitant conditions. These events were reported at similar rates across study interventions, with the exception of abdominal pain and vomiting, which were observed at a lower frequency in participants receiving praziquantel dispersible tablets than those receiving praziquantel tablets or arpraziquantel. • No evidence was found of a dose-response relationship related to incidence and severity of treatment-emergent adverse events within the dose range studied. • The treatment-emergent adverse event reporting rate was similar to the rates for the praziquantel tablet group and seemed to be associated with Schistosoma species and infection intensity. In the arpraziquantel clinical development programme, only 43 children were younger than 2 years. Of these children, 41 received a dose of 50 mg/kg and two received 60 mg/kg. The safety profile of arpraziquantel in children 2 years and younger seems to be similar to the safety profile of arpraziquantel when used in older age groups, however, it remains uncertain due to the limited available data. Therefore, these results need to be interpreted with caution. The uncertainty is particularly relevant for children younger than 1 year. The application highlighted the following potential safety concerns. • The use of arpraziquantel in patients with undiagnosed asymptomatic neurocysticercosis may lead to seizures in these patients. • Arrhythmia is listed as an adverse reaction with unknown frequency in the product information for racemic praziquantel. While no cases of arrhythmia have been reported for arpraziquantel, cardiac monitoring is suggested.

Rapport coût/efficacité

Arpraziquantel was developed specifically for the proposed paediatric population, after a target product profile that was defined in a consultation of experts and WHO (21). To date, no published cost–effectiveness studies or comparative cost information are available for this medicine in different markets. The application stated that arpraziquantel is intended for public health programmes led by the ministries of health from endemic African countries and is expected to be available in the public sector for programme-based approaches or at public health-care facilities. Therefore, the medicine is expected to be free of charge for patients, or at government-subsidized affordable cost, if applicable within the health-care system of a country.

Directives de l'OMS

The 2022 WHO guideline on control and elimination of human schistosomiasis does not include recommendations for the use of arpraziquantel (1). In endemic communities with a prevalence of Schistosoma spp. infection ≥ 10%, the guideline recommends annual preventive chemotherapy with a single dose of praziquantel at ≥ 75% treatment coverage in all age groups from 2 years of age, including adults, pregnant women after the first trimester and lactating women, to control schistosomiasis morbidity and advance towards eliminating the disease as a public health problem (strong recommendation, moderate-certainty evidence)

Disponibilité

The application stated that arpraziquantel is not yet available. In December 2023, the European Medicines Agency’s Committee for Medicinal Products for Human Use adopted a positive scientific opinion, in accordance with Article 58 of Regulation (EC) No. 726/2004, for arpraziquantel 150 mg dispersible tablets within the scope of the EU-medicines for all procedure for high-priority medicines for human use intended for markets outside the European Union. Marketing authorizations have not yet been submitted or granted for arpraziquantel but are foreseen in 2025 for some countries. In May 2024, arpraziquantel 150 mg dispersible tablets were included in the WHO List of Prequalified Medicines. With weight-based dosing, and based on the current estimation by WHO’s Expanded Special Project for Elimination of Neglected Tropical Diseases that about 24 million preschool children aged 2–5 years old in about 48 African countries would require treatment via mass drug administration, the application estimated that a maximum of 120 million tablets per year would be needed to cover 100% of this population. The manufacturing capacity that is currently set up would allow the needs of about 12 million preschool age children to be covered per year, based on the existing manufacturing capacity for the active pharmaceutical ingredient in China and once a Kenyan manufacturer is approved.

Autres considérations

The Department of Control of Neglected Tropical Diseases reviewed the application and provided comments. The department was hesitant about inclusion of arpraziquantel on the EMLc at this time, citing its current lack of market authorization and availability, its suboptimal strength resulting in a high pill burden and financial implications, especially given the need for procurement in contrast to praziquantel which is donated.

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