Preclinical and Clinical Characteristics of the Trichuricidal Drug Oxantel Pamoate and Clinical Development Plans: A Review

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Abstract
Soil-transmitted helminths (Ascaris lumbricoides, hookworm and Trichuris trichiura) infect about one-fifth of the world’s population. The currently available drugs are all highly efficacious against A. lumbricoides. However, they are only moderately efficacious against hookworm and poorly efficacious against T. trichiura. Oxantel, a tetrahydropyrimidine derivative discovered in the 1970s, has recently been brought back to our attention given its high efficacy against T. trichiura infections (estimated 76% cure rate and 85% egg reduction rate at a 20 mg/kg dose). This review summarizes the current knowledge on oxantel pamoate and its use against T. trichiura infections in humans. Oxantel pamoate acts locally in the human gastrointestinal tract and binds to the parasite’s nicotinic acetylcholine receptor (nAChR), leading to a spastic paralysis of the worm and subsequent expulsion. The drug is metabolically stable, shows low permeability and low systemic bioavailability after oral use. Oxantel pamoate was found to be safe in humans, with only a few mild adverse events reported. Several clinical trials have investigated the efficacy of this drug against T. trichiura and suggest that oxantel pamoate is more efficacious against T. trichiura than the currently recommended drugs, which makes it a strong asset to the depleted drug armamentarium and could help delay or even prevent the development of resistance to existing drugs. We highlight existing data to support the use of oxantel pamoate against T. trichiura infections.

1 Background
Soil-transmitted helminths (Ascaris lumbricoides, hookworm and Trichuris trichiura) are the most widespread parasites in the world. They are most common in the poorest regions of the globe where education and access to sanitation and clean water are limited [1]. Soil-transmitted helminthiasis can lead to severe health consequences, particularly in children. For example, heavy infections with T. trichiura are often associated with chronic iron-deficiency anemia, chronic mucoid diarrhea, rectal bleeding, rectal prolapse, and finger clubbing in adults and children. Even mild infections with T. trichiura may be accompanied by growth retardation in children, while
heavy infections may be linked to severe malnutrition and growth stunting [2].

Currently, the main control strategy used against these intestinal parasites is preventive chemotherapy, i.e. the regular distribution of a single dose of anthelmintic drugs to at-risk groups without prior diagnosis [3]. From 2010 to 2015, this low-cost strategy averted an estimated 44% of the disability-adjusted life-years (DALYs) in children [4]. However, the currently used drugs (usually mebendazole and albendazole) are not equally efficacious against all soil-transmitted helminth species [5]. Although these drugs are highly efficacious against *A. lumbricoides*, resulting in a 10% decline in its prevalence over the last years, they are only moderately efficacious against hookworm and poorly efficacious against *T. trichiura* [2]. Despite not being used as regularly as the benzimidazoles alone, levamisole, pyrantel pamoate and albendazole-ivermectin are also recommended by the World Health Organization (WHO) against soil-transmitted helminths (Table 1) [6]. However, with the exception of albendazole-ivermectin, no monotherapy drugs show acceptable efficacy (i.e. an egg reduction rate (ERR) > 90% based on the target product profile for drugs to be used for soil-transmitted helminths) when used as a single dose against *T. trichiura* infections [5, 7].

An alternative anthelmintic compound discovered in the 1970s and known to be highly efficacious against *T. trichiura* is oxantel pamoate. Oxantel pamoate is a tetraphydropyrimidine derivative (Fig. 1) that has been marketed for veterinary use in non-rodent species for several decades as an oral formulation at single doses of 55 mg/kg in dogs. Several drugs containing oxantel are currently commercialized by different pharmaceutical companies, for both veterinary and human use (Table 2).

One of the ultimate goals is to register oxantel pamoate for the treatment of *T. trichiura* infections (for all ages above one year) at a stringent regulatory authority and market it for countries endemic to this parasite. Currently, oxantel pamoate is only approved and marketed for human use in some countries of South America and Asia for children from six months of age onwards in combination with pyrantel pamoate (Quantrel®) (Table 2). The European Union funded project “Establishment of a pan-nematode drug development pipeline”, Helminth Drug Development Platform (HELP, www.eliminat worms.org) aims to establish a pipeline of anthelmintic drug development candidates. In the framework of HELP, we conducted a thorough review of the available literature to determine if any existing data can be used to support clinical development for *T. trichiura*. Preclinical data from prior sponsors could unfortunately not be obtained. We also summarize results from key experiments on the binding affinity of oxantel pamoate to the human and rat nAChR, metabolism and intestinal epithelial permeability using Caco-2 cells, which were conducted during this process. Finally, in discussion with regulatory agencies, a clinical development plan has started to be defined.

Table 1  Recommended preventive chemotherapy drugs (single-dose) and their efficacy against soil-transmitted helminth infections

| Treatment | Mechanism of action | *Trichuris trichiura* | *Ascaris lumbricoides* | Hookworm |
|-----------|-------------------|----------------------|----------------------|---------|
|           | CR (%) ERR (%)    | CR (%) ERR (%)       | CR (%) ERR (%)       |
| ALB       | β-Tubulin binding | 32.1 64.3            | 96.5 99.7            | 78.5 92.2 |
| MEB       | β-Tubulin binding | 44.4 80.7            | 96.8 99.5            | 41.6 65.0 |
| ALB-IVM   | ND                | 60.0 95.5            | 96.7 99.9            | 83.7 94.7 |
| PP        | L-subtype nAChR agonist | 23.4 41.8         | 93.0 97.0            | 52.6 80.4 |
| LEV       | L-subtype nAChR agonist | 28.5 62.3        | 97.5 91.7            | 14.2 65.3 |

*ALB* albendazole, *CR* cure rate, *ERR* egg reduction rate, *IVM* ivermectin, *LEV* levamisole, *MEB* mebendazole, *nAChR* nicotinic acetylcholine receptor, *ND* not determined, *PP* pyrantel pamoate

Data from Moser and colleagues [8]

△ Adis
### Table 2  
Veterinary and human medical products containing oxantel pamoate

| Brand Name | Company              | Countries                                                                 | Application | Indication                                                                 | Composition                                                                 |
|------------|----------------------|---------------------------------------------------------------------------|-------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| **Veterinary use**                                                                                                      |             |                                                                           |                                                                           |
| Dolpac     | Vetoquinol, Vetcare, Vetochas | Ireland, Estonia, Netherlands, Belgium, France, Italy, Switzerland, Israel, Germany, Austria, Finland | Dog         | AL, TT, HK, tapeworms, hydatid tapeworms                                   | 1397.5 mg oxantel pamoate, 360 mg pyrantel pamoate, 125 mg praziquantel      |
| Bayopet All-Wormer | Bayer AH         | South Africa                                                              | Dog         | AL, TT, HK, tapeworms                                                      | 543 mg oxantel pamoate, 143 mg pyrantel pamoate, 50 mg praziquantel        |
| Canex      | Zoetis              | New Zealand                                                               | Dog, Cat    | AL, TT, HK, tapeworms                                                      | 543 mg oxantel pamoate, 143 mg pyrantel pamoate, 50 mg praziquantel        |
| Guardian Complete Worming | MSD Animal Health | Australia                                                                 | Dog         | Heartworms, AL, TT, HK, hydatid tapeworms, tape-worms                      | 543 mg oxantel pamoate, 143 mg pyrantel pamoate, 50 mg praziquantel        |
| Paratak Plus | Bomac              | New Zealand                                                               | Dog         | AL, TT, HK, tapeworms                                                      | 543 mg oxantel pamoate, 140 mg pyrantel pamoate, 50 mg praziquantel        |
| Plerion    | Intervet            | Italy                                                                     | Dog         | AL, TT, HK, tapeworms                                                      | 200 mg oxantel (as pamoate), 50 mg pyrantel (as pamoate), 50 mg praziquantel |
| Pyraquantyl Worm Free | Ilium Veterinary Products | Australia                                                              | NI          | NI                                                                          | Ni                                                                         |
| Human use                                                                                                               |             |                                                                           |                                                                           |
| Quantref® | JNJ                  | Philippines                                                               | Human (children from 6 months and adults) | AL, TT, HK, E. vermicularis, T. colubriformis, T. orientalis             | Oral suspension 20 mg/mL oxantel pamoate, 20 mg/mL pyrantel pamoate        |
| Quantref® | Pfizer              | Venezuela                                                                 | Human                                                | AL, TT, HK, E. vermicularis, T. colubriformis and T. orientalis          | Oral suspension 50 mg/mL oxantel, 50 mg/mL pyrantel (as pamoate)          |
| Combantrin® Compuesto | Pfizer         | Ecuador, Peru                                                             | Human (children from 6 years and adults)          | AL, HK, E. vermicularis                                                  | Oral tablet 100 mg oxantel (as pamoate), 100 mg pyrantel (as pamoate)     |
| Helmintyc® | Etyc                | Colombia                                                                  | Human                                                | AL, TT, HK, E. vermicularis, T. orientalis, T. colubriformis             | Oral suspension 50 mg/mL oxantel pamoate, 50 mg/mL pyrantel pamoate        |
2 Pharmacology

2.1 Pharmacodynamics (PD)

A study investigating the activity of oxantel pamoate against *T. muris*, the mouse-specific *Trichuris* nematode in vitro, reported a half maximal inhibitory concentration (IC$_{50}$) of 2.35 µg/mL, corresponding to 3.9 µM on L4 larvae (the last stage before the adult stage of *Trichuris* spp.) following incubation for 72 h [10]. In an in vivo experiment, different doses of oxantel pamoate, ranging from 1 to 10 mg/kg, were administered to mice infected with *T. muris*. The oral administration of 10 mg/kg achieved the highest worm burden reduction (93%) and worm expulsion rate (88%) and an ED$_{50}$ value of 4 mg/kg was calculated [10], which is significantly lower than the one of other standard anthelmintics [11].

Following oral administration, oxantel pamoate acts locally in the human gastrointestinal tract by binding to the parasite’s nicotinic acetylcholine receptor (nAChR; neuronal (N)-type). Nicotinic acetylcholine receptors are widely expressed in the worms’ nervous system [12]. These receptors are present both on the neuromuscular junctions on the muscle cells and in the neurons themselves [12]. Oxantel pamoate activates the receptor that leads to an excitatory blockage with subsequent spastic paralysis and expulsion of the worm from the host’s gastrointestinal tract. However, the human gastrointestinal tract also has nAChRs that are structurally similar to those of nematodes and undergo similar mechanisms of gating [13]. The main difference lies in the location of these receptors since, in humans, nAChR is primarily located on intestinal epithelial (Caco-2) and enteric glial cells [13]. Still, the human nAChR could be stimulated by oxantel pamoate as well, which might result in secondary pharmacologic effects.

2.1.2 Secondary Pharmacology

In order to reveal the binding affinity of oxantel pamoate to the human and rat α7 nAChR, an in vitro receptor binding assay was conducted. Experimental details are summarized in Supplementary file 1. Receptors were isolated from human recombinant SH-SY5Y cells and from Wistar rat brain and incubated for 2 or 2.5 hours with oxantel pamoate at concentrations between 0.165 nM and 1.65 mM, respectively. Oxantel pamoate was found to bind to the human and rat receptors with IC$_{50}$ values of 3.48 µM and 33.0 µM, respectively, which is in the same order of the IC$_{50}$ value of 3.9 µM against *T. muris* that was described above. The positive control bungarotoxin showed a higher affinity to both...
human and rat receptors with IC₅₀ values of 1.21 nM and 1.69 nM, respectively. However, due to the intended high dose of oral oxantel pamoate treatment (20 mg/kg), high intestinal concentrations are likely. Thus, local intestinal side effects of treatment with oxantel pamoate, which were already observed in clinical studies, might be due to interactions of oxantel pamoate with the human receptor expressed in the gastrointestinal tract. However, these effects observed in clinical studies were of short duration and reversible. The benefit of the drug seems to predominate potential short-term reversible adverse events.

### 2.2 Pharmacokinetics

#### 2.2.1 Absorption and Distribution

The intestinal epithelial permeability of oxantel pamoate was investigated in an in vitro assay using Caco-2 cells (Supplementary file 2). Oxantel pamoate at a concentration of 10 µM was incubated with Caco-2 cells for 60 min at 37 °C. Four reference compounds with known high (propranolol, labetalol), moderate (ranitidine) and low (colchicine) intestinal permeability were incubated under the same conditions. With a mean apical to basolateral and basolateral to apical permeability of 0.2 and 0.4 × 10⁻⁶ cm/s, respectively, the permeability of oxantel pamoate was in the same range as colchicine and is, therefore, considered of low permeability in vitro (Table 3).

The low gastrointestinal absorption of oxantel pamoate was confirmed in a non-GLP (Good Laboratory Practice) study in rats. A single dose of 100 mg/kg oxantel pamoate was applied (together with 100 mg/kg albendazole). Blood samples were taken 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24, and 33 hours post-treatment. At all time points, plasma levels of oxantel pamoate were below a lower limit of quantification (LLOQ) of 0.4 µg/mL (= 0.66 µM). This accounts for a bioavailability of <0.025%, based on the assumption that the entire dose applied (100 mg/kg) would be absorbed and not metabolized, based on an average blood volume of 16 mL and a body weight of 250 g per rat [14]. Also, according to the core data sheet for Quantrel®, oxantel pamoate is poorly absorbed in the gastrointestinal tract because of its low aqueous solubility. It is stated that only around 8 to 10% is absorbed following a single dose of 10 mg/person and 0.5–1.8% at dose levels of 50 mg/kg; however, the underlying data could not be obtained [15]. Further pharmacokinetic (PK) studies will be embedded in the planned Phase I study (Box 1).

#### 2.2.2 Metabolism and Excretion

The metabolic stability was evaluated by incubating oxantel pamoate and reference compounds (midazolam, propranolol and terfenadine) at a respective concentration of 0.1 µM with human and rat intestinal microsomes (0.1 mg/mL) for 0, 30, 60, 90 and 120 min (experimental details are summarized in Supplementary file 3). Following incubations of oxantel pamoate with either rat or human intestinal microsomes up to 120 min, oxantel pamoate was considered metabolically stable with a calculated mean half-life of over 120 min in both rat and human intestinal microsomes (Table 4).

Since oxantel pamoate was found to be metabolically stable, only a very low intestinal permeability was observed in vitro and low oral bioavailability is expected; therefore, the investigation of hepatic metabolism was not considered.

### Box 1 Suggested clinical development plan for oxantel pamoate

1) A two-week repeated dose toxicity study including PK and local tolerability and reversibility of findings (if any)

2) In vitro and in vivo genotoxicity testing

3) One regulatory compliant Phase 1b study comparing single administration on one day versus single administration on three consecutive days with PK/PD in *T. trichiura*-positive patients

4) One regulatory compliant Phase 3 study in *T. trichiura*-positive patients with mild to severe disease in comparison to mebendazole.
It is assumed that oxantel pamoate acts locally in the gastrointestinal tract following oral administration and is excreted unchanged via feces.

### 2.2.3 Pharmacokinetic Drug Interactions

The inhibition of cytochrome (CYP) enzymes by oxantel pamoate has been investigated in two published in vitro studies \[14, 16\]. Oxantel pamoate did not inhibit CYP1A2, CYP2C19 and CYP3A4 (IC50 > 100 µM) \[14\]. CYP2C9 and CYP2D6 were moderately inhibited by oxantel pamoate (IC50 = 7.8 µM and CYP2D6) \[14\]. In the second study, oxantel pamoate showed an inhibitory activity against CYP2C9 and CYP2D6 \[16\]. The inhibition of CYP1A2, CYP2C19, and CYP3A4 by oxantel pamoate was more pronounced than in a previous study by Cowan et al \[14\], which reported no interaction of oxantel pamoate with these enzymes. Overall, the risk for systemic drug-drug interaction is considered low due to the intended treatment schedule and low exposure.

### 2.3 Toxicity

Concerning single-dose toxicity, Marchiondo reported that oxantel pamoate was well tolerated in acute toxicity studies with median lethal dose (LD50) values of 300, 980 and 3200 mg/kg in mice, rats and rabbits, respectively \[17\]. Repeated-dose toxicity testing in rats will need to be conducted to explore any potential risk related to repeated administrations in humans and to examine the reversibility of findings, if any (Box 1). Local effects on the gastrointestinal tract will be explored in this 14-day repeated dose toxicity study in rats (Box 1). Since there are no published studies allowing for the definition of the genotoxicity risk, in vitro and in vivo testing will need to be conducted according to current regulatory requirements.

If a lack of biologically relevant systemic exposure is confirmed in the planned repeated-dose toxicity study in rats and the Phase I study, studies concerning reproductive and developmental toxicity, as well as phototoxicity, are not planned and are not considered to add value to the program. This also considers animal ethics. Carcinogenicity studies are not required considering the short oxantel pamoate treatment duration of a maximum of three days.

### 3 Clinical Efficacy

A PubMed search identified 15 studies, 11 of which were clinical trials assessing the efficacy of at least one treatment arm including oxantel pamoate alone or in combination with other drugs against *T. trichiura*. From the references of these 11 studies, another 14 were identified and will be mentioned in this review. The characteristics of each of these 25 studies are presented in Table 5. Only studies with a follow-up period between two and six weeks after treatment are listed.

The studies assessing the efficacy and safety of oxantel pamoate were conducted in two phases; the first phase took place in the 1970s followed by the second, which took place after the year 2000 with studies conducted by Swiss Tropical and Public Health Institute researchers. The earliest studies were performed in Asian countries and most had relatively small sample sizes, with the exception of the study by Lim and colleagues, which had a larger sample size \[18\]. Most studies were conducted with children and the most common diagnostic method was the Kato–Katz technique. It is likely that differences in infection intensity, as well as the different diagnostic methods used in the different studies (e.g. Kato Katz, formol-ether, Stoll) have an impact on the observed cure rates (CRs) and egg reduction rates (ERRs) \[19, 20\].

### 3.1 Trichuris trichiura Infections

Despite having relatively low sample sizes, the first trials using oxantel pamoate (sometimes in combination with

| Table 4 Intrinsic stability of oxantel pamoate in rat and human intestinal microsomes |
|-----------------------------------------------|
| **Compound**      | **0 min** | **30 min** | **60 min** | **90 min** | **120 min** | **Mean half-life (min)** |
|-------------------|-----------|------------|------------|------------|-------------|------------------------|
| Rat               |           |            |            |            |             |                        |
| Oxantel pamoate   | 100%      | 102%       | 99%        | 93%        | 82%         | > 120                  |
| Midazolam         | Not recorded |          |            |            |             | > 120                  |
| Propranolol       |           |            |            |            |             | > 120                  |
| Terfenadine       |           |            |            |            |             | > 120                  |
| Human             |           |            |            |            |             |                        |
| Oxantel pamoate   | 100%      | 100%       | 99%        | 95%        | 94%         | > 120                  |
| Imipramine        | Not recorded |          |            |            |             | > 120                  |
| Midazolam         |           |            |            |            |             | > 120                  |
| Propranolol       |           |            |            |            |             | > 120                  |
pyrantel pamoate) already suggested a high efficacy of oxantel pamoate against *T. trichiura* (Table 6). All 17 studies conducted in the 1970s and early 1980s reported on the efficacy using CRs and, in most cases, ERRs; CRs ranged from 29% (with a single dose of oxantel, 10–20 mg/kg) to 100% (with 20 mg/kg of oxantel-pyrantel once per day for 2 days).

Several years later, a series of clinical trials testing oxantel pamoate alone and in combination with other drugs were conducted in Lao People’s Democratic Republic (PDR), Côte d’Ivoire and Pemba Island, Tanzania [38–44] (Table 6). In these trials, the treatment arms with the highest efficacy against *T. trichiura* all included oxantel pamoate with ERRs reaching up to 100%, showing that this drug is clearly superior to most available drugs. However, CRs varied considerably among studies.

In a dose-ranging study, Moser and colleagues identified 5 mg/kg as the minimum effective dose and 22 mg/kg was modelled as the maximum effective dose [41]. A weight-independent dose of 500 mg oxantel pamoate for sub-Saharan African children was proposed by the authors. With this dose, 95% of sub-Saharan African school-aged children would receive a minimum of 11.7 mg/kg and a maximum of 32.0 mg/kg oxantel pamoate [41].

A recent network meta-analysis based on data from six randomized controlled studies confirmed the high efficacy of oxantel pamoate against *T. trichiura* [8]. The authors found that a 20 mg/kg single dose of oxantel pamoate resulted in a significantly higher CR (76%) and ERR (85%) than the monotherapies of albendazole, pyrantel pamoate and tribendimidine.

### Table 5  Characteristics of the clinical trials including oxantel pamoate in at least one treatment arm

| Ref | Year | Follow-up sampling (time after treatment) | Diagnostic techniques | N   | Age group | Location       |
|-----|------|-------------------------------------------|-----------------------|-----|-----------|----------------|
| [21] | 1974 | 22 days                                   | Kato-Katz             | 64  | NR        | South Korea    |
| [22] | 1975 | 10th and 22nd day                         | Stoll and formalin-ether sedimentation | 56  | 6–68      | South Korea    |
| [23] | 1975 | 10 days                                   | Kato-Katz             | 104 | 11–13     | Malaysia       |
| [24] | 1977 | 3 weeks                                   | Kato-Katz and Stoll   | 34  | Orphanage children | South Korea |
| [25] | 1978 | 22 days                                   | Kato-Katz and Stoll   | 60  | Children  | South Korea    |
| [26] | 1978 | 10th and 22nd day                         | Kato-Katz, Stoll and acid-ether concentration | 32  | Elementary school | Philippines |
| [18] | 1978 | 10th and 22nd day                         | Kato-Katz, Stoll and formalin-ether sedimentation | 704 | 2–68      | South Korea    |
| [27] | 1978 | 10–12 days, 20–26 days                    | Beaver egg count and brine-flotation method | 66  | 7–11      | Malaysia       |
| [28] | 1978 | 10 or 11th and 20 or 21st day             | Stoll, formalin-ether sedimentation and coproculture (hookworm) | 45  | All age groups | South Korea |
| [29] | 1978 | 10–20 days                                | Formalin-ethic concentration | 193 | 1 to >55 | Philippines |
| [30] | 1979 | 3–4 weeks                                 | Stoll                  | 150 | NR        | South Korea    |
| [31] | 1980 | 10–15 days, 20–25 days                    | Kato-Katz and/or formalin-ether concentration | 71  | 0–NR      | Philippines |
| [32] | 1980 | Days 14, 21 and 28                        | Formalin-ether and direct smear | 51  | 16–67     | Malaysia       |
| [33] | 1981 | 3 weeks                                   | Salt flotation and Beaver egg count | 472 | 6–12      | Malaysia       |
| [34] | 1981 | 4 weeks                                   | NR                     | 28  | 0–69      | South Korea    |
| [35] | 1982 | 14–21 days                                | Formalin-ether         | 24  | 1–60      | Finland        |
| [36] | 1984 | 3 weeks                                   | Formal-ether sedimentation and Bearer’s direct smear | 201 | 6–13      | Malaysia       |
| [37] | 1992 | 2 weeks, 4 weeks                          | Kato-Katz and tube hatching for hookworm | 327 | NR        | China          |
| [38] | 2002 | 21–24 days                                | Kato-Katz              | 1329 | 6–9      | Tanzania       |
| [39] | 2014 | 18–23 days                                | Kato-Katz              | 480  | 6–14      | Tanzania       |
| [40] | 2015 | 18–23 days                                | Kato-Katz              | 431  | 6–14      | Tanzania       |
| [41] | 2016 | 20–26 days                                | Kato-Katz              | 349  | 6–14      | Tanzania       |
| [42] | 2017 | 14–21 days                                | Kato-Katz              | 601  | 15–18     | Côte d’Ivoire |
| [43] | 2018 | 14–21 days                                | Kato-Katz              | 611  | 12–18     | Tanzania       |
| [44] | 2018 | 17–30 days                                | Kato-Katz              | 414  | 6–15      | Laos           |

NA not applicable, NR not reported, N sample size (number of participants infected with *T. trichiura* in each treatment arm)
Despite its high efficacy against *T. trichiura*, laboratory studies [10] and clinical trials found a wide range of efficacy of oxantel pamoate for the other two soil-transmitted helminths. For *A. lumbricoides*, CRs ranged from 2 to 100% and for hookworm from 10 to 100%. Of note, the highest efficacies were reported by the oldest studies.

### Table 6

| Ref   | Year | Drugs and corresponding doses | Regimen | Formulation | N   | CR (%) | ERR (%) |
|-------|------|--------------------------------|---------|-------------|-----|--------|---------|
| [44]  | 2018 | OXP 20 mg/kg + ALB             | Single dose | Tablet | 138 | 100    | 100     |
| [25]  | 1978 | OXP+PP 20 mg/kg               | qd, 2 days | Suspension | 10  | 100    | 100     |
| [23]  | 1975 | OXP 10 mg/kg                  | qd, 3 days | NR       | 33  | 100    | 100     |
| [35]  | 1982 | OXP+PP 150 mg/tablet, 20 mg/kg| Single dose | Tablet | 117 | 98     | NR      |
| [31]  | 1980 | OXP+PP 15 mg/kg               | bid, 1 day | NR       | 34  | 94     | 99      |
| [44]  | 2018 | OXP 20 mg/kg + PP 20 mg/kg + ALB| Single dose | Tablet | 138 | 93     | 100     |
| [18]  | 1978 | OXP 20 mg/kg                  | Tablet    | Syrup    | 15  | 93     | 100     |
| [37]  | 1992 | OXP+PP 150 mg                 | bid, 2 days | Tablet | 56  | 92     | 98      |
| [24]  | 1977 | OXP+PP 125 mg/tablet, 15 mg/kg| Single dose | Tablet | 22  | 91     | 96      |
| [21]  | 1974 | OXP 10 mg/kg                  | Single dose | Suspension | 64  | 91     | 95      |
| [25]  | 1978 | OXP+PP 15 mg/kg               | Single dose | Suspension | 10  | 90     | 100     |
| [26]  | 1978 | OXP+PP 15 mg/kg               | qd, 2 days | Suspension | 10  | 90     | 100     |
| [18]  | 1978 | OXP 15 mg/kg                  | Single dose | Tablet    | 50  | 90     | 91      |
| [18]  | 1978 | OXP+PP 15 mg/kg               | Single dose | Tablet    | 10  | 90     | 100     |
| [44]  | 2018 | OXP 20 mg/kg + PP 20 mg/kg + MEB 500 mg | Single dose | Tablet | 69  | 89     | 99      |
| [29]  | 1978 | OXP 15 mg/kg                  | bid, 1 day | NR       | 37  | 89     | NR      |
| [23]  | 1975 | OXP 15 mg/kg                  | Single dose | Tablet | 34  | 88     | 96      |
| [30]  | 1979 | OXP 15 mg/kg                  | Single dose | Suspension | 49  | 86     | 93      |
| [24]  | 1977 | OXP+PP 100 mg/tablet, 15 mg/kg| Single dose | Tablet | 34  | 85     | 97      |
| [31]  | 1980 | OXP+PP 20 mg/kg               | Single dose | Tablet | 37  | 84     | 97      |
| [32]  | 1980 | OXP+PP+PRR 20 mg              | Single dose | Tablet | 51  | 84     | 99      |
| [26]  | 1978 | OXP+PP 15 to 20 mg/kg         | qd, 3 days | Tablet | 32  | 84     | 98      |
| [18]  | 1978 | OXP 10-15 mg/kg               | Single dose | Tablet | 193 | 84     | 97      |
| [43]  | 2018 | OXP 25 mg/kg + ALB            | Single dose | Tablet | 220 | 83     | 100     |
| [42]  | 2017 | OXP 25 mg/kg + ALB            | Single dose | Tablet | 148 | 83     | 100     |
| [33]  | 1981 | OXP+PP 10 mg/kg               | qd, 3 days | Tablet | 48  | 79     | 95      |
| [18]  | 1978 | OXP+PP 15-20 mg/kg            | Single dose | Tablet | 78  | 78     | 95      |
| [18]  | 1978 | OXP+PP 10 mg/kg               | Single dose | Tablet | 80  | 77     | 81      |
| [30]  | 1979 | OXP+PP 10 mg/kg               | Single dose | Tablet | 24  | 75     | 98      |
| [18]  | 1978 | OXP 25 mg/kg                  | Single dose | Tablet | 12  | 75     | 96      |
| [44]  | 2018 | OXP 20 mg/kg + PP 20 mg/kg    | Single dose | Tablet | 69  | 74     | 98      |
| [22]  | 1975 | OXP 10 mg/kg                  | Single dose | Tablet | 56  | 73     | 92      |
| [34]  | 1978 | OXP+PP+PYR (100 mg/tablet) 20 mg/kg | Single dose | Tablet | 45  | 71     | 91      |
| [25]  | 1978 | OXP+PP 20 mg/kg               | Single dose | Tablet | 10  | 70     | 72      |
| [40]  | 2015 | OXP 20 mg/kg + ALB            | Single dose | Tablet | 108 | 69     | 99      |
| [27]  | 1978 | OXP 10-20 mg/kg               | qd, 3 days | Suspension | 24  | 67     | 95      |
| [42]  | 2017 | OXP 25 mg/kg + TRIB 400 mg    | Single dose | Tablet | 148 | 66     | 100     |
| [23]  | 1975 | OXP 10 mg/kg                  | Single dose | Tablet | 37  | 65     | 90      |
| [18]  | 1978 | OXP+PP 10 mg/kg               | Single dose | Tablet | 286 | 64     | 90      |
| [41]  | 2016 | OXP 25 mg/kg                  | Single dose | Tablet | 50  | 60     | 98      |
| [36]  | 1984 | OXP+PP 15 mg/kg               | Single dose | Tablet | 201 | 60     | 85      |
| [41]  | 2016 | OXP 30 mg/kg                  | Single dose | Tablet | 50  | 59     | 99      |
| [34]  | 1981 | OXP+PP, 75 mg/tablet, 10 mg/kg| Single dose | Tablet | 33  | 55     | 86      |
| [29]  | 1978 | OXP 15 mg/kg                  | Single dose | Tablet | 193 | 53     | NR      |
| [41]  | 2016 | OXP 20 mg/kg                  | Single dose | Tablet | 50  | 50     | 98      |
| [41]  | 2016 | OXP 15 mg/kg                  | Single dose | Tablet | 51  | 49     | 97      |
| [33]  | 1981 | OXP+PP 10 mg/kg               | Single dose | Tablet | 84  | 48     | 86      |
| [38]  | 2002 | OXP+PP 10 mg/kg               | Single dose | Tablet | 440 | 38     | 87      |
| [39]  | 2014 | OXP 20 mg/kg + ALB            | Single dose | Tablet | 119 | 31     | 96      |
| [27]  | 1978 | OXP 10-20 mg/kg               | Single dose | Tablet | 17  | 29     | 97      |
| [39]  | 2014 | OXP 20 mg/kg                  | Single dose | Tablet | 121 | 26     | 93      |
| [41]  | 2016 | OXP 5 mg/kg                   | Single dose | Tablet | 48  | 22     | 85      |
| [41]  | 2016 | OXP 10 mg/kg                  | Single dose | Tablet | 51  | 22     | 86      |

ALB albendazole, bid twice per day, CR cure rate, ERR egg reduction rate, IVM ivermectin, LEV levamisole, N sample size; NR not reported, MEB mebendazole, PP pyrantel pamoate, qd once per day. Two studies [31, 37] had two follow-up time points; in this table we present the CR and ERR for the second time point only (4 weeks and 25 days, respectively).

### 3.2 *Ascaris lumbricoides* and Hookworm Infections

Despite its high efficacy against *T. trichiura*, laboratory studies [10] and clinical trials found a wide range of efficacy of oxantel pamoate for the other two soil-transmitted helminths. For *A. lumbricoides*, CRs ranged from 2 to 100% and for hookworm from 10 to 100%. Of note, the highest efficacies were reported by the oldest studies. On the other
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hand, the dose-ranging study conducted by Moser and colleagues revealed a low efficacy of oxantel pamoate against *A. lumbricoides* and hookworm [41]. However, when combined with albendazole, mebendazole, pyrantel pamoate, or tribendimidine, the efficacy of oxantel pamoate against these two parasites increased considerably, reaching up to 100% CR and 100% ERR [42, 44].

### 4 Clinical Safety

Side effects of the administration of oxantel pamoate are believed to be due to interactions between oxantel pamoate and the human nAChRs located in intestinal cells. Only a few of the studies from the 1970/80s reported side effects from a single dose of oxantel pamoate (Table 7). Clinical trials implemented after the year 2000 reported adverse events in more detail, presenting the number and proportion of adverse events by treatment arm. These studies found that oxantel pamoate was well tolerated by participants, with adverse events being mild to moderate. The frequency of adverse events seemed to be independent of the oxantel pamoate dose [41]. In many cases, participants already suffered from the same adverse events prior to treatment. No serious adverse event or death was ever reported. In all clinical trials, the most common adverse events were stomach pain and headache.

Only four studies administered more than one dose of oxantel pamoate, either 10 mg/kg once per day for three days alone or in combination with pyrantel pamoate [33, 45] or 15–20 mg/kg once per day for three days in combination with pyrantel pamoate [26]. Of these, only Garcia and colleagues reported to have one participant (3%) with an adverse event; no other studies reported adverse events in treatment arms with oxantel pamoate.

Also, according to Quantrel® (oxantel pamoate-pyrantel pamoate) package information leaflet, it is extremely well tolerated and side effects, if encountered, usually relate to the gastrointestinal tract. All adverse drug reactions identified during the post-marketing experience of Quantrel®, such as decreased appetite, insomnia, dizziness, somnolence, headache, abdominal pain, diarrhea, nausea, vomiting, cold sweat, hyperhidrosis, rash, pruritus and urticarial, were very rare (less than one case per 10,000).

Quantrel® is marketed for children who have 6 months of age or more. Although the absorption is known to be influenced by physiologic properties such as gastrointestinal fluid composition and volume, transit time, morphology, microbiota, and drug metabolizing enzymes, none of these properties differed much between one-year-old children and adults [46]. Therefore, no considerable difference regarding gastrointestinal absorption of oxantel pamoate is expected. Additionally, because no biologically relevant systemic exposure is assumed following oral application, although a role in organ development of nAChRs cannot be excluded based on the ubiquitous expression profile of nAChRs, substantial effects from acute oral dosing (1–3 days) of the drug on developing organs are considered unlikely in children aged one year and older.

Animal reproductive studies have found no teratogenic effects of oxantel pamoate. However, no well-controlled trials assessed the effect of oxantel pamoate in pregnant or lactating women [47, 48]. Therefore, breastfeeding should be discontinued if oxantel pamoate is administered to the mother and the risk benefit needs to be carefully assessed before administering the drug to a pregnant woman [49].

### 5 Conclusions

Our review highlights that oxantel pamoate is, unlike the currently approved drugs, an excellent drug for treating *T. trichiura* infections. Oxantel pamoate has also been shown to be a safe drug that is already being used in children aged > 6 months. Thus, we believe that this drug would be a very important addition to the depleted drug armamentarium, not only because of its high efficacy, but also because it can contribute to delaying or even preventing development of resistance to the currently available treatment options. While reviewing the literature and preparing the briefing book prior to discussions with regulatory authorities we identified additional studies, which are summarized in this review (Box 1). Efforts will continue in the framework of HELP to fill the remaining knowledge gaps so that oxantel pamoate can be available for treatment of *T. trichiura* infections in the near future.

△ Adis
| Ref | Year | Drugs and corresponding doses | Regimen | Formulation | N  | Symptoms/adverse events (%) | Most common adverse effects | Age group | Location |
|-----|------|-------------------------------|---------|-------------|----|-----------------------------|-----------------------------|-----------|----------|
| [21] | 1974 | OXP 10 mg/kg                   | Single dose | Suspension | 64 | One participant with hepatitis showed a slightly unusual liver function, but otherwise no apparent adverse effects observed | NR | NR | South Korea |
| [23] | 1975 | OXP 10 mg/kg                  | Single dose | NR | 37 | "The side effect profile of the drug was excellent and only 2 patients receiving 15 mg/kg complained of abdominal cramps and nausea" | NR | 11 to 13 | Malaysia |
| [22] | 1975 | OXP 10 mg/kg                  | Single dose | Suspension | 56 | "Side effects were negligible. Only a few cases complained of mild nausea, abdominal pain and diarrhoea" | NR | 6 to 68 | South Korea |
| [24] | 1977 | OXP+PP 100 mg/tablet, 15 mg/kg | Single dose | Tablet | 34 | NR | | NR | Orphanage children | South Korea |
| [18] | 1978 | OXP 10 mg/kg                  | Single dose | Tablet | 22 | "A few mild and transient upper gastrointestinal tract side-effects" | NR | 2 to 68 | Korea |
| [28] | 1978 | OXP+PYR (100 mg/tablet) 20 mg/kg | Single dose | Tablet | 45 | "Side effects were not noted in all treated cases" | NR | All age groups | South Korea |
| [29] | 1978 | OXP 15 mg/kg                  | Single dose | NR | 193 | "Transient side-effects such as nausea and mild abdominal pain were observed in two adults" | NR | 1 to >55 | Philippines |
| [25] | 1978 | OXP-PP 15 mg/kg | Single dose | Suspension | 10 | "No side effects were observed" | NR | | Children | Korea |
| [26] | 1978 | OXP-PP 15 to 20 mg/kg         | qd, 3 days | Tablet | 32 | NA | 3 | NA | NA | NR | Elementary school | Philippines |
| Ref | Year | Drugs and corresponding doses | Regimen | Formulation | N  | Symptoms/adverse events (%) | Most common adverse events | Age group | Location |
|-----|------|-------------------------------|---------|-------------|----|-----------------------------|---------------------------|------------|----------|
|     |      |                               |         |             |    | pre-treat 3 h<sup>b</sup> 24 h<sup>b</sup> 48 h |                           |            |          |
| 27  | 1978 | OXP 10–20 mg/kg               | Single dose | Suspension | 17 | "Despite a close scrutiny for drug-related side effects, none of the patients was reported to have any" | NR | 7 to 11 | Malaysia |
|     |      | OXP 10–20 mg/kg               | qd, 3 days | Suspension | 24 |                              |                           |            |          |
|     |      | MEB 100 mg                    | bid, 3 days | Tablets    | 25 |                              |                           |            |          |
| 30  | 1979 | OXP-PP 20 mg/kg               | Single dose | Tablet     | 24 | "There were no undesirable side effects" | NR | NR | Korea |
|     |      | OXP 15 mg/kg                  | Single dose | Tablet     | 49 |                              |                           |            |          |
|     |      | PP 5 mg/kg                    | Single dose | Tablet     | 18 |                              |                           |            |          |
|     |      | PP 2.5 mg/kg                  | Single dose | Tablet     | 59 |                              |                           |            |          |
| 32  | 1980 | OXP+PYR 20 mL                 | Single dose | Suspension | 51 | NR                           | NR | NR | Malaysia |
| 31  | 1980 | OXP-PP 20 mg/kg               | Single dose | Tablet     | 34 | NR                           | NR | 0 to NR | Philippines |
| 34  | 1981 | Fenbendazole, 250 mg/tablet, 30–50 mg/kg | Single dose | Tablet     | 28 | "Minor stomach ache, dizziness, diarrhea and headache" | NR | 0 to 69 | South Korea |
|     |      | OXP+PP, 75 mg/tablet, 10 mg/kg | Single dose | Tablet     | 33 |                              |                           |            |          |
|     |      | Placebo                       | Single dose | Tablet     | 40 |                              |                           |            |          |
| 33  | 1981 | PP 10 mg/kg                   | Single dose | Tablet     | 71 | "Side effects were minimal with pyrantel pamoate and oxantel-pyramet pamoate, although there was mild abdominal discomfort and diarrhea in three or four of the mebendazole and levamisole subjects. One child who had been treated with levamisole showed mild epileptic symptoms" | NR | 6 to 12 | Malaysia |
|     |      | PP 10 mg/kg                   | qd, 3 days | Tablet     | 46 |                              |                           |            |          |
|     |      | OXP-PP 10 mg/kg               | Single dose | Tablet     | 84 |                              |                           |            |          |
|     |      | OXP-PP 10 mg/kg               | qd, 3 days | Tablet     | 48 |                              |                           |            |          |
|     |      | LEM 100 mg                    | Single dose | Tablet     | 64 |                              |                           |            |          |
|     |      | LEM 100 mg                    | qd, 3 days | Tablet     | 50 |                              |                           |            |          |
|     |      | MEB 100 mg                    | bid, 3 days | Tablet     | 67 |                              |                           |            |          |
|     |      | MEB 100 mg                    | bid, 6 days | Tablet     | 42 |                              |                           |            |          |
| 35  | 1982 | Thiabendazole 15 mg/kg        | bid, 2 days | Tablet     | 24 | "Minimal side effects were observed in 2 in-patients. One complained of mild tiredness and the other of nausea about 6 h after the treatment. In both, symptoms lasted only a few hours. Neither allergic nor adverse haematological reactions were encountered" | NR | 1 to 60 | Finland |
|     |      | OXP+PP 150 mg/tablet, 20 mg/kg | Single dose | Tablet     | 117 |                              |                           |            |          |
| 36  | 1984 | OXP+PP 15 mg/kg               | Single dose | Tablet     | 201 | "The drugs were well tolerated and side effects were minimal" | NR | 6 to 13 | Malaysia |
| Ref | Year | Drugs and corresponding doses | Regimen | Formulation | N  | Symptoms/adverse events (%) | Most common age group | Location |
|-----|------|-------------------------------|---------|-------------|----|------------------------------|-----------------------|----------|
| [37] | 1992 | ALB 400 mg                     | Single dose | Tablet        | 94 | NR                           | NR                    | NR       |
|      |      | MEB 100 mg + LEV 25 mg         | bid, 3 days |              | 117| NR                           | NR                    | China    |
|      |      | OXP-PP 150 mg                  | bid, 2 days |              | 56 |                             |                       |          |
|      |      | ALB 400 mg                     | qd, 2 days |              | 60 |                             |                       |          |
| [38] | 2002 | MEB 500 mg                     | Single dose | Tablet        | 448| "No adverse events reported after any of the treatments" | NR                    | 6 to 9   |
|      |      | OXP-PP 10 mg/kg                |           |              | 440|                             |                       | Tanzania |
| [39] | 2014 | OXP 20 mg/kg + ALB             | Single dose | Tablet        | 119| 10/13                        | NA Headache and stomach pain | 6 to 14  |
|      |      | OXP 20 mg/kg                   |           |              | 121| 13/12                        |                       | Tanzania |
|      |      | ALB                            |           |              | 120| 11/9                         |                       |          |
|      |      | MEB 500 mg                     |           |              | 120| 7/5                          |                       |          |
| [40] | 2015 | IVM + ALB                      | Single dose | Tablet        | 109| 9/16                         | NA Headache and stomach pain | 6 to 14  |
|      |      | MEB + ALB                      |           |              | 107| 10/8                         |                       | Tanzania |
|      |      | OXP 20 mg/kg + ALB             |           |              | 108| 13/13                        |                       |          |
|      |      | MEB                            |           |              | 107| 6/6                          |                       |          |
| [41] | 2016 | OXP 5 mg/kg                    | Single dose | Tablet        | 48 | 13/2                         | NA Headache and stomach pain | 6 to 14  |
|      |      | OXP 10 mg/kg                   |           |              | 51 | 8/4                          |                       |          |
|      |      | OXP 15 mg/kg                   |           |              | 51 | 4/2                          |                       |          |
|      |      | OXP 20 mg/kg                   |           |              | 50 | 11/7                         |                       |          |
|      |      | OXP 25 mg/kg                   |           |              | 50 | 13/4                         |                       |          |
|      |      | OXP 30 mg/kg                   |           |              | 50 | 9/7                          |                       |          |
|      |      | Placebo                        |           |              | 49 | 8/8                          |                       |          |
| [42] | 2017 | TRIB 400mg                     | Single dose | Tablet        | 151| 20/20                        | NA Headache, vertigo and stomach pain | 15 to 18 |
|      |      | TRIB 400 mg + IVM              |           |              | 154| 20/22                        |                       | Côte d’Ivoire |
|      |      | OXP 25 mg/kg + TRIB 400 mg     |           |              | 148| 20/22                        |                       |          |
|      |      | OXP 25 mg/kg + ALB             |           |              | 148| 12/9                         |                       |          |
| [44] | 2018 | OXP 20 mg/kg + PP 20 mg/kg + ALB| Single dose | Tablet        | 138| 10/0                         | NA Headache and stomach pain | 6 to 15  |
|      |      | OXP 20 mg/kg + ALB             |           |              | 138|                              |                       | Laos     |
|      |      | OXP 20 mg/kg + PP 20 mg/kg     |           |              | 69 |                              |                       |          |
|      |      | OXP 20 mg/kg + PP 20 mg/kg + MEB 500 MG | | | 69 |                              |                       |          |
### Supplementary Information

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#### Conflict of interest

The authors declare that there is no conflict of interest.

#### Availability of data and material

All underlying data is presented in the manuscript and supplementary files.

#### Author contributions

MSP and JK wrote the first draft of the paper; SS, IS, IG, MC reviewed the paper. All authors read and approved the final version of the manuscript before submission.

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