WHO Expert Committee on the Selection and Use of Essential Medicines: Application for inclusion of ivermectin on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the indication of Scabies

Submitted: December 2018

International League of Dermatological Societies,
International Alliance for the Control of Scabies, and
Department of Control of Neglected Tropical Diseases, World Health Organization,
Geneva, Switzerland

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General items

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

This application is made in support of the inclusion of ivermectin as a treatment for scabies in the WHO Model List of Essential Medicines for adults (EML) and children (EMLc) (Proposed Section 6.6). This proposal is an expansion of the indication for ivermectin, which is currently included in the EML as an intestinal anthelminthic and an antifilarial (Sections 6.1.1 and 6.1.2) (WHO 2017). Ivermectin has been used extensively in humans, alone against onchocerciasis and in combination with albendazole against lymphatic filariasis (LF) since the 1980s (WHO 2006). It has played a key role in the elimination programmes of these two neglected tropical diseases and was more recently approved for the treatment for *Strongyloides* infections. Despite being included in the EML as an antifilarial and antihelminthic , ivermectin is considered to be the drug of choice or an alternative therapy for a wide range of diseases, including scabies, , gnathostomiasis and head lice infestation (Omura and Crump 2014). It has also shown potential for use as an insecticidal (e.g. against malaria), antiviral (e.g. against dengue), antibacterial (e.g. against *Chlamydia trachomatis*) and anticancer drug (Omura and Crump 2014).

The purpose of the proposed inclusion on the EML as an antiscabetic is for the use of ivermectin against scabies infestations (an infection for which ivermectin is not currently indicated in the EML), thereby providing support to the control of scabies in endemic communities which was recognised by WHO as a neglected tropical disease in 2017.

The goal of inclusion of ivermectin in the EML and EMLc is to increase the range of drug treatments for this neglected disease in community settings, during outbreaks and clinical settings where alternatives to topical therapies are clinically indicated such as crusted scabies, where other treatments may fail or be difficult to apply.

Effective treatment of patients with scabies using ivermectin has been reported in many different clinical environments from individual patients to institutions and in older persons. There have been a number of clinical trials where it has been found to have clinical and parasitological efficacy in both those with the conventional forms of scabies and those with crusted scabies, a more severe form often seen in the immunocompromised (Rosumeck et al 2018). There have been three large-scale public health programmes using ivermectin in the control of endemic of scabies in Fiji (Romani et al 2015), Australia (Kearns et al 2015) and an ongoing major outbreak in Ethiopia (https://www.afro.who.int/news/ethiopia-scabies-outbreak-response-amhara-regional-state).

At present, scabies is often treated with topical anti mite agents such as permethrin, benzyl benzoate, crotamiton and sulphur containing pastes or soaps (Strong and Johnston 2006). The use of gamma benzene hexachloride has been almost universally discontinued because of concerns over potential neurotoxicity. These topically applied treatments, while effective in individual cases, have major disadvantages when treating large numbers of individuals or patients with severe infestations such as crusted scabies or scabies in older persons. These include the need to apply topical preparations over the entire body, often more than once, as well as the need to simultaneously treat all other family members whether or not symptomatic. Poor compliance with treatment regimens is a major issue in management of endemic scabies.

A listing of ivermectin on the EML for the proposed new indications would appropriately address gaps in clinical practice and public health programmes for scabies and lead to additional benefits due to reduced morbidity from other secondary infections, including streptococcal infections which are associated with nephritis and rheumatic fever in tropical environments (Streeton et al 2005). It is therefore timely to update and harmonize international guidelines to reflect the evidence base

and current and future global demand for ivermectin.

2. Name of the WHO technical department and focal point supporting the application

Paul Cantey, Medical Officer for Onchocercasis Elimination and Scabies Control, Department of Control of Neglected Tropical Diseases, Geneva, Switzerland

canteyp@who.int

+41 22 791 33 15

3. Name of organizations consulted and/or supporting the application

The International League of Dermatology Societies (ILDS). Roderick Hay (UK), Olivier Chosidow (France), Luigi Naldi (Italy), Claire Fuller (UK), Christopher Griffiths (UK) and Lars French (Switzerland).

The International Alliance for the Control of Scabies. Andrew Steer (Australia), Daniel Engelman (Australia), James McCarthy (Australia), Claire Fuller (UK), Patrick Lammie (USA), Aileen Chang (USA), Roderick Hay (UK), Olivier Chosidow (France), Michael Marks (UK), Wendemagegn Enbiale (Ethiopia), Jackson Thomas (Australia).

4. International Nonproprietary Name (INN) and anatomical therapeutic chemical (ATC) code of the medicine

INN: Ivermectin

ATC code: P02CF01 (WHO Collaborating Centre for Drug Statistics and Monitoring)

P **ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**

P02 **ANTHELMINTICS**

P02C **ANTINEMATODAL AGENTS**

P02CF **Avermectines**

5. Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric dosing

5.1 Scabies

5.2 The formulation of ivermectin is a tablet (scored) in 3 mg doses, to be administered in a single or repeated dose of 200 µg ivermectin/kg body weight for both adults and children over the age of 5 or with a minimum body weight of 15 kg. When used in mass drug administration (MDA) programmes current WHO guidelines use a limit based on height; children who are at least 90 cm tall can be treated safely with ivermectin.

The proposed formulation of ivermectin is a tablet (scored) in 3 mg doses, to be administered in a single-dose of 200 µg ivermectin/kg body weight. This may be repeated for up to 8 doses given at weekly intervals. This is the proposed dosing regimen for adults and children over the age of 5 or with a minimum body weight of 15 kg.

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

The request for inclusion in the WHO Essential Medicine List is for an individual medicine.

Pharmacology, treatment details, public health relevance and evidence appraisal and synthesis

Pharmacology and mode of action of Ivermectin in Human Scabies

Ivermectin is absorbed after oral administration. A 12 mg dose in an adult male results in a Cmax of 24-30 ng ml $^{-1}$ and tmax of 5-10 h. The elimination t ½ is between 14-21 h (Gonzalez Canga et al 2008). After an initial peak if plasma levels there is a second rise in these levels between 6 and 12 h suggesting enterohepatic recycling . The volume of distribution in the central compartment is 3.5 l·kg^{-1}, after 12 mg of ivermectin. Ivermectin is bound to fat containing tissue and plasma proteins but is also present in skin peaking at 8 h after oral administration. The drug is largely metabolized by the liver via cytochrome P450. These studies have been carried out in healthy volunteers and patients with onchocerciasis. There have been few studies in breast-feeding women but the maximum recorded concentration in breast milk was 14.1 ng·ml^{-1} . Current recommendations advise that ivermectin should not be used in pregnant women or those currently breast feeding.

The principal targets of the drug are the glutamate-gated chloride ion channels which occur in invertebrate (including *Sarcoptes*) nerve and muscle cells (Mounsey et al 2007). This leads to membrane hyperpolarisation and failure of intermuscular signal transmission. In turn this leads to functional failure in locomotion, feeding and sensory input and death of adult mites. Ivermectin does not destroy mite ova and hence a second dose is often used to eliminate newly hatched larvae and adults.

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

7.1 Scabies treatment

7.1.1 Proposed therapeutic dosage regimen and duration of treatment

A single oral dose of 200µg/kg body weight in tablet form, taken in fasting state, with one glass of water. This may be repeated once. The treatment with ivermectin would be available for individual patients or as a part of mass drug administration (MDA) programmes. This dose schedule is for individuals over the age of 5 or with a minimum body weight of 15 kg. When administered as part of MDA programmes for NTDs, current WHO guidelines use a limit based on height; children who are at least 90 cm tall can be treated safely with ivermectin. The WHO growth standard curves show that this height is reached by 50% of boys by the time they are 28 months old and by 50% of girls by the time they are 30 months old, many children less than 3 years old been safely treated with ivermectin in mass prevention campaigns, albeit at a reduced dose.

Modified treatment may be required for the immune-compromised (including those with HIV or HTLV-1) with crusted scabies. Repeated therapy every 1 week for up to 8 weeks is recommended for immunocompromised individuals with crusted scabies.

7.1.2 Reference to current WHO guidelines

Ivermectin is currently recommended by WHO for treatment of both mild to moderate scabies as an alternative therapy to topical permethrin and as first line treatment for crusted scabies in HIV infected patients (WHO 2014) and is also a recommendation for

scabies on the WHO NTD website (http://www.who.int/neglected_diseases/diseases/scabies/en/).

Ivermectin is indicated as a drug of choice for scabies by the certain countries including Australia and France and as second line therapy in other countries (e.g Netherlands, Brazil, Germany). It is also recommended in the national guidelines of Japan and by the United States Centers for Disease Control and Prevention. It is also recommended by non-governmental organizations, such as the International Union for Sexually transmitted infection, IUSTI)

7.1.3 **Diagnostic tests:** Scabies is primarily diagnosed clinically on the basis of itch, household spread and the distribution of the rash and the finding of burrows or superficial tunnels in the outer layer of the skin, the stratum corneum, that indicate the presence of live adult mites (Chosidow 2006). Other confirmatory tests include dermoscopy, videomicroscopy and the demonstration of mites, larvae or eggs by direct microscopy of skin scrapings

7.1.4 **Other considerations:** Pre-treatment diagnosis is necessary to exclude loiasis, in *Loa loa* endemic areas in Central Africa due to the possibility of serious adverse events (e.g. fatal encephalopathy) in people with with > 30,000 *Loa loa* microfilariae per mL of blood. Determination of *Loa* microfilarial load is carried out through identification and quantification of microfilariae in blood by microscopy taken between 10AM and 4PM. If the *Loa loa* microfilarial load is above 30,000 microfilariae, treatment with ivermectin is contra-indicated. If the microfilarial load is between 8,000 and 30,000 microfilariae per mL there is a risk of adverse events and thus the risks and benefits of treating the individual with ivermectin for scabies should be discussed with the patient prior to offering ivermectin.

Caution should be exercised in patients with hepatic and renal disease (this may require dosage adjustments). Use of ivermectin is contraindicated in people weighing less than 15 kg and in pregnant women (i.e. ivermectin is pregnancy category C) or lactating women in the first week after birth.

7.2 Listing for core or complementary list

The request is to list ivermectin in the core and complementary list.

7.2.1 Scabies Proposed therapeutic dosage regimen and duration of treatment

The proposed regimen is to treat with ivermectin according to body weight (200 µg ivermectin per kg body weight)

Ivermectin should be administered as a single administration in both individuals and as part of large-scale programmes, although it may be repeated once.

- Administration requirements – The administration of ivermectin is recommended based on body weight. Since it can be difficult to accurately measure this in large-scale programmes, it will be recommended that the dose-pole that is used in LF and onchocerciasis programmes continues to be used for calculating the number of tablets needed to distribute to school-age children. Since children under the age of 5, or under the weight of 15 kg, will be excluded, difficulties with chewing or swallowing the tablet (which can be problematic in children under the age of two (Albonico et al.

2008) is not anticipated. As with other infections, treatment is contra-indicated if loiasis is detected (see Section 10 for more detail).

- Monitoring requirements – Current safety monitoring for the single-drug regimens can also be adapted based on monitoring in the onchocerciasis and LF programmes (WHO 2006).
- Modified treatment may be required for the immune-compromised (including those with HIV or HTLV-1) with crusted scabies. Repeated therapy every 1 week for up to 8 weeks is recommended for immunocompromised individuals with crusted scabies.

8. Information supporting the public health relevance

8.1.1 Scabies - Epidemiological information on disease burden

Scabies is seen in all countries. In industrialised societies it is generally a sporadic infection or it may also occur in case clusters in residential homes for older persons where it can spread to other residents as well as to visitors and staff. The situation is different in many resource-poor settings where prevalence rates of infestation can exceed 20% of the population and the most vulnerable members of society, children (Kearns et al 2013) and the elderly, are at highest risk. Among Indigenous Australians scabies is endemic, with prevalences ranging from 4% to 25%. Indigenous infants in particular suffer from a high incidence of scabies, with about 73% presenting to clinics by the age of one 77% by their second year and 75% recording at least one case of scabies by the age of four, with multiple presentations from re-infestation common (Clucas et al 2008). The 2010 analysis of the Global burden of disease (GBD) found a global case load of 130 million affected individuals, now estimated in more recent updates to be closer to 200 million, and it was estimated that the direct effects of scabies infestation on the skin alone led to more than 1.5 million years lived with disability (YLD); the indirect effects of complications on renal and cardiovascular function are far greater but not assessed in the GDB study (Hay et al 2014). In a subsequent more detailed analysis of impact, scabies was responsible for 0·21% of disability adjusted life years or DALYs from all conditions studied by GBD 2015 worldwide. The world regions of east Asia (age-standardised DALYs 136·32), southeast Asia (134·57), Oceania (120·34), tropical Latin America (99·94), and south Asia (69·41) had the greatest burden of DALYs from scabies. The five individual countries with greatest scabies burden were Indonesia (age-standardised DALYs 153·86), China (138·25), Timor-Leste (136·67), Vanuatu (131·59), and Fiji (130·91) (Karimkhani et al 2017).

A major complication of scabies with lasting consequences for health, seen most in resource-poor settings, is symptomatic acute glomerulonephritis (AGN) which was reported in 10% of children in a survey in northern Australia, but, in addition, 24% had microscopic haematuria. Thus, asymptomatic renal damage can also occur. The AGN was closely linked to skin sores due to streptococcal infection, and scabies was identified as the principal cause. Infection with streptococci can also occur in the absence of scabies. It has also been noted that persistent proteinuria can be detected for up to 16 years after the initial infection in 13% of those with recognized post-streptococcal glomerulonephritis vs. 4% of controls in an area *endemic* for scabies-associated infection (Streeton et al 2008). Although the definitive proof remains to be established, scabies infestation is an epidemiological risk factor for rheumatic fever and there is a strong association with scabies-associated streptococcal infections (McDonald et al 2004)

One study has identified a possible link between scabies and bacterial sepsis caused

by *Staphylococcus aureus* in infants (Mulholland et al 1999), in the Gambia.

Not all of the complications of scabies are related to infestation, and household economic loss due to scabies is also a major problem in resource-poor communities. A study in rural Mexico indicated that families were spending a significant part of their household income on ineffective topical treatment of scabies ($24) over each 3-month period (Hay et al 1994). This had a significant impact on the family's ability to purchase other commodities, including food.

In older persons, particularly in institutional settings, diagnosis is difficult because of a reduced level of symptoms, atypical clinical presentation and a higher risk of crusted lesions. However it causes a high level of distress because of an association with dementia, spread to staff and other residents and cost of control of outbreaks (Cassell et al 2018)

Scabies in resource poor environments is therefore both a potential cause of serious morbidity and a source of financial burden, which compounds the impact of disease resulting from this common infection in poor communities. In addition, its high prevalence places a huge burden on stretched health care resources.

8.1.2 Scabies infections – transmission

The transmission of scabies occurs with the burrowing of the mite *Sarcoptes scabiei* into the epidermis of the skin. Fertilised adult female mites burrow into the stratum corneum or outer layer of the skin, laying 0–4 eggs per day for up to 6 weeks before dying. The entire developmental life cycle, from egg to adult, involving three active intermediate stages or instars, takes about 2 weeks. However, classical transmission studies have documented the first observation of an adult female 3 weeks after initial colonization (McArthy et al 2004, Chosidow 2006). In primary infestations, an increase in *S. scabiei* numbers for up to 4 weeks has been reported, with a gradual reduction to *c.* 10–12 mites as host immunity develops. The disease is transmitted to others by spread of adult mites through close contact.

8.1.3 Types of scabies

The clinical features of scabies follow the invasion of the adult mite into the skin. Itching, which may be very severe and worse at night, is the predominant symptom. The length of the incubation period after initial infection and before symptoms first appear is variable, but it may take 14 days or more before itching is noticed. Itching can be constant and very severe, disrupting sleep. Classically, scabies affects several skin sites, predominantly the hands between the fingers, wrists, elbows, shoulders, genital area, particularly the penis, lower legs, particularly the ankles, and the breasts in women. Scratch marks are often more widely distributed. The clinical signs are small (<5 mm) papules or pustules, and small raised or flattened burrows, which mark the course of the mite within the epidermis. Another important clue to infection is the presence of itching with or without a rash in other household members. Usually, in tropical areas, several members of the family or household are affected, possibly due to household overcrowding.

Another clinical variant is the crusted form of scabies, also known as Norwegian scabies, which is seen in the severely ill or immunocompromised. It has also been reported in HIV infected subjects but may occur in otherwise healthy individuals. Here, infestation affects

the same areas as in common scabies, although there is less itching; other family members are affected with the normal disease pattern. The clinical features of crusted scabies are the appearance of dry scales and crusts that are most marked over prominences such as the dorsum of the fingers, wrists, and ears. The face may be involved, and one or more nails may show hyperkeratosis and thickening. These crusted infections are caused by a superinfection with thousands to millions of mites, and such patients are very contagious to anyone with whom they have any contact. To avoid spread of infection rapid and effective treatment is mandatory. If such patients are detected in hospital full barrier precautions are required.

8.1.4 Assessment of current use

Ivermectin is used as a therapy of choice against scabies in a number of countries including Australia, France, Germany, Netherlands, Japan and New Zealand (Table 1). Oral ivermectin is registered for human use in Australia (Stromectol 3mg tablets) (https://www.tga.gov.au/sites/default/files/auspar-ivermectin-131030.pdf for the treatment of onchocerciasis, intestinal strongyloidiasis (anguillulosis), crusted scabies and human sarcoptic scabies when prior topical treatment has failed or is contraindicated. It has been used in many other regions as an alternative off-label treatment, particularly where there are clusters of infected cases (e.g. in nursing homes) or where there are clinical grounds for avoiding topical therapies or in cases of treatment failure. It is also used as the first line treatment for crusted scabies in countries where it is available.

Table 1. World Wide Regulatory Status of use of ivermectin (Stromectol tablets) in scabies/crusted scabies *

Country	**Scabies Indication Approved**	**Date of Approval**
Germany	Treatment of human sarcoptic scabies when prior topical treatment has failed or is contraindicated	February 2016
Australia	Treatment of crusted scabies in conjunction with topical therapy. Treatment of human sarcoptic scabies when prior topical treatment has failed or is contraindicated and when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.	30 October 2013
New Zealand	Treatment of human sarcoptic scabies when prior topical treatment has failed and when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.	2005/2006
Japan	Scabies – Regarding scabies, patients with definite diagnosis or patients with symptoms of scabies who have an opportunity to come into contact with these patients with definite diagnosis should be treated.	21 August 2006
EU (France, The Netherlands)	Treatment of human sarcoptic scabies. Treatment is justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.	8 December 2002

*Sources: https://www.tga.gov.au/sites/default/files/auspar-ivermectin-131030.pdf; https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012994/full

8.1.5.Target population(s)

Key target populations are children older than 5, rural populations in endemic countries, and patients who require an alternative to topical therapy on clinical grounds such as prior treatment failure as well as immunodeficient individuals and those with crusted scabies.

8.1.6 Likely impact of treatment on the disease

At the individual level, treatment should result in complete cure. At the community level, elimination of the disease by topical applications has not been possible. But published clinical trials in communities with high levels of endemic scabies show that oral ivermectin treatment is a highly successful treatment, accompanied by very low levels of relapse (see below).

Community level control will also contribute to minimisation of the disease complications such as secondary streptococcal infection. This is borne out by published studies (see below).

9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings

9.1 Cochrane Review paper

The recent Cochrane review on scabies found response to oral ivermectin was equivalent to response to treatment topical permethrin 2 and 4 weeks after treatment (Rosumeck et al 2018). Oral ivermectin (at a standard dose of 200 µg/kg) leads to slightly lower rates of complete clearance after one week compared to permethrin 5% cream. Using the average clearance rate of 65% in the trials with permethrin, the illustrative clearance with ivermectin is 43% (RR 0.65, 95% CI 0.54 to 0.78; 613 participants, 6 studies; *low-certainty evidence*). However, by the second week post treatment there is no significant difference (illustrative clearance of permethrin 74% compared to ivermectin 68%; RR 0.91, 95% CI 0.76 to 1.08; 459 participants, 5 studies; *low-certainty evidence*). In this review, there did not appear to be any advantage in repeated treatments in conventional cases of scabies. Hence treatments with one to three doses of ivermectin or one to three applications of permethrin led to little or no difference in rates of complete clearance after four weeks' follow-up (illustrative cures with 1 to 3 applications of permethrin 93% and with 1 to 3 doses of ivermectin 86%; RR 0.92, 95% CI 0.82 to 1.03; 581 participants, 5 studies; *low-certainty evidence*).

Seven days after treatment with oral ivermectin at a standard dose of 200 µg/kg or one application of permethrin 5% lotion , there is little or no difference in complete clearance rates (illustrative cure rates: permethrin 73%, ivermectin 68%; RR 0.93, 95% CI 0.74 to 1.17; 120 participants, 1 study; *moderate-certainty evidence*). After two weeks, one initial dose of systemic ivermectin compared to one application of permethrin lotion produce similar complete clearance rates (extrapolated cure rates: 67% in both groups; RR 1.00, 95% CI 0.78 to 1.29; 120 participants, 1 study; *low-certainty evidence*).

9.2 Ivermectin Dose studies

Studies in conventional scabies (described below) have utilised doses of between 150 mg/kg and 200 mg/kg as a single dose. Other studies have added the option to give a further dose of ivermectin one week after the initial if the patient is still symptomatic. The evidence from the studies suggests that the higher dose of 200mg/kg gives better results (see below).

9.3 Summary of available estimates of comparative effectiveness in scabies in individuals or communities

There have been several studies of ivermectin in scabies compared with other medications such as permethrin in outpatient or community settings. In selecting these examples, the authors have rejected studies where either diagnosis was poorly defined or there was inadequate documentation of methodology such as enrolment and definition of end response.

9.3.1 Studies comparing oral ivermectin with topical permethrin

Usha et al in 2000 (Usha et al 2000) compared single dose oral ivermectin (200 µg/kg) which was repeated in non-responders one week later versus a topical single application of permethrin repeated after a week in non-responders in 85 subjects. The results showed that 29 of 40 patients on ivermectin versus 45 of 45 patients receiving permethrin cleared by week 4 after the initiation of treatment.

However, all subsequent studies have shown similar efficacy rates between ivermectin and topical permethrin. These formed the basis of the Cochrane review (9.1.2). For instance, Chhaiya et al (Chhaiya et al 2012) showed that 99/105 patients on ivermectin versus 99/105 using permethrin achieved complete remission of infection. Mushtaq et al (Mushtaq et al 2010) found remission rates of 35 of 44 individuals on ivermectin versus 37 of 42 receiving permethrin. Whereas Rohatgi et al (Rohatgi et al 2013) reported that 47/50 of patients on ivermectin versus 46/50 on permethrin achieved remission at the fourth week after the start of treatment. All used a single dose of 200 mg of ivermectin.

9.3.2 Studies comparing ivermectin with benzyl benzoate, lindane or crotamiton

In a study by Manjhi et al 2014 (four groups of 60 patients in each group allocated by simple random sampling) were compared. Treatments given to each group were as follows - Group 1: ivermectin (200 µg/kg body weight) oral in a single dose, Group 2: topical permethrin 5% cream single application, Group 3: topical gamma benzene hexachloride (GBHC) lotion 1% single application and Group 4: topical benzyl benzoate (BB) lotion 25% single application. All of the patients were assessed for improvement in terms of severity of disease and severity of pruritus at the end of the 1st week and 6th week. Efficacy of ivermectin, permethrin, GBHC and BB lotion using improvement in severity of pruritus as a key parameter were 85%, 90%, 75% and 68.33% respectively at the 2nd 6-week follow-up. Similarly, there was improvement in the severity of lesions of 80%, 88.33%, 71.66% and 65% respectively at the 6 week follow up. Topical permethrin (5%) was more effective compared to topical benzyl benzoate lotion and topical gamma benzene hexachloride lotion ($p<0.05$) but there was no statistical difference between the efficacy of topical permethrin and oral ivermectin ($p>0.05$). The results suggested that oral ivermectin and topical permethrin (5%) were equally efficacious compared with the other medications, but the end points in this study were based on symptom assessment. A further study compared three different treatment modalities conducted in 103

participants, randomly allocated to three groups (Bachewa et al 2009). The first group received benzyl benzoate 25% lotion applied on two consecutive nights, the second group received permethrin 5% cream applied once, whereas the third group received a single oral ivermectin of 200 µg/kg. The participants were reviewed after one week for follow-up evaluation. If there were no signs of improvement, the same intervention was repeated. The participants were followed up for a further two weeks for cure (defined clinically) and adverse drug reaction (ADR) monitoring. Ivermectin showed 100% cure rate after two weeks of treatment. Permethrin decreased pruritus by 76% with cure of 96% and benzyl benzoate achieved cure rates of 92% at the end of week two. The study included a cost-effectiveness analysis and treatment regimens were formulated hypothetically for comparison using the Markov population tree for decision analysis. It was found that BB and ivermectin at follow up were the most cost-effective regimens giving complete cure in four weeks, while ivermectin was the fastest regimen giving the same results in just two weeks.

A study in Senegal (Ly et al 2009) included patients aged 5-65 years with scabies. The randomized, open trial compared three treatments: a single application of 12.5% BB over 24 hours (BB1 group), two applications of BB, each separated by 24 hours (BB2 group), and oral ivermectin, 150-200 µg/kg (IV group). The primary endpoint was the disappearance of skin lesions and itching at day 14. If necessary, treatment was repeated, and patients were evaluated until cured. Results were analysed on an intention-to-treat basis. At day 28, 46 patients (95.8%) in the BB2 group were cured versus 52 (76.5%) in the BB1 group and 28 (43.1%) in the IV group ($p < 10^{-5}$). A concern about the design of this study is that the majority of the patients in the ivermectin group received a lower dose of ivermectin than in other studies – 150 µg/kg rather than 200 µg/kg.

Another observer-blinded randomized controlled trial using the higher dose of ivermectin (200 µg/kg) was undertaken at Vila Central Hospital, Vanuatu (Brooks et al 2002). One hundred and ten children aged from 6 months to 14 years were randomized to receive either ivermectin 200 µg/kg orally or 10% benzyl benzoate topically (a lower concentration than used in other studies). Follow up was at 3 weeks post-treatment. Eighty patients completed the study protocol. There was no significant difference between the two treatments; both produced a significant decrease in the number of scabies lesions seen at follow up. Ivermectin cured 24 out of 43 patients (56%), and benzyl benzoate 19 out of 37 patients (51%) at 3 weeks post-treatment. No serious side effects were noted with either treatment, but benzyl benzoate was more likely to produce local skin reactions (P = 0.004, OR 6.4, 95% CI 1.6-25.0).

A study in Iran compared the efficacy of oral ivermectin vs lindane (GBHC) lotion 1% for the treatment of scabies (Goldust et al 2013). Four hundred forty patients with scabies were enrolled and randomized into two groups: the first group received a single dose of oral ivermectin 200 µg/kg, and the second group was treated with two applications of topical lindane lotion 1%, with a 1-week interval. Treatment was evaluated at intervals of 2 and 4 weeks, and if there was treatment failure at the 2-week follow-up, treatment was repeated. Single dose of oral ivermectin provided a cure rate of 63.6% at the 2-week follow-up, which increased to 81.8% at the 4-week follow-up. Treatment with two applications of lindane lotion 1%, with a 1-week interval between them, was effective in 45.4% of patients at the 2-week follow-up, which increased to 63.6% at the 4-week follow-up after this treatment was repeated. Single dose ivermectin was as effective as two applications of lindane lotion 1% at the 2-week follow-up. After the option of repeating the treatment, ivermectin was superior to lindane lotion 1% at the 4-week

follow up. A further comparison with GBHC has been carried out (Madan et al 2001). Two hundred scabies patients were randomly allocated to one of two groups: one group received oral ivermectin in a single dose of 200 µg/kg body weight, while the other received 1% lindane lotion for topical application overnight. Patients were assessed after 48 hours, two weeks and four weeks. After a period of four weeks, 82.6% of the patients in the ivermectin group showed marked improvement; only 44.44% of the patients in the lindane group showed a similar response. Side effects in the form of severe headache were noted in one patient in the ivermectin group. The authors concluded that the oral ivermectin was more effective for scabies than the traditional topical lindane lotion.

Ivermectin has also been compared with another topical treatment, crotamiton 10% (Goldust et al 2014). In total, 320 patients with scabies were enrolled, and were randomized into two groups: the first group received a single dose of oral ivermectin 200 µg/kg body weight, and the second group were treated with crotamiton 10% cream and were told to apply this twice daily for five consecutive days. Treatment was evaluated at intervals of two and four weeks, and if there was treatment failure at the two-week follow-up, the treatment was repeated. A single dose of ivermectin provided a cure rate of 62.5% at the two-week follow-up, which increased to 87.5% at the four-week follow-up after repeating the treatment in non-responders. Treatment with crotamiton 10% cream was effective in 46.8% of patients at the two-week follow-up, which increased to 62.5% at the four-week follow-up after this treatment was repeated. The authors concluded that ivermectin was superior to crotamiton 10% cream at the four-week follow up.

A Nigerian study compared the effectiveness of oral ivermectin (200 µg/kg) with topical 25% benzyl benzoate plus another antiscabetic, monosulfiram soap in 210 subjects aged 5 to 65 years with scabies (Sule & Thacher 2007). Subjects with persistent lesions after 2 weeks received a second course of the same treatment. All lesions had resolved after 2 weeks in 77 of 98 (79%) subjects treated with ivermectin and in 60 of 102 (59%) subjects treated topically ($P = 0.003$). The improvement in severity score was greater in the ivermectin group than in the topical treatment group ($P < 0.001$). The overall cure rate after 4 weeks was 95% in the ivermectin group and 86% in the topical treatment group ($P = 0.04$). Compared with topical benzyl benzoate and monosulfiram in the treatment of scabies, oral ivermectin was at least as effective

9.3.3 Mass drug treatment of ivermectin given as a public health intervention in endemic communities

In 2005 a clinical study (Lawrence et al 2005) was designed to assess the effects of a programme aimed at controlling scabies on five small lagoon islands in the Solomon Islands by monitoring scabies, skin sores, streptococcal skin infection, serology and haematuria in the island children. Control was achieved by treating almost all residents of each island once or twice within 2 weeks with ivermectin (160-250 µg/kg), except for children who weighed less than 15 kg and pregnant women, for whom 5% permethrin cream was used. Reintroduction of scabies was controlled by treating returning residents and visitors, whether or not they had clinically evident scabies. Prevalence of scabies dropped from 25% to less than 1% ($P < 0.001$); prevalence of sores from 40% to 21% ($P < 0.001$); in addition, isolates of streptococci from the fingers in those with and without sores decreased significantly ($P = 0.02$ and 0.047, respectively) and anti-DNase B levels, a marker for Group A streptococcal infection, decreased ($P = 0.002$). Both the proportion of children with haematuria and its mean level fell ($P = 0.002$ and $P < 0.001$, respectively)

over the course of the study. No adverse effects due to the treatments were seen.

The results showed that ivermectin was an effective and practical agent in the control of scabies and that control of the latter reduced the occurrence of streptococcal skin disease and possible signs of renal damage in children thereby integrating community-based control of scabies and streptococcal skin disease. A subsequent visit to the island 15 years later identified only one case of scabies (Marks et al 2015).

A study of the use of ivermectin to control scabies was set up in an area of the Northern Territory of Australia where it is endemic with many infants infected in the first year of life (Kearns et al 2015). Non-pregnant participants weighing ≥15 kg were administered a single 200 µg/kg ivermectin dose, repeated after 2-3 weeks if scabies was diagnosed, others followed a standard alternative regimen using topical permethrin. Scabies prevalence fell from 4% amongst the baseline cohort to 1% at month 6. Prevalence rose to 9% at month 12 amongst the baseline cohort in association with an identified exposure to a presumptive crusted scabies case indicating the importance of this variant in disseminating and perpetuating scabies infection in communities. At month 18, scabies prevalence fell to 2%.

In another study designed to test the efficacy of ivermectin in a community setting, patients with scabies were recruited in three urban slums in Fortaleza, Northeast Brazil (Worth et al 2012). Diagnosis was established by dermoscopy, skin scraping, or the adhesive film test (a form of direct microscopic examination of skin samples). Severity of scabies-associated morbidity (itch and extent of lesions) was assessed semi-quantitatively. Ninety-five patients and close contacts were treated with oral ivermectin (200 µg/kg, repeated after 7 days) and followed up for 2 weeks. Intense or severe itch decreased from 37.5% to 6.3% 2 weeks after treatment ($p=0.02$). One week after the first dose of ivermectin, the intensity of itching and of sleep disturbance decreased significantly ($p<0.001$). Treatment with ivermectin rapidly restored health in almost all cases.

In 2015 a large-scale randomised study funded by the Australian National Health and Medical Research Council (Romani et al 2015) was conducted in three island communities in Fiji. Three island communities were randomised to one of three different interventions for scabies control: standard care involving the administration of permethrin to affected persons and their contacts (standard-care group), mass administration of permethrin (permethrin group), or mass administration of ivermectin (ivermectin group). The primary outcome was the change in the prevalence of scabies and of impetigo from baseline to 12 months. A total of 2051 participants were enrolled; 803 were in the standard-care group, 532 in the permethrin group, and 716 in the ivermectin group. From baseline to 12 months, the prevalence of scabies declined significantly in all groups, with the greatest reduction seen in the ivermectin group. The prevalence declined from 36.6% to 18.8% in the standard-care group (relative reduction in prevalence, 49%; 95% confidence interval [CI], 37 to 60), from 41.7% to 15.8% in the permethrin group (relative reduction, 62%; 95% CI, 49 to 75), and from 32.1% to 1.9% in the ivermectin group (relative reduction, 94%; 95% CI, 83 to 100). The prevalence of impetigo also declined in all groups, with the greatest reduction seen in the ivermectin group. The prevalence declined from 21.4% to 14.6% in the standard-care group (relative reduction, 32%; 95% CI, 14 to 50), from 24.6% to 11.4% in the permethrin group (relative reduction, 54%; 95% CI, 35 to 73), and from 24.6% to 8.0% in the ivermectin group (relative reduction, 67%; 95% CI, 52 to 83). Adverse events were mild and were reported more frequently in the ivermectin group than in the permethrin group (15.6% vs. 6.8%). The team concluded that mass drug administration of

ivermectin, was effective for the control of scabies and impetigo in a community setting.

Further indirect evidence for the efficacy of oral ivermectin as a mass treatment designed to control diseases in communities can be adduced from field data obtained after the mass administration of ivermectin in endemic communities for other recognised NTDs from onchocerciasis and lymphatic filariasis to intestinal parasitosis. For instance, Mohamad et al (Mohamad et al 2012) analysed the numbers of cases diagnosed with intestinal helminths and scabies and who received prescriptions for treatment in 50 health centres in Zanzibar. Records were examined from 2000, prior to the initiation of MDA for lymphatic filariasis to 2005, after six rounds of MDA for lymphatic filariasis had taken place. Health centre records showed a consistent decline in the number of cases of intestinal helminths and scabies diagnosed by community health workers in Zanzibar and the number of prescriptions issued across five age groups. A 68-98% decline in scabies infections was recorded. Poisson regression models aggregated to both the island-level and district-level indicated that the decline was statistically significant. Another example is provided by a study of lymphatic filariasis (LF) from Tanzania (Martin et al 2018) where the effect of ivermectin MDA for LF on scabies prevalence over 4 years was assessed in eight Tanzanian villages. At baseline, 4.4% (95% confidence interval [CI]: 3.7-5.4) of individuals tested positive for scabies, decreasing to 0.84% (95% CI: 0.51-1.4) after one round of ivermectin MDA. The group found that prevalence increased in Year 3 (2.5% [95% CI: 1.9-3.3]) and Year 4 (2.9% [95% CI: 2.2-3.8]). Most scabies cases were seen in children younger than 15 years. The data suggest that single-dose ivermectin MDA may not be effective in attaining long-term decreases when scabies prevalence is less than 5%.

A retrospective study in the Netherlands in asylum seekers focussing on a single unit showed reductions in scabies prevalence from 42% to 27.2% after a single dose of ivermectin. This was in the absence of treatment of other contacts (Beeres et al 2016).

Since its initiation in 1995, the African Program for Onchocerciasis Control (APOC) has had a substantial impact on the prevalence and burden of onchocerciasis through annual ivermectin mass treatment. In a study of off target infections, including scabies a group of investigators used data on the number of ivermectin treatments in APOC regions and the latest estimates of the burden of disease, to calculate the impact of APOC activities on off-target infections in terms of disability-adjusted life years (DALYs) averted. They estimated that between 1995 and 2010, annual ivermectin mass treatment has averted about 116 thousand DALYs from co-endemic scabies (Krotneva et al 2015).

9.4 Ivermectin for crusted scabies

Crusted scabies is a hyper transmissible form of scabies where patients are infected with very large populations of scabies mites. It is mainly seen in those who are immunocompromised including HIV infected individuals, transplant recipients and those on high doses immuno-modulating drugs or biologic agents; it may also occur in endemic settings in apparently healthy individuals. It is rare but can cause a major problem with transmission to susceptible populations. In view of its rarity there are no clinical trials using ivermectin, but case collections and individual cases are recorded. Crusted scabies poses a significant risk of infection to all other individuals in proximity to the patient. Cross infection has been recorded in many closed settings including elderly care homes, hospital wards, gaols and schools, and control of the outbreak is a major health priority. These cases all record the efficacy of ivermectin using from 2- 6 weekly or intermittent doses. They are difficult to assess as the

number of doses has varied depending on the patient's response. Examples include the following:

- 1 dose ivermectin 200µg/kg plus permethrin topically
  (Yee BE, Carlos CA, Hata T Crusted scabies of the scalp in a patient with systemic lupus erythematosus. Dermatol Online J. 2014;20(10). pii: 13030/qt9dm891gd)
- 2-3 doses of ivermectin 200 µg/kg plus permethrin in 8 patients
  (Nofal A. Variable response of crusted scabies to oral ivermectin: report on eight Egyptian patients. J Eur Acad Dermatol Venereol. 2009;23(7):793-7)
- 3 doses ivermectin 200 µg/kg weekly
  (Sandre M, Ralevski F, Rau N. An elderly long-term care resident with crusted scabies. Can J Infect Dis Med Microbiol. 2015;26:39-40)
- 2-6 doses of ivermectin 200 µg/kg
  (Roberts LJ, Huffam SE, Walton SF, Currie BJ. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. J Infect. 2005;50:375-81)
- 7 doses of 200mg/kg ivermectin.
  (Ortega-Loayza AG, McCall CO, Nunley JR. Crusted scabies and multiple dosages of ivermectin. J Drugs Dermatol. 2013;12:584-5)

9.5 Summary of available estimates of comparative effectiveness

Overall evidence of efficacy:

- Ivermectin is highly effective for the treatment of scabies and is as efficacious as permethrin and other alternative antiscabetic topical agents.
- Ivermectin is effective in individual patients with scabies but RCT data support the use of two doses separated by 2 weeks
- Ivermectin is particularly effective when given as a single dose mass drug administration (MDA) regimen for the control of scabies in community settings where the prevalence of infection is high; ivermectin also reduces the prevalence of streptococcal infection – and consequent risk of glomerulonephritis – secondary to scabies when given as MDA
- Ivermectin is effective in more extensive cases of scabies in the immunocompromised patients with crusted scabies

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

10.1 Summary of methods

The Cochrane review critically analysed the adverse reactions recorded in the studies cites

where ivermectin had been used for the treatment of scabies. There were no withdrawals recorded in these studies; in total 4% of patients receiving permethrin recorded adverse reaction compared with 5% of those receiving ivermectin over a 4 weeks period of observation. There was no difference in the incidence of adverse effects at the two-week point (3%). There is no evidence that this frequency is altered at different doses of ivermectin. The sides effects reported with ivermectin included itching, nausea, headache and secondary bacterial infection. The main side effects with permethrin were itching or burning of the skin. There was no effect of repeated dosing ivermectin on the frequency of adverse events.

10.2 Estimate of total patient exposure to date

Estimates of the number of people exposed to ivermectin come from the Mectizan Donation Program, which donates ivermectin of onchocerciasis and lymphatic filariasis, and from WHO Department of Control of Neglected Tropical Diseases. In 2011, the Mectizan Donation Program approved its 1 billionth treatment. Between 2012 and 2018, WHO reported that an addition 707 million ivermectin treatments had been distributed for onchocerciasis alone (this does not count the additional treatments that are given in areas where mass treatment occurs more one time per year). Conservatively, at least 200 million unique individuals have received treatment with ivermectin, though the actually number is higher.

10.2.1 Description of the adverse effects/reactions and estimates of their frequency

Most side effects reported in studies including those in the Cochrane scabies review were transient and mild. Loose stool, fatigue and headache were most frequently reported, and the incidence among the randomised control trials (best available evidence) of all side effects was highest in the studies involving children. Other adverse events recorded include transient disturbances in liver function and skin rashes. One study reported an unusually high incidence of liver function abnormalities which has not been recorded elsewhere. Zaha (2004) found significant liver abnormalities in both dosage groups (110 µg/kg body weight and 200 µg/kg. In the 110µg/kg group, a rise in glutamic pyruvic transaminase (GPT) or glutamic oxaloacetic transaminase (GOT) was observed in 6.9% (19/274) of the patients whose liver function was normal before treatment. Sixty-eight percent (13/19) of these liver dysfunctions were observed after the first administration. GPT or GOT levels in 15 of these patients were less than 100 IU/l, but in 4 patients, they exceeded 100 IU/l. The second treatment was discontinued in 1 of these 4 patients because GPT had increased to 200 IU/l. In the 200µg/kg group, liver dysfunction was observed in 6.5% (6/92) of patients. GOT and GPT levels exceeded 100 IU/l in 1 patient. The frequency of liver dysfunction was not significantly different between the two treatment groups. The abnormalities were mild, transient and assessed as not clinically important in both groups. An earlier report suggested a temporal association between increased death rates when ivermectin was used in a care home for the elderly (Barkwell and Shields 1997). An extensive review of adverse event reports and other documents provided no evidence of a causal association between ivermectin and increased risk of death, despite the apparent temporal association reported (Coyne and Addiss 1997). There have been no further reports of such associations in connection with either scabies or other parasitic infections and subsequent analyses provide no support for the conclusion that there was a causal association (NICE 2014)

10.2.2 Ivermectin in areas where Loa loa is endemic

Of note, if ivermectin is administered to subjects with high *Loa loa* microfilariaemia, severe adverse reactions such as neurological signs, encephalopathy and coma have been reported (WHO/APOC 2013). These findings, dating back to 1991 and revealed during a community directed treatment with ivermectin (CDTi) campaign against onchocerciasis in Cameroon, have so far represented a major obstacle for national control programs against lymphatic filariasis and onchocerciasis, where ivermectin is used as a standard treatment (Molyneux et al. 2014). In *Loa loa* endemic countries, mainly countries in central and western Africa (i.e. Angola, Cameroon, Central African Republic, Chad, Congo, DRC, Equatorial Guinea, Gabon, Nigeria and Sudan) (Zouré et al. 2011), potential co-infection with this parasite has to be considered prior to using ivermectin. The risk of severe adverse events occurs when microfilarial levels are above 30,000 microfilariae per mL of blood. Mass drug administration for onchocerciasis is acceptable in co-endemic areas when the prevalence of onchocercal infection is above 40% and the community-prevalence of microfilarermia above 30,000 per ml is greater than 2% (this is measured using a procedure call Rapid Assessment Procedures for *Loa loa* (RAPLOA)) and a system for the detection and management of severe adverse events is in place. When individual determination of microfilaremia is performed, treatment is given when the level is less than 30,000 microfilariae per mL but it is becoming more common to inform individuals with between 8,000 and 30,000 microfilariae that there is an increased risk of adverse events and letting the individual decide whether to proceed with treatment.

10.3 Reports for ivermectin in the WHO global database of reports of adverse drug reactions (VigiBase)

There were a total of 1656 reports for ivermectin in VigiBase (out of a total of over 14 million reports in the database). Reports in males and females were of similar proportions. The majority of reports were in adults aged 18 years and older. A common indication in the reports for ivermectin was rosacea (137) (but here it was used topically), and for purely oral therapy - filariasis (167), onchocerciasis (108), scabies (102), acrodermatitis (92), strongyloidiasis (59).

Reports originated from a total of 37 countries, mainly Africa and the Americas. The majority of reports originated from Sierra Leone (461), USA (460), France (198), Ghana (152) and Democratic Republic of Congo (102). Of the 1656 reports, 525 (31.7%) contained both ivermectin and albendazole, which mostly originated from Sierra Leone (397). Sierra Leone has a rigorous active pharmacovigilance component to their large-scale drug distribution programmes, which likely explains the higher proportion of reports coming from this country. Between 2007 and 2015, there have been over 33 million tablets of ivermectin administered with albendazole in the LF programme (WHO PCT databank http://www.who.int/neglected_diseases/preventive_chemotherapy/lf/en/). This corresponds to approximately 11 adverse events per one million treatments, without considering drugs administered before 2007 or in 2016. All of these reported events were considered minor.

The most commonly reported ADRs for ivermectin alone and ivermectin co-administered with albendazole included pruritus, headache, dizziness, vomiting, rash, urticarial and diarrhoea.

These are all known ADRs. Of the 1656 ICSRs, there were a total of 268 different ADRs reported with ivermectin that had a causality assessment. Approximately 2% of ICSRs had an ADR that was judged to have a certain likelihood of being caused by ivermectin. The most common were itching, rash and headache, which are known adverse effects. These same

adverse effects were often reported as probable and possible in other reports.

Ivermectin was commonly administered concomitantly with other medications. The most common were albendazole (525), levamisole (35), praziquantel (32), doxycycline (3), paracetamol (23), acetylsalicylic acid (22), amocarzine (22), permethrin (21) and prednisone (21).

In total, 459 reports of ivermectin were reported to have a serious ADR. Sixty three resulted in death. These were based on individuals undergoing treatment for onchocerciasis and lymphatic filariasis including those residing in Loa loa endemic areas. The deaths occurred mainly in individuals aged 18-44 and those greater than 75 years of age. Concomitant medication was frequently administered and included albendazole (12), ceftriaxone (8), metronidazole (8), vancomycin (8), ciprofloxacin (7), betamethasone (6), prednisolone (6) and digoxin (5). The most frequent ADRs reported in cases that resulted in death include: Strongyloidiasis (16), drug ineffective (7), pneumonia (7), pyrexia (7), multiple organ dysfunction syndrome (5), acute respiratory distress syndrome (4), cardiac arrest (4), septic shock (4), Stevens-Johnson syndrome (4), thrombocytopenia (4), and toxic epidermal necrolysis (4).

Two deaths were in individuals under 18 years of age, both occurring in the U.S. The timing of exposure was not reported in either case. In one report, the ADR was indicated as still birth; however, the age of the infant was reported to be six months. Twelve other suspected drugs were also listed in this case. A second case of death occurred in a 6-year old child. No other suspected or concomitant drugs were listed, but a number of other suspected ADRs were reported, such as abnormal behaviours, agitation, cerebral disorder. The indication was not reported and the reported date of death occurred prior to the reported date of ivermectin, indicating a possible reporting error.

Overall, there were mostly minor and transient ADRs associated with ivermectin use, alone or in combination with albendazole. Causality assessments were infrequently reported; however, of these reports, few were considered to have certainty of being caused by ivermectin, and all were minor events. Some reactions were consistent with those expected with treatment for onchocerciasis or LF (i.e. related to the effect on microfilariae), including areas where loiasis is endemic. The use of concomitant drugs and the types of ADRs reported in cases of death indicate probable causes other than the drug itself (e.g. related to other drugs, diseases, or in the case of strongyloidiasis, hyperinfection); however, it is clear that proper assessment of the health status of individuals before treatment to exclude sick individuals, as recommended (WHO 2006), is essential.

Overall evidence of safety:

- Over one billion treatments of ivermectin alone or co-administered with albendazole have been delivered in large-scale preventive chemotherapy programmes against lymphatic filariasis and onchocerciasis since 2000.
- Adverse events associated with ivermectin treatment for the indication of scabies are primarily minor and transient and associated with the baseline infection status and intensity of infection.

- No serious adverse events have been reported in the published literature with the exception of IVR administration in loiasis patients.
- As a precaution, ivermectin should not be administered to children less than 90 cm tall or weighing less than 15 kg, pregnant women, lactating women in the first week after birth, or severely ill individuals.
- The geographical distribution of *Loa loa* is well known. Treatment of individuals in co-endemic areas should be based on knowledge microfilarial loads and weighing the risks and benefits of treatment. Mass drug administration should in these areas, unless they are already receiving ivermectin mass drug administration under current WHO guidelines, should not be considered until WHO makes recommendations for scabies programmes.

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

There have been no cost benefit analyses carried out focusing on the use of ivermectin in scabies. However it is likely that effective interventions with ivermectin may reduce personal, institutional and governmental expenditure. The direct cost of a pack of 100mg tablets of ivermectin is approximately $2.90 with a unit price of 0.029 per tablet. These costs are subject to variations in different countries.

Large scale treatment of scabies infection is also associated with low indirect cost as distribution of drugs can be incorporated into existing infrastructure, can be undertaken by local health workers and only requires low cost screening. Additional costs include those associated with training, surveys, education programmes and drug storage. Using a similar example of MDA provided at community level the mean additional cost of albendazole or mebendazole, for instance, distributed through school based programmes per child has been estimated as 0.30 US$. This increases to 0.63 US$ for treating an individual through mass drug administration via community programmes (WHO Guideline 2017). These costs can be reduced further if there is co-administration of medication for other diseases where there is co-endemicity.

Because scabies has a profound economic impact on poor communities intervention with ivermectin is likely to provide cost savings. For instance using the example cited previously from a study carried out in Mexico an average cost saving of 34$ (US) over three months per household could be anticipated with successful treatment (Hay et al 1994). Scabies in residential care facilities outbreaks can also result in a significant burden of additional resources including medications, external health workers and laundry. In a review carried out that focused on the patterns seen in institutional outbreaks it was found that, on average, scabies outbreaks lasted for 3 months, with a median attack rate of 38%, all accounting for additional work and personnel. An outbreak of scabies in a Canadian long-term care facility with two index cases resulted in significant additional costs (De Beer et al 2006) of 200,000 $CDN in order to control the outbreak. There was also potential cost through loss of business through adverse publicity. Rapid intervention with effective therapy such as ivermectin can be expected to provide substantial savings in different health settings.

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

Table 1. World Wide Regulatory Status of use of ivermectin (Stromectol tablets) in scabies/crusted scabies *

Country	Scabies Indication Approved	Date of Approval
Germany	Treatment of human sarcoptic scabies when prior topical treatment has failed or is contraindicated	February 2016
Australia	Treatment of crusted scabies in conjunction with topical therapy. Treatment of human sarcoptic scabies when prior topical treatment has failed or is contraindicated and when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.	30 October 2013
New Zealand	Treatment of human sarcoptic scabies when prior topical treatment has failed and when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.	2005/2006
Japan	Scabies – Regarding scabies, patients with definite diagnosis or patients with symptoms of scabies who have an opportunity to come into contact with these patients with definite diagnosis should be treated.	21 August 2006
EU (France, The Netherlands)	Treatment of human sarcoptic scabies. Treatment is justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.	9 December 2002

*Sources: https://www.tga.gov.au/sites/default/files/auspar-ivermectin-131030.pdf; https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012994/full

13. Availability of pharmacopoeial standard

Ivermectin is currently included in:

i) The British Pharmacopoeia (https://www.pharmacopoeia.com/Catalogue/Preview?uri=%2Fcontent%2Ffile%2Fproducts%2Fleaflets%2FBPCRS%20Leaflet_Cat%20864_BPCRS3549_2.pdf)
ii) The United States Pharmacopoeia (http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/ivermectinTablets.pdf)
iii) The European Pharmacopoeia

14. Conclusion

In the light of the data presented in this dossier we would like to request that the World Health Organisation consider the inclusion of ivermectin as a treatment for scabies in both adult and paediatric Essential Medicines Lists.

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