Subject information for participation in a medical-scientific study

Controlled human *Schistosoma mansoni* infection study with female cercariae

Official title: Establishing a Female-only Controlled Human Schistosoma mansoni Infection Model: a safety and dose finding study (CoHSI2)

Introduction

Dear Sir/Madam,

You are being asked to take part in a medical-scientific study. Participation is voluntary. In order to participate your written consent is required. Before you decide whether you want to take part in this study, you will be given an explanation about what the study involves. Please take your time to read this information and ask the investigators if you have any questions. You can also ask the independent expert mentioned at the end of this letter for additional information. You can also discuss with you partner, friends or family. You can find more information about participating in a study in the attached brochure “Medical-scientific research”.

1. General information

This study is conducted at the “Leids Universitair Medisch Centrum”. For this study we expect 22 healthy subjects to participate in The Netherlands.
The Medical Ethics Review Committee Leiden Den Haag Delft has approved this study.
General information about the assessment of research can be found in the brochure “Medical-scientific research”.

2. Purpose of the study

In this study, subjects are exposed to female *Schistosoma mansoni* larvae. We are investigating whether healthy subjects become infected with *Schistosoma* worms and if any changes in the immune system or gut bacteria occur after infection. This information can be used for vaccine research.

3. Background of the study

Schistosomiasis is a common tropical infection with *Schistosoma* worms. Most symptoms are caused by eggs that eggs that get trapped in the body and cause damage to tissue. There is no effective vaccine against schistosomiasis. In this study, subject are exposed to a small number of female Schistosoma larvae in a controlled setting. Because only female Schistosoma larvae are used, the adults worms will produce no or only few eggs. This

controlled infection will provide important information that will be used to develop a Schistosoma vaccine.

More information on the background of the study can be found in attachment E.

4. What participation involves

The participation in the study lasts 12 months.

Screening

Before you can participate in the study, we will assess first assess whether you are eligible to participate. The investigator performs a physical examination; measures your weight, length, blood pressure, and heart rate; will take urine and blood for health tests. The investigator will also ask about your medical history and ethnicity. You will also be tested for HIV and hepatitis B and C. If you have any of these conditions, the investigator will tell you. If you do not want to know these test results, you cannot participate. You will also be screened for drugs use and. If you are female, a pregnancy test will be performed.
During screening we sometimes find results that need medical follow up. We will always tell you about these. Follow-up will be with your own general practitioner or medical specialist. These costs follow under your own medical insurance. It may also happen that you are healthy, but are not suitable for participation.

Study design

A maximum of 22 volunteers will participate in this study. Volunteers are exposed to a pre-defined dose of female, young Schistosoma larvae, also called cercariae. First, three volunteers are exposed to the lowest dose of cercariae (group A). If all three become infected and show a positive schistosomiasis test, the next seven volunteers are exposed to the same dose (group B). If not all volunteers get a positive schistosomiasis test, three new volunteers are exposed to a higher dose of larvae (group A). In figure 1 you can see how these doses will increase. The highest dose is 60 cercariae. If in total 10 volunteers (from A and B together) are exposed to the same dose, the study stops. All volunteers will be treated with praziquantel two times to cure the infection.

Infection with Schistosoma worms

Infection will take place by exposure to cercariae. On the day of infection, you will come to the hospital where your blood and urine are checked to see if you’re still eligible for participation. That day you will also hand in a container with stool.
The infection takes place by applying water with cercariae onto the skin. This will stay for half an hour. You cannot see or feel the cercariae. After infection, you will stay for another half hour in hospital. The entire visit for infection lasts about three hours.

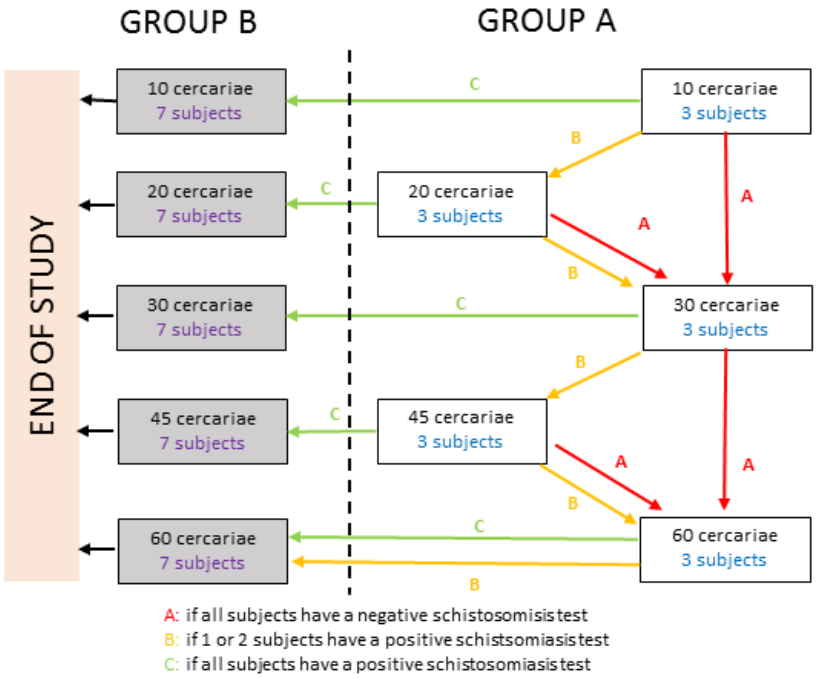


Figure 1. Study design. If all three volunteers from group A have a positive schistosomiasis test another seven volunteers from group B will be infected with the same dose (green arrows). If not all three volunteers from group A have a positive schistosomiasis test, the dose is altered (yellow and red arrows)

Visit and tests

For this study there are 17 visits. It is necessary that you visit the study centre every week during the first 16 weeks after infection. After this, you will visit the study centre every two weeks (week 18 and week 12). The last visit takes place one year after infection. Each visits takes about 15 minutes. In figure 2 you can find a study visit overview.

Figure 2. Overview study visits

Each visit we will ask about symptoms you may have had. You will get a diary in which you can keep track of the symptoms. This will be discussed at each visit. If needed, the investigator will perform a physical examination. We will also collect blood and urine every week to monitor the infection. On certain visits we will also examine your stool In appendix C you can find what tests are performed at each of the visits

5. What will be expected of you

For the study to run smoothly and for your own safety, it is important that you follow the following agreements:

The agreements are that you:

- contact the research team when you have symptoms (the study team is available 24 hours a day, 7 days a week);
- do not participate in other medical-scientific research;
- comply with visit schedule;
- do not travel to areas where there is Schistosoma (during the study).

It is important that you contact the investigator:

- before you use other medicine:. Even if these are homeopathic medicines, natural medicines, vitamins and/or over the counter medicines;
- if you are admitted or treated in hospital;
- if you suddenly experience health symptoms;
- if you no longer wish to participate in the study;
- if your contact details change.

Your pregnancy or your partner's

Pregnant women or women who are breastfeeding, cannot participate in the study. Women should not become pregnant during the study, because it could have effects on the unborn child. It is unclear what these could be. It is important you tell this to your partner. The investigator will discuss appropriate contraception. If you do get pregnant during the study, you should let the investigator know immediately.

6. Possible side effect and discomforts

A schistosomiasis infection may gave symptoms. We expect these to occur in some volunteers. These can start right after infection or later.

These symptoms occur frequently (in 1 out of 10 people, or more):

- Itch and rash at place of infection. This happens very often. In our earlier study with male cercariae nearly everyone (16 out of 17) had a mild rash. The itch went away within one day in all volunteers, but the rash disappeared in half of the people after 3 weeks. In one volunteer the rash resolved after 9 weeks.
- Acute schistosomiasis syndrome (Katayama fever) – this is a illness with flu-like symptoms. These symptoms can be fever, headache, tiredness, coughing and feeling

weak. If you get these, they can be treated with paracetamol or anti-inflammatory drugs. Acute schistosomiasis syndrome can last 2-10 weeks. In our earlier study with male cercariae, about 1 in 3 volunteers had symptoms. These started approximately four weeks after infection. In 80% of the volunteers (4 out of 5) these symptoms resolved within two weeks, but one had symptoms for six weeks.

- Schistosomiasis infection can also have unknown side effects. Because we only use female cercariae, the chance that eggs are produced is small. From animal experiments we know that sometimes a female worm can produce eggs without male worms. To make this risk as small as possible, you are treated with praziquantel as soon as the worms are mature. This is eight weeks after infection. Before this time, no eggs are produced. You are treated for a second time with praziquantel at 12 weeks after infection to kill any left-over worms. We expect that two treatments are enough to kill all worms, but we are not entirely sure. Therefore there is a small risk that you are infected for a longer time. After the second treatment, we will test the blood to see if there are worms left. If needed, we will treat for a third time.

Praziquantel is a safe drug with few side-effects. The most common side-effect of the drug is tiredness. This occurs in more than 1 out of 10 people. Side-effects that are less common (in more than 1 out of 100) are abdominal symptoms and dizziness. Meer information about praziquantel can be found in the drug information letter (see appendix F).

Tests

Blood draws: Blood collection may cause pain or bruising. In total we draw 560 mL blood in the first 20 weeks. At the last visit, one year after infection, we draw another 70 mL of blood. This amount should not be a problem for adults. For comparison: at the blood bank 500 mL is drawn each time.

Urine collection: Each visit we ask you to provide us urine. You will get containers for collection.

Stool collection: A couple of times we ask you to bring a stool sample that you collect at home. We will give you materials that help collection.

Visit to study centre: You will visit the study centre 20 times in total. Each visit lasts about 15 minutes. For the infection, we need about three hours. It is important that you visit the study centre as agreed and are on time for visits and infection.

7. Possible advantages and disadvantages

It is important that you properly consider the possible advantages and disadvantages before you decide to participate. You do not benefit from participation. However your participation can help the development of a vaccine against schistosomiasis.

Disadvantages of participation in the study may be:

- possible symptoms of a schistosomiasis infection;
- possible discomforts from the tests;
- possible side-effects of treatment with praziquantel.

Participation in the study also means:

- that it costs you time;
- that you have appointments that you need to attend.

All these things are described above under section 4,5, and 6.

8. If you do not want to participate, or would like to stop participating in the study

You decide for yourself whether you want to participate in the study. Participation is voluntary. If you do participate, you can always change your mind and stop, even during the study. You do not have to state why you are stopping. However, you should immediately inform the investigator. If you want to stop after being infected, you will first need to be treated. This means that you will need to come a couple of times for your safety and to monitor treatment.
Any information collected until the moment you inform us about stopping, will be used for the study. Information collected afterwards (treatment and safety tests) will only be collected to monitor safety, but will not be used for the study. If there is any new information about the study that is important for you, the investigator will inform you of this. You will then be asked if you wish to continue your participation.

9. End of the study

Your participation in the study ends when:

- all visits have been completed;
- you personally choose to stop;
- the investigator finds that it is better for you to stop;
- the safety monitoring committee, the government or the assessing Medical Ethics Review Committee, decide to stop the study.

The entire study ends when all participants are finished. After processing all the data, the investigator will inform you about the most important outcomes of the study. This will happen at the last visit. If you do not want to be informed, you can tell the investigator. In that case, he will not inform you.

10. Use and storage of your data and body materials

For this study, your personal data and body materials will be collected, used and stored. This concerns data such as your name, address, date of birth and data about your health. For this study we also need blood, urine, and stool. The collection, use and storage of your data and body materials is required to answer the questions asked in this study and to publish the results. We ask you permission for the use of your data and body materials.

Confidentiality of your data

To protect your privacy, your data will be given a code. Your name and other information that can directly identify you, will be omitted. Data can only be traced back to you with the encryption key. The encryption key remains safely stored in the local research institute. The data that is sent to the sponsor will only contain the code, not your name or other data with which you can be identified. The data cannot be traced back to you in reports and publications about the study.

Access to your data for verification

Some people can access all your data at the research location. Including the data without a code. This is necessary to check whether the study is being conducted in a good and reliable manner. Persons who have access to your data for review are: the committee that monitors the safety of the study, an internal monitor working for the LUMC, national and international supervisory authorities, for example, the Healthcare and Youth Inspectorate (IGJ). They will keep your data confidential. We ask you to consent to this access.

Retention period of your data

Your data must be kept for 15 years at the research location. Your body material will not be destroyed immediately after use. It is kept so new measurements can be performed that have to do with the study.

Storage and use of data for other research

Your data may also be of importance for other scientific research in the field of schistosomiasis. To this end, your data will be stored for 15 years. You can indicate on the consent form whether or not you agree with this. If you do not agree with this, you can still participate in the current study.

Information about unexpected findings

During the study, we may encounter unexpected findings that are not relevant for the study, but are for you. If this is important for your health, the investigator will inform you about this. You can then discuss with your general practitioner or medical specialist what should be done. You also give consent for this.

Withdrawing consent

You can withdraw your consent to the use of your personal data at any time. This applies to this study and also to storage and use for additional research. The study data collected until the moment you withdraw your consent will still be used in the study. Your body materials will be destroyed after withdrawing consent. If tests have already been performed on the body materials, these data will still be used.

Passing on to countries outside the European Union (EU)
In this study, your encoded data and body material will also be sent to countries outside the EU. This is because this study is part of a bigger project. This project aims to develop vaccines against schistosomiasis. It is important that we can exchange information. We work together with “Texas Tech University” in the United States and the “Uganda Virus Research Institute” in Uganda. In Uganda and the United States the EU rules on the protection of your personal data do not apply. However your privacy will be protected at an equal level.

More information about your rights when processing data
For general information about your rights when processing your personal data, you can consult the website of the Dutch Data Protection Authority.

If you have questions about your rights, please contact the person responsible for the processing of your personal data. For this study, that is the data protection officer at the LUMC. See contact details in Appendix A.

If you have questions or complaints about the processing of your personal data, we advise you to first contact the investigators.

More information about privacy is found in the LUMC privacy statement on the LUMC website: see appendix A. You can also contact the data Protection officer of the LUMC via email: infoavg@lumc.nl or the “Autoriteit Persoonsgegevens”.

Registration of the study
Information about this study is also included in a summary of medical research i.e. clinicaltrials.gov. No data that can be traced back to you is included. After the study, the website may contain a summary of the results of this study. You can find the study under CoHSI2 with number: NCT04269915.

11. Insurance for subjects

Insurance has been taken out for everyone who participates in this study. The insurance covers damage resulting from the study. Not all damage is covered. In Appendix B you can find more information about the insurance and the exceptions. It also states who you should report damages to.

12. Informing general practitioner

We always send your general practitioner a letter to inform them that you participate in the study. This is for our own safety. If you do not agree to this, you cannot participate in this study. You cannot participate if you do not have a general practitioner.

13. Compensation for participation

For participating in this study you will receive a compensation (including travel expenses) of € 1100,-. This amount consists of a fee per visit of € 50,- and a bonus of €100,- if you complete the study. If you withdraw before the study end, you will receive a lower compensation.

14. Do you have any questions?

If you have any questions, please contact the investigator. If you would like independent advice about participation in this study, please get in touch with the independent doctor. He knows a lot about the study, but has nothing to do with this study. If you have any complaints about the study, you can discuss this with the investigator or your regular doctor. If you would rather not do that, you can contact the complaints' officer at your hospital. All data can be found in **Appendix A**: Contact information.

15. Signing of informed consent form

When you have had a sufficient reflection period, you will be asked to decide about participation in this study. If you consent, you will be asked to confirm this on the corresponding consent form, in writing. With your written consent, you indicate that you have understood the information and agree to participate in the study.
Both you and the investigator will receive a signed version of this consent form.

Thank you for your attention.

16. Appendices with this information

A. Contact information
B. Information about the insurance [in Dutch]
C. Schedule study measurements / description study procedures
D. Consent form subject
E. Additional background information for study
F. Drug information praziquantel (biltricide®)
G. Informatie ‘Medisch-wetenschappelijk onderzoek. Algemene informatie voor de proefpersoon’ [in Dutch]

Appendix A: Contact information

Investigators:
Leids Universitair Medisch Centrum
Dr. M. Roestenberg, internist-infectiologist
Drs. J.P.R. Koopman, research physician
Department of Parasitology
Tel: 06-20942061
Email: vaccinonderzoek@lumc.nl

Independent physician:
Dr. M.P. Bauer, internist-infectiologist
Tel: 071-562381
Email: M.P.Bauer@lumc.nl
Leids Universitair Medisch Centrum

Klachten:
Complaints: In case of complaints, you can report to the patient service desk in the LUMC, location H2-11 (route number 473, opposite Leidseplein). Here you can report your dissatisfaction and fill in the complaint form. The patient service bureau will inform you as soon as possible about a possible solution and can possibly engage the complaints officer. You can also fill in the complaint form digitally via the LUMC website https://www.lumc.nl/patientenzorg/praktisch/klacht-indienen/.

Contact details patiëntenservicebureau
LUMC Patiëntenservicebureau
Postbus 9600
2300 RC Leiden
Phone number: +31 71-5262989

Data Protection Office of the institution
If you have any questions about the protection of your privacy, please contact the LUMC data protection officers (FG) at infoavg@lumc.nl..

For more information about your rights
Contact details LUMC
Albinusdreef 2
2333 ZA Leiden
Central phone number: (071) 526 91 11
For more information about your rights please see the LUMC website
www.lumc.nl/over-het-lumc/privacy/

Appendix B: Information about the insurance [in Dutch]

Voor iedereen die meedoet aan dit onderzoek, heeft het Leids Universitair Medisch Centrum een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde van uw deelname aan het onderzoek. Schade moet u binnen die vier jaar aan de verzekeraar hebben gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt.
Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (https://wetten.overheid.nl).

Bij schade kunt u direct contact leggen met de verzekeraar

De verzekeraar van het onderzoek is:	
Naam:	Centramed
Adres:	Maria Montessorilaan 9, 2719 DB Zoetermeer
Telefoonnummer:	070-3017070
E-mail:	info@centramed.nl
Polisnummer:	624.530.305

De verzekering biedt een dekking van: € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.

De verzekering dekt de volgende schade **niet**:

- schade door een risico waarover u in de schriftelijke informatie bent ingelicht. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
- schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan;
- schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
- schade aan uw nakomelingen, als gevolg van een negatief effect van het onderzoek op u of uw nakomelingen;
- schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.

Appendix C: Schedule study measurements

Below you will find an overviews of all study visits and tests.

		Blood draw	Urine collection	Stool collection	Treatment with praziquantel
Screening		X	X		
Week 0 (day of infection)		X	X	X	
Week 1		X	X		
Week 2		X	X		
Week 3		X	X		
Week 4		X	X	X	
Week 5		X	X		
Week 6		X	X		
Week 7		X	X		
Week 8		X	X	X	X
Week 9		X	X		
Week 10		X	X		
Week 11		X	X		
Week 12		X	X	X	X
Week 13		X	X		
Week 14		X	X		
Week 15		X	X		
Week 16		X	X	X	
Week 18		X	X		
Week 20		X	X	X	
Week 52		X	X	X	

Appendix D: Consent form subject

Controlled human *Schistosoma mansoni* infection study with female cercariae

- I have read the information letter. I was also able to ask questions. My questions have been answered sufficiently. I have had enough time to decide whether or not to participate.
- I understand that participation is voluntary. I also know that I may decide at any time to not participate or to stop participating in the study. Without having to provide any reason.
- I give consent for my general practitioner to be informed of my participation in this study.
- I give permission for the collection and use of my data and body samples to answer the research question in this study
- I give permission for storing (a copy of) the signed consent form at the LUMC
- I know that for monitoring of the study some people will have access to my data. These people are mentioned in the information letter. I give consent that these people have access
- I know that I should not become pregnant during the study
- The investigator has discussed the most suitable contraceptives for me
- I □ **give**

  □ **do not give**
  consent to keeping my personal data after the study to use for future research in the field of schistosomiasis, as written in the information letter..
- I □ **give**

  □ **do not give**
  consent to keeping my body material after the study to use for future research in the field of schistosomiasis, as written in the information letter.
- I □ **give**

  □ **do not give**
  consent to share my personal data and body material with partner research institutes located outside the EU.
- I □ **give**

  □ **do not give**
  consent to be approach for follow up research after this study. toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolgonderzoek.
- I want to participate in this study

Name of subject:
Signature: Date : __ / __ / __

I certify that I have fully informed this subject about the said study.

If information becomes known during the study that could influence the consent of the subject, I will inform him/her of this on time.

Name of investigator (or his/her representative):
Signature: Date: __ / __ / __

---

* Cross out what is not applicable

The subject will receive a complete information letter, together with a signed version of the informed consent form.

Appendix E: Additional background information for study

Schistosomiasis (also known as bilharzia) is a tropical infection with Schistosoma worms. These parasites are transmitted by *Schistosoma*-infected water snails. It is estimated that worldwide 250 million people are infected with Schistosoma worms. The disease mainly occurs in Africa, but also in Latin-America, South-East Asia and in Corsica.
Infected water snails excrete large amounts of larvae, also called cercariae. When exposed to freshwater in which these snails live, cercariae penetrate the skin and develop into worms. Males and females pair and produce eggs that are expelled through urine or stool. Most symptoms of *Schistosoma* infection are caused by eggs that get stuck in the body and cause harm to tissue. There is no effective vaccine against schistosomiasis.
In the Department of Parasitology at the LUMC, we do research to develop a vaccine against schistosomiasis. In an early study (CoHSI1), we infected 17 volunteers with male *Schistosoma* worms. In this study (CoHSI2) volunteers are exposed to a small number of female *Schistosoma* worms in a controlled setting. We detect infection with a new, sensitive test. Because we only use female cercariae, the chance of egg production is very small. This controlled infection gives us important information that will be used to develop a *Schistosoma* vaccine.

Appendix F: Drug information praziquantel (biltricide®)

Appendix G: Informatie ‘Medisch-wetenschappelijk onderzoek: informatie voor de proefpersoon’ [in Dutch]

More information about participating in medical-scientific research can be found on:

https://www.rijksoverheid.nl/onderwerpen/medisch-wetenschappelijk-onderzoek

PRODUCT INFORMATION

BILTRICIDE®

(praziquantel)

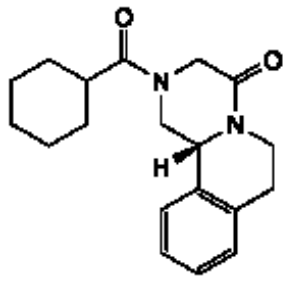
NAME OF THE MEDICINE

praziquantel

Praziquantel is 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino (2,1a) isoquinolin-4-one. CAS Number: 55268-74-1

DESCRIPTION

Praziquantel is a white crystalline powder of bitter taste. The compound is stable under normal conditions and melts at 136°C-140°C with decomposition. The active substance is hygroscopic. Praziquantel is easily soluble in chloroform and dimethylsulfoxide, soluble in ethanol and very slightly soluble in water. The molecular formula is $C_{19}H_{24}N_2O_2$. The structural formula is as follows:



Biltricide lacquer coated tablets are available as 600 mg of praziquantel.
Besides the active ingredient, Biltricide tablets also contain the following excipients: maize starch, magnesium stearate, microcrystalline cellulose, povidone 25, sodium lauryl sulfate, macrogol 4000, hypromellose, titanium dioxide (CI77891).

PHARMACOLOGY

Pharmacodynamic Properties

Animal studies show that praziquantel induces a rapid contraction of schistosomes by a specific effect on the permeability of the cell membrane. The drug further causes vacuolisation and disintegration of the schistosome tegument. The effect is more marked on the adult than on young worms.

Pharmacokinetic Properties

After oral administration praziquantel is rapidly absorbed (80%). It is, however, subject to first pass effect and extensive metabolism. One hour after administration approximately 6% only of the drug in serum is in the unmetabolised form. Both the unchanged drug and the metabolites are excreted primarily by the kidneys.

Maximal serum concentration is achieved 1-3 hours after dosing. The half life of praziquantel in serum is 0.8-1.5 hours.

INDICATIONS

Treatment of schistosoma infections due to various types of blood fluke (eg *Schistosoma haematobium, S.japonicum, S.mekongi, S.mansoni*).

CONTRAINDICATIONS

Known hypersensitivity to praziquantel or any of the excipients.
Ocular cysticercosis - parasite destruction within the eye may cause irreparable damage.
The concomitant administration of strong inducers of Cytochrome P 450 such as rifampicin must be avoided as therapeutically effective plasma levels may not be achieved.

PRECAUTIONS

Since 80% of praziquantel and its metabolites are excreted in the kidneys, excretion might be delayed in patients with impaired renal function. Nephrotoxic effects of praziquantel are not known.

In uncompensated liver insufficiency and in patients with hepatosplenic schistosomiasis caution should be taken, since due to reduced drug metabolisation in the liver, considerably higher and longer lasting concentrations of unmetabolised praziquantel can occur in vascular and/or collateral circulation leading to prolonged plasma half-life. If necessary, the patient may be hospitalised for the duration of the treatment.

Published *in vitro* data have shown a potential lack of efficacy of praziquantel against migrating schistosomulae. Data from two observational cohort studies in patients indicate that treatment with praziquantel in the acute phase of infection may not prevent progression into chronic phase.

In addition, the use of praziquantel in patients with schistosomiasis may be associated with clinical deterioration (paradoxical reactions, serum sickness Jarisch-Herxheimer like reactions: sudden inflammatory immune response suspected to be caused by the release of schistosomal antigens). These reactions predominantly occur in patients treated during the acute phase of schistosomiasis. They may lead to potentially life-threatening events .e.g. respiratory failure, encephalopathy, and/or cerebral vasculitis.

Patients suffering from cardiac irregularities should be monitored during treatment.

When schistosomiasis or fluke infection is found in patients living in or coming from areas with endemic human cysticercosis, it is advised to hospitalise the patient for the duration of treatment.

As praziquantel can exacerbate central nervous system pathology due to schistosomiasis, paragonimiasis or *Taenia solium* cysticercosis, as a general rule this drug should not be administered to individuals reporting a history of epilepsy and/or other signs of potential central nervous system involvement such as subcutaneous nodules suggestive of cysticercosis.

Neurocysticercosis is not an approved indication due to insufficient data. In animals, venous thrombosis and the development of granulomas at the site of worm attachment has been observed following treatment with praziquantel. Patients treated with praziquantel (for neurocysticercosis) have had a high incidence of severe headache and seizures. Some patients also developed intracranial hypertension. Because of the potential for undiagnosed neurocysticercosis to be present in patients originating from endemic areas, extra care is necessary in managing such patients. If cerebral cysticercosis is present and treatment is still considered essential, the patient should be hospitalised under specialist care.

Use in Pregnancy (Category B1)

Reproduction studies performed so far in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to praziquantel. An increase in abortion rate was seen in rats given single doses of 300 mg/kg. There are no adequate and well controlled studies on the use of praziquantel in pregnant women.

Because animal reproduction studies are not always predictive of human response, for safety reasons praziquantel should not be used in pregnancy unless clearly needed.

Use in Lactation

Praziquantel has been reported to be excreted in the milk of nursing women. Women should not nurse on the day of Biltricide treatment and during the subsequent 72 hours.

Paediatric Use

Safety in children has not been established.

Effects on Ability to Drive or Use Machines

Patients should be warned not to be drive or operate machinery on the day of treatment (and during the subsequent 24 hours), as their ability to do so may be temporarily impaired by the use of praziquantel.

INTERACTION WITH OTHER MEDICINES

Praziquantel is believed to be metabolised via the CYP450 enzyme system. Many categories of drugs are known to inhibit or induce CYP450 enzymes causing an increase or decrease in serum concentrations or bioavailability. Care must therefore be exercised when co-administering such drugs.

Concomitant administration of drugs that increase the activity of drug metabolising liver enzymes (CYP450 inducers), e.g. antiepileptic drugs, dexamethasone may reduce plasma levels of praziquantel. Concomitant administration of strong inducers of CYP450 such as rifampicin must be avoided. Chloroquine, when taken simultaneously, can lead to lower concentrations of praziquantel in blood.

Concomitant administration of drugs that decrease the activity of drug metabolising liver enzymes (CYP450 inhibitors) e.g. cimetidine, ketoconazole, itraconazole, erythromycin, may increase plasma levels of praziquantel.

Co-administration of grapefruit juice and praziquantel is not recommended. Co-administration has been reported to increase praziquantel C_{max} by 1.6 (90% CI 1.05, 2.0)

and AUC by 1.9 (90% CI 1.03, 2.47). The effect of this increase in exposure on efficacy and safety of praziquantel has not been studied.

ADVERSE EFFECTS

Side effects vary according to dose and duration of praziquantel medication; furthermore they are dependent on the parasite species, extent of parasitisation, duration of infection and localisation of the parasites in the body. Side effects occur earlier and are more frequent and pronounced in patients with severe parasitic infestation. Mild increases in liver enzymes have been reported in some patients.

Adverse Reactions are based on publications and on spontaneous reports sorted by CIOMS III categories of frequency and MedDRA System Organ Classes (in internationally agreed order). Frequencies of Adverse Reactions are mainly based on data from medical literature.

	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Immune System Disorders					Allergic reaction Polyserositis Eosinophilia
Nervous System Disorders	Headache Dizziness	Vertigo Somnolence			Seizures
Cardiac Disorders					Unspecified arrhythmias
Gastrointestinal Disorders	Gastrointestinal and abdominal pains Nausea Vomiting	Anorexia Diarrhoea (very rarely bloody diarrhoea)			
Skin and Subcutaneous Tissue Disorders	Urticaria	Rash			Pruritus
Musculoskeletal, Connective Tissue and Bone Disorders		Myalgia			
General Disorders and Administrative Site Conditions	Fatigue	Feeling unwell (asthenia, malaise) Fever			

It is often not clear whether the complaints reported by patients or the undesirable effects reported by the physician are caused by praziquantel itself (I, direct relation), or may be considered to be an endogenous reaction to the death of the parasites produced by praziquantel (II, indirect relation), or are symptomatic observations of the infestation (III, no relation). It may be difficult to differentiate between the possible variations I, II and III.

DOSAGE AND ADMINISTRATION

The doctor must prescribe individual doses for individual cases, according to the diagnosis.

Schistosoma haematobium
Schistosoma mansoni

} 20 mg/kg body weight three times a day

Schistosoma japonicum	at four hourly intervals
Schistosoma mekongi	for one day.

The tablet has 3 score marks, each fragment contains 150 mg active substance, thus allowing a precise dose to be given, corresponding to the patient's body weight.

If 1/4 of a tablet is required, it is convenient to begin by breaking the tablet at one of the outer grooves.

The simplest way to break the tablet is to place the thumbnail in the groove.

Conversion Table

	BODY WEIGHT IN KG								
	20-25	26-33	34-41	42-48	49-56	57-63	64-70	71-78	79-86
No. of tablets corresponding to 1 x 20 mg/kg	¾	1	1¼	1½	1¾	2	2¼	2½	2¾

Biltricide should be swallowed whole with a little liquid, preferably after meals.

Children: see PRECAUTIONS
Hepatic impairment: see PRECAUTIONS
Renal impairment: see PRECAUTIONS

OVERDOSAGE

Information on overdosage in humans is not available. Treatment should be supportive and provide symptomatic care.

Activated charcoal may reduce absorption of the drug if given within one to two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Biltricide is sold in bottles of 8 tablets.

Biltricide tablets contain 600 mg praziquantel. The tablets are white to pale yellow lacquer-coated oblong shaped tablets with three scores with Bayer on one side and "LG" on the reverse. Store below 25 degrees Celsius.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714

875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

8 October 1991

DATE OF MOST RECENT AMENDMENT

28 July 2017

® Registered Trademark of Bayer AG