Ivermectin (Stromectol) for typical and crusted scabies (eye-ver-MEK-tin)

**KEY POINTS**

Reserve ivermectin as second line for typical scabies
Maintain topical treatments (permethrin 5% cream or benzyl benzoate 25% lotion) as first line for typical scabies. Mite-resistance through overuse of ivermectin may limit future treatment options.

If permethrin or benzyl benzoate does not cure typical scabies, consider and address possible reasons for failure
If the cause of treatment failure cannot be identified, oral ivermectin may be indicated.

For typical scabies, minimise the risk of treatment failure and mite-resistance by using two doses of ivermectin
Ivermectin is not ovicidal — a single dose may be inadequate to eradicate the different stages of the parasite.

Ivermectin in conjunction with topical therapy is the only treatment option indicated or proposed in guidelines for crusted scabies
However, no randomised controlled trials have compared ivermectin with other treatments for crusted scabies.

The optimal dosing schedule for crusted scabies is uncertain
Response to treatment varies and inadequately treated patients may transmit infestation.

**PBS listing**

**Authority required (Streamlined) for the treatment of:**

- typical scabies where the patient has completed and failed sequential treatment with topical permethrin and benzyl benzoate and the most recent course of topical treatment at least 4 weeks prior has failed, or when topical therapy is contraindicated
- crusted scabies in conjunction with topical therapy except for when topical therapy is contraindicated.

The condition must be established by clinical and/or parasitological examination. The patient must weigh 15 kg or over and be aged 5 years or over.

**What is it?**

Ivermectin is an avermectin acaricide* that works by interrupting the functioning of a class of ligand-gated chloride ion channels in the scabies mite, causing persistent channel opening.1

Although the in-vivo target in the scabies mite is yet to be identified, it has been postulated that ivermectin causes excessive release of the neurotransmitter gamma-aminobutyric acid (GABA) in the nervous system of the parasite, resulting in its death.1

Because of life-cycle-dependent variability in ligand-gated chloride ion channel expression, ivermectin may not be effective against all stages of the parasite.2

In comparison, permethrin acts by disrupting the sodium channel current, resulting in delayed repolarisation, causing paralysis and death of the mite. As sodium channels are ubiquitous, permethrin is active against all stages of the life cycle of the parasite.

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* acaricide: a substance that kills ticks and mites.
Ivermectin resistance may result from exposure-induced alterations to chloride ion channels affecting ivermectin binding affinity. Biochemical studies in mites have linked detoxification genes associated with metabolic resistance as a potential cause of ivermectin resistance.

Ivermectin is the only acaricide indicated for scabies treatment that can be taken orally, making it convenient for use where application of topical therapy is logistically difficult, and for crusted scabies, when topical application may not completely penetrate the thick crusts.

Ivermectin is also used to treat onchocerciasis and strongyloidiasis.

**Who is it for?**

Ivermectin is indicated for treatment of scabies, a parasitic infestation of the skin caused by the scabies mite, which causes itch, inflammation and discomfort, and in some populations is associated with the development of serious secondary infection.

In Australia the two groups most at risk for scabies infestation are Aboriginal and Torres Strait Islander communities and people in residential aged-care facilities. In both settings ivermectin has advantages over topical treatments.

Ivermectin is a treatment option for people with typical scabies when:

- treatment with sequential topical permethrin and benzyl benzoate at least 4 weeks prior has been completed and has failed, or
- topical treatment is contraindicated when the patient has:
  - an allergy to pyrethrins or pyrethroids and cannot use permethrin, and/or
  - acutely inflamed, raw or weeping skin and cannot use benzyl benzoate.

Ivermectin is also used for treatment of crusted scabies in conjunction with topical scabicides and keratolytics.

Only begin treatment when the diagnosis of scabies has been established clinically and/or by parasitological examination. Treatment is not justified in cases of pruritus alone.

**Advantages over topical treatments**

**in Indigenous communities**

In Australia, scabies and associated complications such as acute post-streptococcal glomerulonephritis disproportionately affect remote Indigenous communities.

The prevalence of scabies in remote central and northern Indigenous communities has been estimated at up to 50% in children and up to 25% in adults.

Low levels of uptake of topical treatment have been observed in areas with endemic scabies. Environmental factors, including crowded living space, lead to limited opportunity for privacy to apply topical treatments and poor infrastructure for washing it off. Hot and humid weather also inhibits optimal use of topical treatments. Consequently there is low motivation to repeat the treatment process.

Being an oral treatment, ivermectin overcomes the problem of inconvenience, incomplete application or the treatment being washed off.

Although there are no specific clinical trials in these settings to determine best practice, it is likely that ivermectin will be useful for community-based treatment in remote Aboriginal communities. Oral ivermectin has been used successfully in the community management of endemic scabies in other regions.

For example, in a 3-year program in the Solomon Islands, mass single-dose ivermectin was administered to around 1600 people, combined with treatment of any close contacts, and reduced scabies prevalence significantly from 25% to < 1% after 4 months. Prevalence of impetigo also decreased significantly from 40% to 21%.

**Advantages over topical treatments**

**in aged-care homes**

In two open studies in 33 and 128 aged-care facility residents ivermectin showed almost 100% efficacy, with treatment failing in only one patient.

Residents were treated with 200 micrograms/kg oral ivermectin, repeated after 2 weeks, along with treatment of clothing and bed linen.

Treating all affected contact subjects simultaneously (family, medical and other residents) is an important step in community epidemic settings such as aged-care facilities.
Ivermectin is an avermectin acaricide—a class of broad-spectrum antiparasitic agents active against a range of nematodes and ectoparasites.

While this medicine has been available for some time it was only recently given TGA approval for treatment of scabies. It is also TGA approved and PBS listed for the treatment of onchocerciasis and stronglyloidiasis.

Oral ivermectin has been shown to be superior to placebo and has been used successfully in the community management of endemic scabies.

While ivermectin is successful at curing scabies (defined as no new lesions caused by the mite) after two separated doses, it is not ovicidal and has been shown to be slower to eliminate lesions compared with permethrin.

It is difficult to draw a conclusion regarding the comparative efficacy of ivermectin versus benzyl benzoate due to significant heterogeneity across trials.

Ivermectin, when used to treat scabies, is generally well tolerated, with only mild, transient adverse effects.

In the RCTs conducted using ivermectin for typical scabies there has been substantial heterogeneity in study methodology, making the clinical efficacy of ivermectin difficult to evaluate. Furthermore there are issues regarding the applicability of the trial population to the proposed PBS population.

No controlled clinical trials have been published to evaluate the appropriate dosing regimen of ivermectin to treat typical or crusted scabies. Potential dosing regimens have been evaluated in cohort and case series studies.

Overall, trials comparing ivermectin with topical treatments for typical scabies suggest a single dose may not be effective against all stages in the life cycle of the scabies parasite.

Although there is a lack of clinical trial evidence for the efficacy of ivermectin specific to the Aboriginal and Torres Strait Islander population, ivermectin has been shown to be successful for treating typical and crusted scabies in mass treatment of communities with endemic scabies.

There are limited data regarding the safety of ivermectin in the very old and very young and also in patients with liver impairment.
Inadequate contact precautions, and delayed or inaccurate diagnosis can lead to prolonged infestation. 23

Local area health authorities usually provide a scabies control protocol for co-ordinated treatment in aged-care facilities when patients have different GPs. 9, 24

Where does it fit?

Current pharmacological management of scabies is aimed at eradicating mites, alleviating symptoms and reducing the incidence of secondary infection. 11

Initial therapy for typical scabies with topical permethrin

Australian guidelines recommend use of permethrin 5% cream as scabies treatment of choice for adults and children aged 2 months and over, due to low toxicity, high efficacy and being generally well tolerated. 10

The Australian Medicines Handbook Children’s Dosing Companion provides instructions for approximate amounts of cream for a single application in children of different ages. 10

Benzyl benzoate 25% lotion is an alternative for people who are allergic to permethrin or if permethrin fails. 10, 11 Some guidelines recommend avoiding use of benzyl benzoate in children, as it is an irritant and when diluted to reduce irritation, efficacy can be reduced. 10, 25

Treat impetigo, if present, concomitantly. Treatment choice while waiting for results will depend on setting (non-remote vs Indigenous community in central and northern Australia). 11 Refer to the Therapeutic Guidelines for detailed information on treating impetigo. 11

An important consideration is that itching may persist for 1–2 weeks after treatment, even if the mites are successfully eradicated. 6 Symptomatic post-treatment itch and dermatitis may be treated with a moderately potent topical corticosteroid 2–3 times daily or an emollient such as glycerol 10% in sorbolene cream. 11

Consider reasons for treatment failure before starting oral ivermectin for typical scabies

Always start with a complete course of topical treatments before using ivermectin. If symptoms persist 3 weeks after topical treatment with permethrin or benzyl benzoate, consider and address possible reasons for failure, including:

- the patient not using topical treatment correctly
- incorrect diagnosis or no diagnosis
- an unidentified source of re-infestation
- inadequate contact tracing
- post-treatment itch mistaken for treatment failure. Death of mites commonly causes transient worsening of itch as a result of sensitisation of the human host to mite antigens, with a consequent immunological reaction. 6

If none of the above is the cause of treatment failure, oral ivermectin may be indicated. 11

Reserve use of ivermectin as second line in typical scabies

Very few effective medicines are available for treatment of scabies, and the development of new medicines is unlikely in the near future. 5

Clinical resistance to ivermectin has been documented, with in-vitro confirmation in people with crusted scabies in whom resistance developed after administration of repeated regimens of multiple doses of ivermectin. 26

As ivermectin is not ovicidal, a second dose of ivermectin is necessary to ensure total eradication. Taking both doses of ivermectin has been shown to increase the efficacy of treatment and may mitigate the development of resistance to ivermectin. 2, 27

Consider ivermectin if topical treatments are contraindicated

When topical treatments are contraindicated (see ‘Who is it for?’, page 4), it is preferable to use ivermectin. 10

For crusted scabies use as initial treatment only in consultation with a specialist. Treatment may be complicated, as these people are likely to have some form of immune deficiency, such as HIV infection. 28, 29 Crusted scabies is associated with human T-cell lymphotropic virus in Central Australia. 30

Consider ivermectin therapy in discussion with a dermatologist or infectious-diseases physician, and base frequency of therapy on severity of crusted scabies. (See ‘Dosing issues’, page 10.)
To reduce scaling, apply topical keratolytics (eg, salicylic acid 5% to 10% in sorbolene cream, or lactic acid 5% plus urea 10% in sorbolene cream) once daily after washing on days when scabicides are not applied. 11

Prevent person-to-person contact and environmental transmission of scabies
The evidence is limited for efficacy of interventions, including medicines, barrier precautions, personal hygiene measures or environmental decontamination, for close contacts of people infected with scabies to prevent them from acquiring and spreading scabies infestation. 31

Some treatment guidelines recommend contact tracing, notification and treatment of close contacts, to prevent treatment failure. 11, 15

Clothes, towels and bedding should be washed or subjected to heat from an iron or a clothes dryer. If this is not possible they can simply be stored for a week, as the mites survive for a maximum of 36 hours away from the host. 11

Guidelines also recommend putting bedding, clothes and mattresses in the sun. 32

Use in conjunction with scabies programs in communities with endemic scabies
Scabies programs have been successful in reducing the prevalence of scabies and related skin infections when appropriate treatment and follow-up are implemented. 14

How does it compare?
No other treatment options are indicated or proposed in guidelines for typical scabies:

- in patients in whom topical treatment is contraindicated
- after the failure of both permethrin and benzyl benzoate
- for crusted scabies in conjunction with topical treatments.

The efficacy and safety of ivermectin have been assessed in comparison with topical scabies treatments in patients with typical scabies in a number of RCTs and review articles, including a Cochrane review, and in patients with crusted scabies in observational studies, small uncontrolled trials and case series.

The primary outcome in the Cochrane review was treatment failure defined as the persistence of original lesions, the appearance of new lesions or confirmation of a live mite. The secondary outcome was persistence of patient-reported itch.

The following issues have been identified regarding applicability of many of the trial populations to the proposed PBS population:

- RCTs were undertaken in patients with typical scabies but not crusted scabies 8
- in many trials topical therapy had not failed first or was not contraindicated 8
- many studies were conducted in countries with healthcare systems very different from that of Australia, such as India, and so the applicability of their results may not be relevant to an Australian population 27, 33, 34
- patients were treated with a single dose of ivermectin, 2, 27, 33, 35-40 which may underestimate its effect — in clinical practice at least two doses separated by an interval of 8-15 days are recommended, as ivermectin is not ovicidal 41
- insufficient length of follow-up (eg, 7 or 15 days) used to define clinical cure 2, 27, 33, 35, 39, 40, 42 — recovery is considered definite only if the patient is asymptomatic and has no new lesions 4 weeks after treatment. 43

Typical scabies
Ivermectin superior to placebo
Only one study is available in which ivermectin was compared with placebo. In their PBAC submission the sponsor presented a placebo-controlled trial to demonstrate applicability to the proposed PBS population. 35

In this study there were significantly fewer treatment failures in the ivermectin group at 7 days (26 patients [79.3%] cured with ivermectin compared with four [15.38%] in the placebo group).

Limitations of this study are that efficacy was measured at 7 days rather than 4 weeks, and that the effect may have been underestimated by using only a single dose of ivermectin. The apparent cure of four patients given placebo treatment is an unexpected result, which may reflect uncertainty around the diagnosis.
**Permethrin works faster than ivermectin**

A Cochrane systematic review included two RCTs that compared oral ivermectin with topical permethrin. Both trials found 200 micrograms per kilogram body weight of oral ivermectin inferior to permethrin at 1 or 2 weeks. In one of these trials, ivermectin was given as either a single dose or two doses separated by 1 week, depending on response to the first dose. After the 2-week follow-up, ivermectin had a 100% cure rate (defined as no new lesions), but when comparing ivermectin and permethrin at 1 week, permethrin had a significantly faster cure rate than ivermectin (82.14% vs 55.56%).

Permethrin performed better than ivermectin in the other trial included in the review, with a single application being effective in 97.8% of patients, compared with a single dose of ivermectin with a 70% cure rate that increased to 95% after the second dose at 2 weeks.

Four other RCTs were published after the Cochrane review. Ivermectin was found to be inferior to permethrin in one RCT at 1 week, and not statistically significantly different in three RCTs. Differences in the length of follow-up may explain some of the heterogeneity in the results of these trials.

**The effect of ivermectin versus benzyl benzoate is unclear**

The significant heterogeneity across trials comparing ivermectin and benzyl benzoate makes it difficult to draw a conclusion as to which is more efficacious. In all trials only a single dose of ivermectin was used, so treatment efficacy may have been underestimated. The Cochrane systematic review included five RCTs comparing oral ivermectin with topical benzyl benzoate. Ivermectin was:

- superior to benzyl benzoate in one trial at 4 weeks
- not statistically significantly different in three trials (at 1, 3 and 4 weeks)
- inferior in one trial (at 2 weeks) in which a higher rate of treatment failure occurred with single-dose ivermectin than with topical benzyl benzoate.

Differences in treatment regimens and the length of follow-up may explain some of the heterogeneity in the results.

**Crusted scabies**

Ivermectin is the only option indicated or proposed in guidelines as first-line treatment in conjunction with topical treatment for crusted scabies. There are no RCTs comparing ivermectin with other treatments of crusted scabies.

**Use oral ivermectin in combination with topical therapy**

Observational studies have shown that ivermectin is effective after the failure of topical therapy in people with crusted scabies. There are data from small uncontrolled trials and case series studies using multiple doses of oral ivermectin and/or ivermectin in combination with topical therapy.

In an open-label study undertaken in Australia in 20 patients treated for crusted scabies refractory to topical therapy, eight people (40%) showed a complete response after the last dose of oral ivermectin plus permethrin 5% and keratolytics.

Keratolytic therapy was applied on the days when permethrin was not used, and patients were treated with up to three doses of 200 micrograms per kilogram oral ivermectin at 14-day intervals. Nine people had at least a partial response and three had minimal improvement.

**Safety issues**

Ivermectin is generally considered a safe medicine in the adult population. This has allowed mass-drug distribution programs in parts of west Africa by the Onchocerciasis Control Program. Ivermectin has been shown to be safe at higher and more frequent doses than required for TGA-approved indications. A dose escalation study found administering ivermectin to up to 10 times the maximum FDA-approved dose of 200 micrograms per kilogram did not precipitate any adverse effects.

Between 1 January 1971 and 20 December 2013, 17 adverse events for ivermectin (three fatal adverse drug reaction reports) were reported to the TGA, but a causal relationship with ivermectin has not been established.
Ivermectin is generally safe in all ages

Scabies is frequently seen in the very young and very old age groups.

The East Arnhem Regional Healthy Skin Program reported in 2002–2005 that first presentations of scabies peaked at the age of 2 months. By 1 year of age, 63% of children presented with scabies. Outbreaks are common in aged-care facilities, and scabies can be transmitted to nursing staff. Untreated typical scabies is associated with increased morbidity in both these settings.

There are some case studies and small open studies supporting the use of ivermectin in older people and children weighing < 15 kg. Ivermectin may have an increasing role in these age groups as safety data accumulate.

Adverse effects are usually mild and transient

Transient exacerbation of pruritus may occur at the beginning of treatment.

Ivermectin is well tolerated, with a low number of adverse effects. The Cochrane Review analysed adverse events in nine RCTs in which ivermectin was used in the treatment arm (vs placebo, permethrin, benzyl benzoate or lindane).

Overall, mild and transient adverse events were observed in about 5% of 385 trial participants receiving ivermectin. Some of these adverse effects included:

- aggravation of symptoms (including pruritus)
- headache
- hypotension
- abdominal pain
- vomiting
- pustular rash
- cellulitis
- mild diarrhoea.

Serious adverse effects when treating onchocerciasis

Due to more extensive experience in the use of ivermectin to treat onchocerciasis, a range of often serious adverse effects has been reported for this indication.

Cutaneous and/or systemic reactions of varying severity (Mazzotti-type reaction) and ophthalmological reactions may occur in patients treated for onchocerciasis, but these are rare and mostly attributable to an allergic reaction to the residue after the death of large numbers of microfilariae.

Several cases of encephalopathy have been reported with ivermectin use in people heavily infected with microfilariae of *Loa loa* (loiasis). Such effects are not expected when treating scabies.

Other safety issues

Do not use in pregnancy, as safety has not been established. Ivermectin caused cleft palates in mice and rats at oral doses of 0.4 and 10 mg/kg/day, respectively, and cleft palates and clubbed feet in rabbits dosed at 3 mg/kg/day.

In pregnant women for whom treatment with permethrin 5% cream has failed, sulfur 10% in white soft paraffin or crotamiton 10% cream may be used topically instead.

Ivermectin is excreted in breast milk, and safety in newborn infants has not been established.

Ivermectin is eliminated in the liver. Administering multiple doses of ivermectin in patients with severe liver disease has not been studied.

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website or use the ‘Blue Card’ distributed with the October 2013 issue of Australian Prescriber.
Typical scabies

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<thead>
<tr>
<th>Day 1</th>
<th>First dose*</th>
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<tbody>
<tr>
<td>Between day 8 and day 15</td>
<td>Second dose</td>
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<tr>
<td>When required</td>
<td>Treatment of impetigo and To relieve itch use moderately potent topical corticosteroid 2-3 times daily or an emollient, eg, glycerol 10% in sorbolene cream</td>
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* A single dose aims to deliver approximately 200 micrograms per kilogram body weight; see Product Information for further detail

Dosing issues

More studies required to confirm optimal dosing of ivermectin

While no controlled clinical trials have been published that evaluate the appropriate dosing regimen to treat typical or crusted scabies, potential dosing regimens have been suggested in cohort reports and case series.59

Dose adjustment is not necessary in patients with kidney impairment.41

Australian guidelines recommend the dosing regimens for typical and crusted scabies shown in Tables 1 and 2.11

Crusted scabies

Consultation with a dermatologist or infectious-disease physician is recommended.

<table>
<thead>
<tr>
<th>Mild cases</th>
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<tr>
<td>Day 1</td>
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<td>Between day 8 and day 15</td>
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<th>Moderate cases</th>
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<td>Day 1</td>
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<td>Day 2</td>
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<td>Day 8</td>
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<tr>
<th>Severe cases</th>
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<tbody>
<tr>
<td>Day 1</td>
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<td>Day 9</td>
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<td>Day 15</td>
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For extremely severe cases add

| Day 22 | Sixth dose |
| Day 29 | Seventh dose |

Throughout treatment

Use a topical scabicide, eg, permethrin 5% cream. Use two applications, 1 week apart11 and

Topical keratolytics, eg, salicylic acid 5% to 10% in sorbolene cream, or lactic acid 5% plus urea 10% in sorbolene cream applied once daily after washing on days when scabicides are not applied, to assist with the reduction of scaling that harbours the mite44 and

Anticipate and treat secondary bacterial infection with aggressive, early, intravenous broad-spectrum antibiotics44.

* A single dose aims to deliver approximately 200 micrograms per kilogram body weight; see Product Information for further detail
A large case-series in Indigenous Australians found a significant decrease in mortality when using intensive ivermectin dosing together with a protocol for early use of antibiotics in suspected secondary bacterial sepsis. The study was limited by a lack of efficacy endpoints such as cure rates marked by clearing of lesions and symptoms.

Take with food
Because ingestion of food increases the bioavailability of ivermectin by a factor of more than two, taking the drug with food will enhance the penetration of the drug into the epidermis.

Information for patients
Do not share this (or any) medicine
Sharing this medicine rather than taking the required doses may result in treatment failure from taking too little or toxicity from taking too much. Inappropriate dosing may also contribute to antimicrobial resistance, reducing the number of options available for treating scabies in the future.

Ensure patients are aware of common adverse effects
Patients should be aware of the following possible side effects:
- tiredness
- stomach discomfort
- rash
- dizziness
- headache
- joint pain
- loss of appetite
- itch, which may persist after successful treatment — not to be mistaken for ongoing infestation.

Discuss the Stromectol Consumer Medicine Information (CMI) leaflet with the patient.

MEDICINE UPDATE
An NPS Medicine Update article on ivermectin is available for consumers at www.nps.org.au/medicine-update/ivermectin. Medicine Update helps consumers to ask the right questions about new medicines, and helps them compare the potential benefits and harms of a new medicine with other medicines.

1 Available at www.nps.org.au/medicines/stromectol
REFERENCES

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