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REVIEW ARTICLE

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

Key Points

Oxantel pamoate is a safe and efficacious drug against *Trichuris trichiura* infections.

Oxantel pamoate is metabolically stable, shows low permeability and low systemic bioavailability after oral use.

The use of this drug in preventive chemotherapy as a combination treatment (e.g. with pyrantel pamoate) could greatly improve the success of this control strategy and prevent or postpone the development of resistance to benzimidazoles.

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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 anthelminthic 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 anthelminthic compound discovered in the 1970s and known to be highly efficacious against *T. trichiura* is oxantel pamoate. Oxantel pamoate is a tetrahydropyrimidine 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.eliminateworms.org) aims to establish a pipeline of anthelminthic 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.

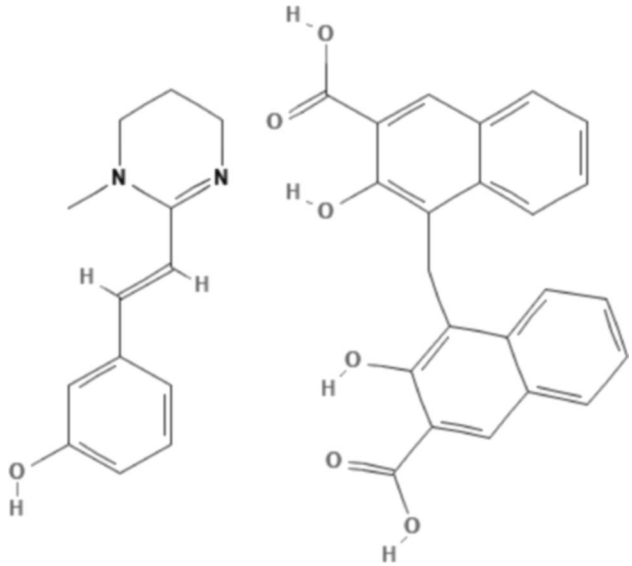

Fig. 1 Structure of oxantel pamoate [9]

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 pamoates

Data from Moser and colleagues [8]

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	545 mg oxantel pamoate 140 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, tapeworms	543 mg oxantel pamoate 143 mg pyrantel pamoate 50 mg praziquantel 0.06 mg ivermectin
Paratak Plus	Bomac	New Zealand	Dog	AL, TT, HK, tapeworms	545 mg oxantel pamoate 140 mg pyrantel pamoate 50 mg praziquantel
Plerion	Intervet	Italy	Dog	AL, TT, HK, tapeworms, hydatid tapeworms	200 mg oxantel (as pamoate) 50 mg pyrantel (as pamoate) 50 mg praziquantel
Pyraquantyl	Ilium Veterinary Products	Australia	NI	NI	NI
Worm Free	Ranvet	Australia	Dog	AL, TT, HK, tapeworms, hydatid tapeworms	542 mg oxantel pamoate 143 mg pyrantel pamoate 50 mg praziquantel
Human use					
Quantrel®	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
Quantrel®	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

Table 2 (continued)

Brand Name	Company	Countries	Application	Indication	Composition
Dualid®	Biotech	Venezuela	Human (children from 6 months and adults)	AL, TT, HK, *E. vermicularis*	Oral suspension: 50 mg/mL oxantel pamoate, 50 mg/mL pyrantel pamoate Chewable tablet: 100 or 250 mg oxantel pamoate, 100 or 250 mg pyrantel pamoate
COMTEL® COMPUESTO	Laboratorios Karnel	Honduras	Human (children from 6 months and adults)	NI	Oral suspension (NI on composition)

AL Ascaris lumbricoides, E. vermicularis, Enterobius vermicularis, HK hookworm, *NI* no information available, *T. colubriformis Trichostrongylus colubriformis, T. orientalis Trichostrongylus orientalis, TT Trichuris trichiura*

2 Pharmacology

2.1 Pharmacodynamics (PD)

2.1.1 Primary Pharmacology

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 anthelminthics [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 IC_{50} 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).

Table 3 Permeability of oxantel pamoate in Caco-2 cells

Compound	Mean A–B permeability (10^{-6} cm/s)	Mean B–A permeability (10^{-6} cm/s)	Mean recovery (%)
Oxantel pamoate	0.2	0.4	85–89
Colchicine	0.3	4.0	71–72
Labetalol	5.1	34.1	84–99
Propranolol	26.3	21.5	88–96
Ranitidine	0.8	2.2	83–95

A–B apical to basolateral, *B–A* basolateral to apical

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.

applicable. 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 (IC_{50} > 100 µM) [14]. CYP2C9 and CYP2D6 were moderately inhibited by oxantel pamoate (IC_{50} = 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 (LD_{50}) 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						16
Human	Oxantel pamoate	100%	100%	99%	95%	94%	> 120
	Imipramine	Not recorded					> 120
	Midazolam						40
	Propranolol						> 120

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)

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 6 *Trichuris trichiura* cure rates (%, CRs) and egg reduction rates (%, ERRs) resulting from all the treatment arms of clinical trials testing the efficacy of oxantel pamoate either alone or in combination with other drugs. The treatment arms were ranked from the highest to lowest CR

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	Single dose	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
[25]	1978	OXP-PP 15 mg/kg	qd, 2 days	Suspension	10	90	100
[18]	1978	OXP 15 mg/kg	Single dose	Syrup	50	90	91
[18]	1978	OXP-PP 15 mg/kg	Single dose	Syrup	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	NR	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	NR	37	84	97
[32]	1980	OXP+PYR 20 ml	Single dose	Suspension	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	Syrup	80	77	81
[30]	1979	OXP-PP 20 mg/kg	Single dose	Tablet	24	75	98
[18]	1978	OXP 25 mg/kg	Single dose	Syrup	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	Suspension	56	73	92
[34]	1978	OXP+PYR (100 mg/tablet) 20 mg/kg	Single dose	Tablet	45	71	91
[25]	1978	OXP-PP 20 mg/kg	Single dose	Suspension	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	NR	37	65	90
[18]	1978	OXP 10 mg/kg	Single dose	Syrup	266	64	90
[41]	2016	OXP 25 mg/kg	Single dose	Tablet	50	60	98
[36]	1984	OXP+PP 15 mg/kg	Single dose	NR	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	NR	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	Suspension	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

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 administrated 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.

Table 7 Percentage of participants with adverse events in each treatment arm before treatment and 3 h, 24 h and 48 h after treatment

Ref	Year	Drugs and corresponding doses	Regimen	Formulation	*N*	Symptoms/adverse events (%)				Most common	Age group	Location
						pre-treat	3 h[ab]	24 h[b]	48 h			
[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
		OXP 15 mg/kg	Single dose		34							
		OXP 10 mg/kg	qd, 3 days		33							
[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
		OXP 10 mg/kg	qd, 3 days	Suspension	4							
[24]	1977	OXP+PP 100 mg/tablet, 15 mg/kg	Single dose	Tablet	34	NR				NR	Orphanage children	South Korea
		OXP+PP 125 mg/tablet, 15 mg/kg	Single dose	Tablet	22							
[18]	1978	OXP 10 mg/kg	Single dose	Syrup	266	"A few mild and transient upper gastrointestinal tract side-effects"				NR	2 to 68	Korea
		OXP 10–15 mg/kg		Tablet	193							
		OXP 15 mg/kg		Syrup	50							
		OXP 20 mg/kg		Syrup	15							
		OXP 25 mg/kg		Syrup	12							
		OXP-PP 10 mg/kg		Syrup	80							
		OXP-PP 15 mg/kg		Syrup	10							
		OXP-PP 15–20 mg/kg		Tablet	78							
[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
		OXP 15 mg/kg	bid, 1 day	NR	37							
[25]	1978	OXP-PP 15 mg/kg	Single dose	Suspension	10	"No side effects were observed"				NR	Children	Korea
		OXP-PP 15 mg/kg	qd, 2 days		10							
		OXP-PP 20 mg/kg	Single dose		10							
		OXP-PP 20 mg/kg	qd, 2 days		10							
		MEB 100 mg	bid, 3 days	Tablet	20							
[26]	1978	OXP-PP 15 to 20 mg/kg	qd, 3 days	Tablet	32	NA	3	NA	NA	NR	Elementary school	Philippines

Table 7 (continued)

Ref	Year	Drugs and corresponding doses	Regimen	Formulation	*N*	Symptoms/adverse events (%)	Most common	Age group	Location
						pre-treat 3 h[ab] 24 h[b] 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		Suspension	49				
		PP 5 mg/kg		Dry syrup	18				
		PP 2.5 mg/kg		Tablet	59				
[32]	1980	OXP+PYR 20 mL	Single dose	Suspension	51	NR	NR	16 to 67	Malaysia
[31]	1980	OXP-PP 20 mg/kg	Single dose	NR	37	NR	NR	0 to NR	Philippines
		OXP-PP 15 mg/kg	bid, 1 day		34				
[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-pyrantel 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		46				
		OXP-PP 10 mg/kg	Single dose		84				
		OXP-PP 10 mg/kg	qd, 3 days		48				
		LEV 100 mg	Single dose		64				
		LEV 100 mg	qd, 3 days		50				
		MEB 100 mg	bid, 3 days		67				
		MEB 100 mg	bid, 6 days		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	NR	201	"The drugs were well tolerated and side effects were minimal"	NR	6 to 13	Malaysia

Table 7 (continued)

Ref	Year	Drugs and corresponding doses	Regimen	Formulation	*N*	Symptoms/adverse events (%)				Most common	Age group	Location
						pre-treat	3 h[ab]	24 h[b]	48 h			
[37]	1992	ALB 400 mg	Single dose	Tablet	94	NR				NR	NR	China
		MEB 100 mg + LEV 25 mg	bid, 3 days		117							
		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	Tanzania
		OXP-PP 10 mg/kg			440							
		Placebo			441							
[39]	2014	OXP 20 mg/kg + ALB	Single dose	Tablet	119	10	8/13[a]	15/13	NA	Headache and stomach pain	6 to 14	Tanzania
		OXP 20 mg/kg			121	18	13/12	17/21				
		ALB			120	11	13/9	10/13				
		MEB 500 mg			120	11	7/5	18/10				
[40]	2015	IVM + ALB	Single dose	Tablet	109	19	9	16	NA	Headache and stomach pain	6 to 14	Tanzania
		MEB + ALB			107	10	8	11				
		OXP 20 mg/kg + ALB			108	12	13	17				
		MEB			107	15	6	16				
[41]	2016	OXP 5 mg/kg	Single dose	Tablet	48	4	13	2	NA	Headache and stomach pain	6 to 14	Tanzania
		OXP 10 mg/kg			51	10	8	4				
		OXP 15 mg/kg			51	6	4	2				
		OXP 20 mg/kg			50	2	11	7				
		OXP 25 mg/kg			50	4	13	4				
		OXP 30 mg/kg			50	4	9	7				
		Placebo			49	4	8	8				
[42]	2017	TRIB 400mg	Single dose	Tablet	151	23	15	20	NA	Headache, vertigo and stomach pain	15 to 18	Côte d'Ivoire
		TRIB 400 mg + IVM			154	20	17	22				
		OXP 25 mg/kg + TRIB 400 mg			148	24	20	22				
		OXP 25 mg/kg + ALB			148	16	12	9				
[44]	2018	OXP 20 mg/kg + PP 20 mg/kg + ALB	Single dose	Tablet	138	10	1	0	NA	Headache and stomach pain	6 to 15	Laos
		OXP 20 mg/kg + ALB			138							
		OXP 20 mg/kg + PP 20 mg/kg			69							
		OXP 20 mg/kg + PP 20 mg/kg + MEB 500 MG			69							

Table 7 (continued)

Ref	Year	Drugs and corresponding doses	Regimen	Formulation	*N*	Symptoms/adverse events (%)				Most common	Age group	Location
						pre-treat	3 h[ab]	24 h[b]	48 h			
[43]	2018	MOX + ALB	Single dose	Tablet	129	10	12	18	6	Stomach pain, constipation, and headache	12 to 18	Tanzania
		OXP 25 mg/kg + ALB			220	11	8	19	2			
		MOX + TRIB 200/400 mg			130	9	7	24	4			
		MOX			132	11	5	19	3			

The doses of the following drugs were the same in all studies: moxidectin 8 mg, albendazole 400 mg and ivermectin 200 µg/kg

ALB albendazole, *IVM* ivermectin, *LEV* levamisole, *MEB* mebendazole, *MOX* moxidectin, *OXP* oxantel pamoate, *PP* pyrantel pamoate, *Pre-treat* pre-treatment, *TRI* tribendimidine

[a]2 h in the case of Moser and colleagues [41].

[b]Adverse events to oxantel pamoate (3 h and 24 h)/adverse events to albendazole and mebendazole (3 h and 24 h) and to oxantel pamoate (48 h).

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

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