Difficult-to-treat scabies: oral ivermectin

Evidence summary

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Key points from the evidence

> The content of this evidence summary was up-to-date in March 2014. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Summary

Oral ivermectin appears to be effective for treating people with classical or crusted scabies. However, differences in treatment regimens and the length of follow-up make interpreting comparisons with topical treatments difficult. Transient exacerbation of pruritus may occur at the beginning of treatment.

Regulatory status: unlicensed

The topic was prioritised because there was a high volume of requests from the NHS for information on this topic and there is uncertainty about the evidence-base for using

ivermectin in scabies.

Effectiveness	Safety
• In classical scabies, most RCTs used a single oral dose of ivermectin 200 micrograms/kg — Ivermectin was superior to placebo (1 RCT, n=55). — Ivermectin was superior to benzyl benzoate in 1 RCT (n=58), not statistically significantly different in 3 RCTs (total n=176) and inferior in 1 RCT (n=162). — Ivermectin was inferior to permethrin in 3 RCTs (total n=339) and not statistically significantly different in 3 RCTs (4 comparisons: total n=479). — Treatment failure rates with ivermectin varied widely from 7% to 70% (see tables 1, 2 and 3 for details). • In crusted scabies, uncontrolled trials and case series used multiple doses of oral ivermectin and/or ivermectin in combination with topical therapy (see table 4).	• The European summary of product characteristics for ivermectin states that safety in children weighing less than 15 kg has not been established. • A report in 1997 suggested that ivermectin was associated with an increased risk of death among a group of elderly people with scabies in a long-term care facility, but the validity of this report has been questioned. • Ivermectin has been used globally in the treatment of onchocerciasis (river blindness) – serious adverse effects have been rare, even with repeated doses.

Patient factors	Resource implications
- Ivermectin is an oral tablet where other treatments for scabies are topical. - Ivermectin is taken as a single dose, which may need to be repeated (especially in crusted scabies). - The European summary of product characteristics states that transient exacerbation of pruritus may occur at the beginning of treatment, but no frequency for this is given.	- Ivermectin is unlicensed in the UK and can be supplied from 'special order' manufacturers or specialist importing companies. No costs could be obtained from standard published sources.* - Permethrin 5% cream is £6.96 for 30 g, malathion 0.5% aqueous liquid (Derbac-M) is £2.37 for 50 ml and £5.93 for 200 ml, and 25% benzyl benzoate emulsion is £2.50 for 500 ml.

* informal sources suggest that the cost is around £160 for 20×3 mg tablets.

Key points

Ivermectin is an anthelmintic used to treat infections caused by various parasites. Oral ivermectin has been used to treat crusted scabies (also known as hyperkeratotic, Norwegian or atypical scabies) that does not respond to topical treatment alone. It has also been used to treat other forms of 'difficult-to-treat' scabies (for example, if a topical treatment cannot be used or has not worked).

Ivermectin is unlicensed in the UK. It is available on a named-patient basis from 'special order' manufacturers or specialist importing companies.

The European summary of product characteristics for ivermectin 3 mg tablets (Stromectol) (Merck Sharp & Dohme: personal communication December 2013) states that the recommended dose for scabies is a single oral dose of ivermectin 200 micrograms/kg body weight. For classical scabies, recovery is considered definite only after 4 weeks have elapsed since treatment. Persistence of pruritus or scraping lesions does not justify a second treatment before this date. Administration of a second dose within 2 weeks after the initial dose should only be considered when new specific lesions occur or when

parasitological examination is positive. For crusted scabies, a second dose within 8–15 days of the initial dose of ivermectin and/or concomitant topical therapy may be necessary.

A Cochrane systematic review that included 7 randomised controlled trials (RCTs) of oral ivermectin compared with placebo or topical treatments available in the UK was identified, along with 4 additional RCTs of oral ivermectin that were published after the Cochrane review. All of these trials assessed the efficacy and safety of oral ivermectin (mostly as a single oral dose of ivermectin 200 micrograms/kg) for the treatment of classical or uncomplicated scabies.

Oral ivermectin was superior to placebo in 1 RCT. Ivermectin was superior to benzyl benzoate in 1 RCT, not statistically significantly different in 3 RCTs and inferior in 1 RCT. Ivermectin was inferior to permethrin in 3 RCTs and not statistically significantly different in 3 RCTs (4 comparisons, 2 from the same trial). Treatment failure rates with ivermectin varied widely in these RCTs, from 7% to 70% (see tables 1, 2 and 3 for details). Differences in treatment regimens and the length of follow-up may explain some of the heterogeneity in the results of the different studies.

No RCTs comparing oral ivermectin with malathion were identified.

Adverse events reported in people receiving oral ivermectin in RCTs for classical or uncomplicated scabies included aggravation of symptoms (including pruritus), irritation, headache, nausea, pustular rash, cellulitis, abdominal pain and mild diarrhoea. The trials were too small to assess serious but rare potential adverse effects.

No RCTs of oral ivermectin for the treatment of crusted scabies were identified.

This evidence summary includes the results of 5 uncontrolled trials and case series with 4 or more participants with crusted scabies that reported cure rates or treatment failures. Multiple doses of oral ivermectin and/or ivermectin in combination with topical therapy were frequently administered in these studies, and treatment failure rates varied widely (see table 4 for details). More robust studies are needed to further evaluate the safety and efficacy of ivermectin for the treatment of crusted scabies.

Because ivermectin is unlicensed in the UK, no costs could be obtained from standard published sources. No data were identified that reported the extent to which ivermectin is currently being used to treat scabies in the UK.

> **About this evidence summary**
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> 'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.
>
> The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.
>
> The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

Overview for healthcare professionals

Ivermectin is an anthelmintic that acts against infections caused by parasitic worms (helminths). It also appears to be effective against other endoparasites and ectoparasites. Oral ivermectin has been used to treat crusted scabies that does not respond to topical treatment alone (British National Formulary 2014). It has also been used to treat other forms of 'difficult-to-treat' scabies (for example, if a topical treatment can't be used or hasn't worked). There are also reports in the literature about using oral ivermectin to treat outbreaks of scabies in mass care settings, such as nursing homes.

Regulatory status of ivermectin

Ivermectin is unlicensed in the UK.

Oral ivermectin is licensed in the USA for the treatment of strongyloidiasis and onchocerciasis parasitic infections, and in France for the treatment of strongyloidiasis and scabies. It is available on a named-patient basis in the UK from 'special order' manufacturers or specialist importing companies (British National Formulary 2014).

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using ivermectin.

Evidence statements

For the treatment of classical or uncomplicated scabies

- Most randomised controlled trials (RCTs) used a single oral dose of ivermectin 200 micrograms/kg.

- Ivermectin was superior to placebo (1 RCT).

- Ivermectin was superior to benzyl benzoate in 1 RCT, not statistically significantly different in 3 RCTs and inferior in 1 RCT.

- Ivermectin was inferior to permethrin in 3 RCTs and not statistically significantly different in 3 RCTs (4 comparisons, 2 from the same trial).

- Treatment failure rates with ivermectin varied widely in these RCTs, from 7% to 70% (see tables 1, 2 and 3 for details).

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

- Adverse events reported in people receiving oral ivermectin include aggravation of symptoms (including pruritus), irritation, headache, nausea, pustular rash, cellulitis, abdominal pain, and mild diarrhoea.

For the treatment of crusted scabies

- No RCTs that assessed oral ivermectin for the treatment of crusted scabies were identified. Five uncontrolled trials and case series with 4 or more participants with crusted scabies that reported cure rates or treatment failures were identified.

- Multiple doses of oral ivermectin and/or ivermectin in combination with topical therapy were frequently administered to cure scabies in the studies identified.

- Treatment failure rates varied widely (see table 4 for details).

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is

given in the Evidence review section.

Efficacy

Classical or uncomplicated scabies

A Cochrane systematic review has evaluated topical and systemic drugs for treating scabies. The review included 1 RCT that compared oral ivermectin with placebo, 5 RCTs that compared oral ivermectin with benzyl benzoate and 2 RCTs that compared oral ivermectin with permethrin. Since the publication of the Cochrane systematic review, 4 RCTs comparing oral ivermectin with permethrin have been published.

The primary outcome of the Cochrane systematic review was treatment failure, defined as the persistence of original lesions, the appearance of new lesions or confirmation of a live mite. Treatment failure has been calculated for the 4 additional RCTs identified.

Table 1 shows the results of the only RCT that compared oral ivermectin with placebo. Ivermectin was superior to placebo at 1 week.

Table 1 Treatment failure in trials of oral ivermectin compared with placebo

Trial	Ivermectin	Placebo	Analysis
Macotela-Ruíz and Peña-González (1993)[a] 200 micrograms/kg ivermectin vs. placebo, follow-up at 7 days	6/29 (21%)	22/26 (85%)	RR 0.24 (95% CI 0.12 to 0.51) Statistically significant difference in favour of ivermectin
Abbreviations: CI, confidence interval; RR, risk ratio (or relative risk). [a] Results extracted from the Cochrane systematic review.			

Five RCTs compared oral ivermectin with topical benzyl benzoate. Ivermectin was superior to benzyl benzoate in 1 trial at 4 weeks, not statistically significantly different in 3 trials (at 1, 3 and 4 weeks) and inferior in 1 trial (at 2 weeks). Differences in treatment regimens and the length of follow-up may explain some of the heterogeneity in the results (see table 2).

Table 2 Treatment failure in trials of oral ivermectin compared with topical benzyl

benzoate

Trial	Ivermectin	Benzyl benzoate	Analysis
Glaziou et al. (1993)[a] 100 micrograms/kg ivermectin vs. 10% benzyl benzoate 2×12 h, follow-up at 30 days	7/23 (30%)	11/21 (52%)	RR 0.58 (95% CI 0.28 to 1.22) No statistically significant difference
Nnoruka and Agu (2001)[a] 200 micrograms/kg ivermectin vs. 25% benzyl benzoate 72 h, follow-up at 30 days	2/29 (7%)	15/29 (52%)	RR 0.13 (95% CI 0.03 to 0.53) Statistically significant difference in favour of ivermectin
Brooks and Grace (2002)[a] 200 micrograms/kg ivermectin vs. 10% benzyl benzoate overnight, follow-up at 3 weeks	19/43 (44%)	18/37 (49%)	RR 0.91 (95% CI 0.57 to 1.46) No statistically significant difference
Bachewar et al. (2009)[a] 200 micrograms/kg ivermectin vs. 25% benzyl benzoate overnight × 2, follow-up at 1 week	14/27 (52%)	6/25 (24%)	RR 2.16 (95% CI 0.98 to 4.74) No statistically significant difference
Ly et al. (2009)[a] 150–200 micrograms/kg ivermectin vs. 12.5% benzyl benzoate 1 or 2 overnights, follow-up at 14 days	38/54 (70%)	38/108 (35%)	RR 2.00 (95% CI 1.47 to 2.72) Statistically significant difference in favour of benzyl benzoate
Abbreviations: CI, confidence interval; h, hours; RR, risk ratio (or relative risk). [a] Results extracted from the Cochrane systematic review			

The Cochrane systematic review included 2 RCTs that compared oral ivermectin with topical permethrin. Both trials found that ivermectin was inferior to permethrin at 1 or 2 weeks. Four other RCTs were published after the Cochrane review, 1 of which compared 2 dosing strategies of ivermectin. In these 4 trials, ivermectin was found to be inferior to

permethrin in 1 RCT at 1 week, and not statistically significantly different in 3 RCTs (4 comparisons, 2 from the same trial) at 2 or 4 weeks. Differences in the length of follow-up may explain some of the heterogeneity in the results (see table 3).

Table 3 Treatment failure in trials of oral ivermectin compared with topical permethrin

Trial	Ivermectin	Permethrin	Analysis
Usha and Gopalakrishnan Nair (2000)[a] 200 micrograms/kg ivermectin vs. 5% permethrin overnight, follow-up at 2 weeks	12/40 (30%)	1/45 (2%)	RR 13.50 (95% CI 1.84 to 99.26) Statistically significant difference in favour of permethrin
Bachewar et al. (2009)[a] 200 micrograms/kg ivermectin vs. 5% permethrin overnight, follow-up at 1 week	14/27 (52%)	5/28 (18%)	RR 2.90 (95% CI 1.21 to 6.96) Statistically significant difference in favour of permethrin
Sharma and Singal (2011) 200 micrograms/kg ivermectin vs. 5% permethrin overnight, follow-up at 4 weeks	4/40 (10%)	2/38 (5%)	p=0.769 for treatment failure No statistically significant difference
Sharma and Singal (2011) 2 doses of 200 micrograms/kg ivermectin 2 weeks apart vs. 5% permethrin overnight, follow-up at 4 weeks	4/39 (10%)	2/38 (5%)	p=0.769 for treatment failure No statistically significant difference

Chhaiya et al. (2012) 200 micrograms/kg ivermectin vs. 5% permethrin >8 h, follow-up at 1 week	70/100 (70%)	25/99 (25%)	p<0.05 for clinical cure Statistically significant difference in favour of permethrin[b]
Goldust et al. (2012) 200 micrograms/kg ivermectin vs. 5% permethrin 2×12 h 1 week apart, follow-up at 2 weeks	17/121 (14%)	9/121 (7%)	p=0.42 for clinical cure No statistically significant difference
Saqib et al. (2012) 200 micrograms/kg ivermectin vs. 5% permethrin 10–12 h, follow-up at 2 weeks	20/60 (33%)	20/60 (33%)	p=1.0 for clinical cure No statistically significant difference
Abbreviations: CI, confidence interval; h, hours; p, p value; RR, risk ratio (or relative risk). [a] Results extracted from the Cochrane systematic review. [b] In this trial clinical cure was assessed weekly. If there were no signs of cure the treatment was repeated. By the third week there was no statically significant difference between ivermectin and permethrin.			

No RCTs comparing oral ivermectin with malathion were identified.

Crusted scabies (also known as hyperkeratotic, Norwegian or atypical scabies)

No RCTs of oral ivermectin for the treatment of crusted scabies were identified.

Uncontrolled trials and case series with 4 or more participants with crusted scabies that reported cure rates or treatment failures are summarised in table 4.

Table 4 Ivermectin for crusted scabies

Trial	Population	Intervention	Treatment failure rate
Huffam and Currie (1998)	20 people with crusted scabies refractory to initial treatment	1 to 3 doses of ivermectin, 14 days apart; 3 treatments with 5% permethrin overnight during 1 week plus keratolytic therapy with 10% urea and 5% lactic acid	12/20 (60%)
Larralde et al. (1999)	2 people with Down's syndrome and crusted scabies refractory to topical 5% permethrin	1 dose of 200 micrograms/kg ivermectin	2/2 (100%)
		2 doses of 200 micrograms/kg ivermectin 2 to 3 weeks apart	0/2 (0%)
	2 HIV-positive people with crusted scabies	2 doses of 200 micrograms/kg ivermectin 1 week apart	0/2 (0%)
Alberici et al. (2000)	8 HIV-positive people with crusted scabies	1 dose of 200 micrograms/kg ivermectin	1/1 (100%)
		Topical 15% benzyl benzoate solution applied twice daily for 3 days	3/3 (100%)
		1 dose of 200 micrograms/kg ivermectin plus topical 15% benzyl benzoate solution applied twice daily for 3 days	0/4 (0%)
Paasch and Haustein (2000)	12 people with crusted scabies from 3 residences for the elderly	1 or 2 doses of 12 mg ivermectin (second dose after 8 days)	0/12 (0%)
Nofal (2009)	8 people with crusted scabies	1 dose of 200 micrograms/kg oral ivermectin	6/8 (75%)
		2 doses of 200 micrograms/kg oral ivermectin 2 weeks apart	2/6 (33%)
		3 doses of 200 micrograms/kg oral ivermectin 2 weeks apart plus topical therapy with permethrin 5% and salicylic acid 5%	0/2 (0%)

Safety

Adverse events reported in people receiving oral ivermectin in RCTs for classical or uncomplicated scabies include aggravation of symptoms (including pruritus), irritation, headache, nausea, pustular rash, cellulitis, abdominal pain and mild diarrhoea. The adverse events reported in individual trials are summarised in tables 5, 6 and 7.

Table 5 Safety in trials of oral ivermectin compared with placebo

Trial	Ivermectin	Placebo	Analysis
Macotela-Ruíz and Peña-González (1993)[a] 200 micrograms/kg ivermectin vs. placebo, follow-up at 7 days	None recorded	None recorded	
[a] Results extracted from the Cochrane systematic review.			

Table 6 Safety in trials of oral ivermectin compared with topical benzyl benzoate

Trial	Ivermectin	Benzyl benzoate	Analysis
Glaziou et al. (1993)[a] 100 micrograms/kg ivermectin vs. 10% benzyl benzoate 2×12 h, follow-up at 30 days	None reported	Mild increase in pruritus: 5/21 (24%)	Not reported
Nnoruka and Agu (2001)[a] 200 micrograms/kg ivermectin vs. 25% benzyl benzoate 72 h, follow-up at 30 days	None reported	Pruritus and irritation: 7/29 (24%)	Not reported
Brooks and Grace (2002)[a] 200 micrograms/kg ivermectin vs. 10% benzyl benzoate overnight, follow-up at 3 weeks	Pustular rash: 3/43 (7%) Cellulitis: 1/43 (2%)	Burning or stinging: 6/37 (16%) Dermatitis: 6/37 (16%)	Not reported
Bachewar et al. (2009)[a] 200 micrograms/kg ivermectin vs. 25% benzyl benzoate overnight × 2, follow-up at 1 week	None reported	None reported	

Ly et al. (2009)[a] 150–200 micrograms/kg ivermectin vs. 12.5% benzyl benzoate 1 or 2 overnights, follow-up at 14 days	Abdominal pain: 5/65 (8%) Mild diarrhoea: 2/65 (3%)	Irritant dermatitis: 30/116 (26%)	Not reported
Abbreviations: h, hours [a] Results extracted from the Cochrane systematic review.			

Table 7 Safety in trials of oral ivermectin compared with topical permethrin

Trial	Ivermectin	Permethrin	Analysis
Usha and Gopalakrishnan Nair (2000)[a] 200 micrograms/kg ivermectin vs. 5% permethrin overnight, follow-up at 2 weeks	Aggravation of symptoms: 3/43 (7%)	None recorded	Not reported
Bachewar et al. (2009)[a] 200 micrograms/kg ivermectin vs. 5% permethrin overnight, follow-up at 1 week	None recorded	None recorded	
Sharma and Singal (2011) 1 or 2 doses of 200 micrograms/kg ivermectin vs. 5% permethrin overnight, follow-up at 4 weeks	Headache: 4/80 (5%) Nausea: 2/80 (3%)	Transient burning sensation: 3/40 (7.5%) Pruritus: 2/40 (5%)	Not reported
Chhaiya et al. (2012) 200 micrograms/kg ivermectin vs. 5% permethrin >8 h, follow-up at 1 week	Headache: 1/100 (1%) Increase in pruritus: 1/100 (1%)	Mild burning sensation: 1/99 (1%)	Not reported
Goldust et al. (2012) 200 micrograms/kg ivermectin vs. 5% permethrin 2×12 h 1 week apart, follow-up at 2 weeks	Irritation: 3/121 (2%)	Irritation: 6/121 (5%)	Not reported

Saqib et al. (2012) 200 micrograms/kg ivermectin vs. 5% permethrin 10–12 h, follow-up at 2 weeks	None reported	None reported	
Abbreviations: h, hours. [a] Results extracted from the Cochrane systematic review.			

Three of the studies on the use of ivermectin for crusted scabies reported either no side effects or that no adverse effects were observed (Huffam and Currie 1998, Larralde et al. 1999 and Alberici et al. 2000). Nofal (2009) reported that no major adverse effects occurred. One person complained of gastric upset and 2 people experienced a transient increase in pruritus. Paasch and Haustein (2000) reported that one-third of people experienced an increase in pruritus for 2 days and haematomas developed in 2 people with an increase in prothrombin time.

Cost effectiveness and cost

Because ivermectin is unlicensed in the UK, no costs could be obtained from standard published sources. Informal sources suggest that the cost is around £160 for 20×3 mg tablets. No cost-effectiveness studies were identified.

Relevance to NICE guidance programmes

This use of oral ivermectin for scabies is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

There is no NICE guidance on the treatment of scabies.

Intervention and alternatives

Ivermectin is an anthelmintic that acts against infections caused by parasitic worms (helminths). It also appears to be effective against other endoparasites and ectoparasites.

Oral ivermectin is licensed in the USA (Stromectol) for the treatment of strongyloidiasis and onchocerciasis (river blindness) parasitic infections, and in France for the treatment of strongyloidiasis and scabies (see Welsh Medicines Information Centre 2012) It is available

on a named-patient basis in the UK from 'special order' manufacturers or specialist importing companies (see [British National Formulary 2014](#)). Oral ivermectin has been used to treat crusted scabies (also known as hyperkeratotic, Norwegian or atypical scabies) that does not respond to topical treatment alone. It has also been used to treat other forms of 'difficult-to-treat' classical scabies (for example, if a topical treatment cannot be used or has not worked). There are also reports in the literature about using oral ivermectin to treat outbreaks of scabies in mass care settings, such as nursing homes.

The manufacturer of ivermectin has provided a European summary of product characteristics for Stromectol 3 mg tablets (Merck Sharp & Dohme: personal communication December 2013), which states that the recommended dose for scabies is a single oral dose of ivermectin 200 micrograms/kg body weight. For classical scabies, recovery is considered definite only after 4 weeks have elapsed since treatment. Persistence of pruritus or scraping lesions does not justify a second treatment before this date. Administration of a second dose within 2 weeks after the initial dose should only be considered when new specific lesions occur or when parasitological examination is positive. For crusted scabies, a second dose within 8–15 days of the initial dose of ivermectin and/or concomitant topical therapy may be necessary.

Condition

Scabies is a parasitic infection of the skin. It is caused by the *Sarcoptes scabiei* mite. The female mite burrows into the skin to lay eggs. Larvae emerge from the eggs. These develop through two nymphal stages into adult males and females. It takes 10–13 days for adult mites to appear after eggs have been laid. Female mites make new burrows, and male mites move actively between burrows seeking to mate with females.

Scabies is recognised by a delayed hypersensitivity reaction to the saliva and faecal material excreted by the mite. It causes intense itching, particularly at night, with eruptions on the skin. The classical sites of infestation are between the fingers, the wrists, axillary areas, female breasts (particularly the skin of the nipples), peri-umbilical area, penis, scrotum and buttocks.

The infection usually spreads from person to person via direct skin contact. Transfer via inanimate objects such as clothing or furnishings is possible, although this normally only occurs in cases of crusted scabies.

NICE Clinical Knowledge Summaries (CKS) for [scabies](#) recommends that people with

scabies and all members of their household, close contacts and sexual contacts need to be treated at the same time (within a 24-hour period), even if they do not have symptoms of scabies. Contacts can be treated with topical treatments even if the person with scabies is treated with ivermectin.

Crusted scabies (also known as hyperkeratotic, Norwegian or atypical scabies) is a more severe form of scabies associated with disorders of the immune system (such as HIV infection), reduced ability to scratch (for example, because of physical incapacity or because the itch is not perceived because of skin anaesthesia) and learning difficulties, dementia, or Down's syndrome. Clinically, this atypical form of scabies presents with a hyperkeratotic dermatosis resembling uncomplicated xeroderma or with a granular appearance. Lymphadenopathy and eosinophilia can be present, but itching may be unexpectedly mild. Patients with extensive crusted scabies may harbour millions of mites and are highly infectious. The dermatological distribution of mites in such patients is often atypical (for example, it may include the head), and treatment in hospital is often advised.

Alternative treatment options

NICE Clinical Knowledge Summaries (CKS) for scabies recommends permethrin 5% dermal cream as the first-line treatment for scabies. Malathion 0.5% aqueous liquid can be used if permethrin cream is inappropriate. However, malathion liquid is currently unavailable in the UK.

These topical treatments should be applied to the whole body, with special attention to the areas between the fingers and toes and under the nails. The treatments should be applied twice, with applications 1 week apart. The treatment should be applied for a prolonged period (8–12 hours for permethrin and 24 hours for malathion) before being washed off.

Benzyl benzoate is another topical treatment for scabies, but it is not as effective as permethrin or malathion and is generally no longer used. It is an irritant and should be avoided in children (British National Formulary 2014).

Evidence review: efficacy

Classical or uncomplicated scabies

A Cochrane systematic review has evaluated topical and systemic drugs for treating scabies. It included 22 randomised controlled trials (RCTs) that compared drug treatments, herbal or traditional treatments, or any combination of these with placebo, no intervention or a different intervention. Participants included children or adults with a clinical or parasitological diagnosis of scabies and their contacts. Most trials were conducted in countries with healthcare systems that are very different to the UK, such as India. The primary outcome 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 review included 9 RCTs of oral ivermectin. One trial compared oral ivermectin with placebo, 5 trials compared oral ivermectin with benzyl benzoate, and one of these plus another trial compared oral ivermectin with permethrin. Two trials compared oral ivermectin with lindane but because this was withdrawn from the UK market in 1996, these trials are not discussed further.

Macotela-Ruíz and Peña-González (1993) compared a single dose of 200 micrograms/kg body weight oral ivermectin with placebo in 55 participants aged over 5 years. There were fewer treatment failures in clinically diagnosed cases in the ivermectin group at 7 days. Treatment failure occurred in 21% of people treated with ivermectin (6/29) compared with 85% of people treated with placebo (relative risk [RR] 0.24, 95% confidence interval [CI] 0.12 to 0.51).

Five trials, with data for a total of 462 participants, compared a single dose of oral ivermectin with various strengths and applications of topical benzyl benzoate. Three trials found no statistically significant difference between the treatments, 1 trial found benzyl benzoate to be more effective, and 1 trial found ivermectin to be more effective.

Brooks and Grace (2002) compared a single dose of 200 micrograms/kg body weight ivermectin with a single application of 10% benzyl benzoate in 110 children aged 6 months to 14 years. No statistically significant difference in treatment failure in clinically diagnosed cases between the groups was found at 3 weeks in the 80 children who completed follow-up. Treatment failed in 44% of children treated with ivermectin (19/43) compared with 49%

of people treated with benzyl benzoate (18/37) (RR 0.91, 95% CI 0.57 to 1.46). This trial also reported on itch persistence, and no statistically significant difference in the number of participants who reported night-time itch at 3 weeks was found (30% with ivermectin [10/33] and 56% with benzyl benzoate [14/25] [RR 0.54, 95% CI 0.29 to 1.01]).

Glaziou et al. (1993) compared a single dose of 100 micrograms/kg body weight ivermectin with 2 applications of 10% benzyl benzoate in 44 participants aged 5–56 years. At 30 days, no statistically significant difference in treatment failure in clinically diagnosed cases was found between the groups. Treatment failure occurred in 30% of people treated with ivermectin (7/23) and 52% of people treated with benzyl benzoate (11/21) (RR 0.58, 95% CI 0.28 to 1.22).

Two trials compared 200 micrograms/kg bodyweight ivermectin with 25% benzyl benzoate. Bachewar et al. (2009) initially compared a single dose of ivermectin with 2 applications of benzyl benzoate 25% in 69 adults (a further 34 adults were randomised to 1 application of permethrin cream). Treatment failure was assessed after 1 week, and no statistically significant difference between groups was found in the 52 adults who were followed up. Treatment failure in clinically diagnosed cases occurred in 52% of people treated with ivermectin (14/27) compared with 24% of people treated with benzyl benzoate (6/25) (RR 2.16, 95% CI 0.98 to 4.74). Nnoruka and Agu (2001) compared a single dose of ivermectin with a 72-hour application of 25% benzyl benzoate in 58 participants aged 5–63 years. They assessed treatment failure after 30 days. This trial found a statistically significant difference in favour of ivermectin, with treatment failure occurring in 7% of people treated with ivermectin (2/29) compared with 52% of people treated with benzyl benzoate (15/29) (RR 0.13, 95% CI 0.03 to 0.53).

Ly et al. (2009) compared 150–200 micrograms/kg body weight ivermectin with 1 and 2 applications of 12.5% benzyl benzoate in 181 participants aged 5–65 years. After 14 days, a statistically significant difference in favour of benzyl benzoate was found in the 162 participants who completed follow up. Treatment failure in clinically diagnosed cases occurred in 70% of people treated with ivermectin (38/54) compared with 35% of people treated with benzyl benzoate (38/108) (RR 2.00, 95% CI 1.47 to 2.72).

There was significant heterogeneity between trials, which could be explained by the different drug regimens and follow-up periods.

Two trials compared 200 micrograms/kg body weight oral ivermectin with 5% topical permethrin cream. Both trials reported more treatment failures in clinically diagnosed

cases in the ivermectin group. Usha and Gopalakrishnan Nair (2000) compared a single dose of ivermectin with a single application of permethrin cream in 88 participants aged over 5 years. Treatment failure was reported in 30% of people treated with ivermectin (12/40) compared with 2% of people treated with permethrin (1/45) at 2 weeks (RR 13.50, 95% CI 1.84 to 99.26). Bachewar et al. (2009) compared a single dose of ivermectin with 1 application of permethrin cream in 68 adults (a further 35 adults were randomised to 1 application of benzyl benzoate [see above]). They reported treatment failure in 52% of people treated with ivermectin (14/27) compared with 18% of people treated with permethrin (5/28) at 1 week follow-up (RR 2.90, 95% CI 1.21 to 6.96). The combined relative risk of treatment failure for the 2 trials comparing ivermectin with permethrin (n=140) was 4.61 (95% CI 2.07 to 10.26, fixed effect model), favouring permethrin.

Since the publication of the Cochrane systematic review 4 RCTs comparing the efficacy of oral ivermectin with permethrin in classical or uncomplicated scabies have been published.

Chhaiya et al. (2012) was an open-label RCT that initially compared a single application of topical 5% permethrin cream, a single application of topical 1% ivermectin lotion and a single dose of oral ivermectin (200 micrograms/kg body weight) in 315 people aged 5 to 80 years in India. People were followed up at 1, 2, 3 and 4 weeks. If scabies was not cured, the same intervention was repeated at each follow-up. The primary end point of the trial was clinical cure of scabietic lesions, the secondary end point was complete relief of pruritus.

At the end of the first week, after 1 dose or application of treatment, the clinical cure rate was statistically significantly lower with oral ivermectin (30/100 [30%]) compared with permethrin (75/99 [75%], p<0.05) or topical ivermectin (69/101 [69%], p<0.05). In other words, treatment failure was 70% with oral ivermectin and 25% with permethrin.

At the end of the second week, when people who had not previously been cured had received a second dose or application of treatment, the cure rate was still statistically significantly lower with oral ivermectin (63%) compared with permethrin (99%, p<0.05) or topical ivermectin (100%, p<0.05). At the end of the third week, when people who had not previously been cured had received a third dose or application, there was no statistically significant difference between the clinical cure rates (p=0.367): 99% with oral ivermectin, 100% with permethrin and 100% with topical ivermectin (100%). These rates remained the same at the end of the fourth week.

The cure rate for itching was statistically significantly better with permethrin and topical

ivermectin compared with oral ivermectin at the end of weeks 2 and 3 (p<0.05), but itching was cured in a similar proportion of people in all groups at the end of week 4.

Goldust et al. (2012) was a single-blind RCT that compared 2 applications of 5% permethrin cream (1 week apart) with a single dose of 200 micrograms/kg body weight ivermectin in 272 people aged 2–84 years in Iran. Cure was defined as the absence of new lesions and all old lesions healed. At 2 weeks, ivermectin was as effective as permethrin. Of the 242 participants followed-up, cure was seen in 112/121 people (93%) treated with 5% permethrin cream and 104/121 people (86%) treated with ivermectin (p=0.42). In other words, treatment failure occurred in 9/121 (7%) of people treated with 5% permethrin cream and 17/121 (14%) of people treated with ivermectin.

Saqib et al. (2012) was an open-label RCT that compared a single dose of 200 micrograms/kg body weight ivermectin with a single application of topical 5% permethrin in 120 adults in Pakistan. Cure was defined as the absence of itching, lesions and microscopic evidence of mites. After 1 and 2 weeks, the number of participants considered to be cured was similar with both treatments. After 1 week, the cure rate was 73% (44/60) with permethrin and 68% (41/60) with ivermectin (p=0.54), and after 2 weeks it was 67% (40/60) with both permethrin and ivermectin (p=1.00). In other words, treatment failure was 27% with permethrin and 32% with ivermectin after 1 week, and 33% with both treatments after 2 weeks.

Sharma and Singal (2011) was a double-blind RCT that compared a single application of topical 5% permethrin cream with a single dose of 200 micrograms/kg body weight ivermectin and 2 doses of 200 micrograms/kg body weight ivermectin (2 weeks apart) in 120 people aged over 5 years in India. Placebo tablets and cream were given to ensure blinding. Complete clinical cure was defined as reduction in both the number of lesions and the grade of pruritus by at least 50%, and negative microscopy. Treatment was considered to have failed if, at the end of the 4 weeks, there was no improvement in pruritus and skin lesions, there were new lesions or there was microscopic evidence of mites.

At the end of the first week, more people who received permethrin achieved complete clinical cure (27/40 [68%]) compared with those who were randomised to either a single dose (14/40 [35%]) or 2 doses (12/40 [30%]) of ivermectin (no statistical analysis given). After 2 weeks, clinical cure was achieved by 87% (33/38) of people who received permethrin, 78% (31/40) who received 1 dose of ivermectin and 67% (26/39) who received 2 doses of ivermectin (no statistical analysis given). After 4 weeks, 95% (36/38) of people

who received permethrin, 90% (36/40) of people who received 1 dose of ivermectin and 90% (35/39) of people who received 2 doses of ivermectin achieved complete clinical cure. There was no statistically significant difference between these cure rates at 4 weeks.

In other words, of the 117 participants that were followed up at 4 weeks, treatment failure occurred in 2 people randomised to 5% permethrin (2/38 [5%]), 4 people randomised to 1 dose of ivermectin (4/40 [10%]) and 4 people randomised to 2 doses of ivermectin (4/39 [10%]). This difference was not statistically significant (p=0.769).

This study also reported on pruritus, self-assessed on a visual analogue scale of 0 to 10. The improvement in itching was better with permethrin after 1 week. However, at the end of the fourth week there was no statistically significant difference between groups: 36/38 people (95%) who received permethrin, 36/40 people (90%) who received 1 dose of ivermectin and 35/39 people (90%) who received 2 doses of ivermectin reported at least a 50% improvement in pruritus.

Crusted scabies

No RCTs of ivermectin for the treatment of crusted scabies were identified.

Uncontrolled trials and case series with 4 or more participants with crusted scabies that reported cure rates or treatment failures are included in this evidence summary.

Huffam and Currie (1998) was an Australian open-label study of oral ivermectin in combination with topical therapy for crusted scabies that had not responded to previous treatment with topical therapies. Twenty aboriginal people with refractory crusted scabies were hospitalised for 1 week and given 3 supervised applications of overnight 5% permethrin over the first week. Keratolytic therapy with 10% urea and lactic acid 5% cream were applied on the days when permethrin was not used. In addition, people were treated with up to 3 doses of 200 micrograms/kg oral ivermectin at 14-day intervals. Complete response, defined as normal skin 4 weeks or longer after the last dose of ivermectin, occurred in 8 people (40%), 9 people had at least a partial response and 3 had minimal improvement. It is unclear whether the results of this study would be applicable to patients in the UK with crusted scabies.

Larralde et al. (1999) described the use of ivermectin to successfully treat 4 people with crusted scabies in Argentina. Two people had Down's syndrome, and their crusted scabies

was refractory to repeated treatment with topical 5% permethrin. Two to 3 weeks after 1 dose of 200 micrograms/kg oral ivermectin, plaques were still present in 1 person, and new plaques appeared in the other person. However, no signs and symptoms of scabies were present 2 weeks after a second dose. Two people were HIV positive and were treated with 2 doses of 200 micrograms/kg oral ivermectin 1 week apart. No signs of crusted scabies developed during 6 months of follow-up.

Alberici et al. (2000) was a retrospective analysis of 39 people with scabies who were HIV positive and were admitted to a hospital in Italy during a scabies epidemic. Eight of these people had crusted scabies. People were treated with topical 15% benzyl benzoate solution applied twice daily for 3 days, a single dose of 200 micrograms/kg ivermectin or a combination of both of these treatments. Complete clinical response was defined as both resolution of itching and either dermatological or microbiological cure, and treatment failure as persistent microbiological evidence of infestation within 4 weeks of treatment. Of the 8 people with crusted scabies, treatment failed in all 3 people treated with benzyl benzoate alone and in the 1 person treated with ivermectin alone. All 4 people treated with a combination of ivermectin and benzyl benzoate had a complete treatment response.

Paasch and Haustein (2000) reported on the management of endemic outbreaks of scabies in 3 residences for the elderly in Germany. They reported on 252 patients, staff and family members living in these residencies who showed recurrent infestations over more than 1 year. Twelve people had crusted scabies and received 12 mg ivermectin once (n=5) or twice (n=7) after an interval of 8 days. No treatment failures were reported in people given ivermectin, although the length of follow-up was not reported and it was unclear whether additional topical treatment was given. The other 240 people received topical treatment with either permethrin cream or allethrin spray.

Nofal (2009) was an uncontrolled study of oral ivermectin for crusted scabies in Egypt. Eight people with crusted scabies were given a single oral dose of 200 micrograms/kg ivermectin and re-examined at 2, 4, 6 and 8 weeks. A second dose of ivermectin was given if treatment failed, defined as persistence of pruritus, or clinical signs or microscopic evidence of scabies, at the end of the second week. A third dose of ivermectin, combined with topical permethrin 5% and salicylic acid 5%, was given at the end of the fourth week to people whose scabies did not respond to the second dose. Two people were cured at the end of week 2, after a single dose of ivermectin. Four people were cured at the end of week 4, after 2 doses of ivermectin. The remaining 2 people were cured at the end of week 6, after 3 doses of ivermectin combined with topical therapy.

Evidence review: safety

Adverse events in studies of ivermectin

Adverse events reported in people receiving oral ivermectin in randomised controlled trials (RCTs) for classical or uncomplicated scabies include aggravation of symptoms (including pruritus), irritation, headache, nausea, pustular rash, cellulitis, abdominal pain and mild diarrhoea.

Three trials reported no adverse events with either ivermectin or the comparator treatment (Macotela-Ruíz and Peña-González 1993, Bachewar et al. 2009 and Saqib et al. 2012).

Glaziou et al. (1993) and Nnoruka and Agu (2001) reported no adverse events with ivermectin but adverse events with benzyl benzoate (pruritus in 5/21 people in Glaziou et al. 1993 and pruritus and irritation in 7/29 people in Nnoruka and Agu 2001). Brooks and Grace (2002) reported adverse events in 4/43 participants in the ivermectin group (pustular rash or cellulitis) and in 12/37 participants in the benzyl benzoate group (burning, stinging or dermatitis). Ly et al. (2009) reported adverse events in 7/65 participants in the ivermectin group (abdominal pain or mild diarrhoea) and in 30/116 participants in the benzyl benzoate groups (irritant dermatitis).

In Usha and Gopalakrishnan Nair (2000), 3/43 participants in the ivermectin group reported aggravation of symptoms compared with none of 45 participants who received permethrin. In Sharma and Singal (2011), 6/80 people reported adverse events with ivermectin (headache and nausea) compared with 5/40 people who were treated with permethrin (transient burning sensation or pruritus). In Chhaiya et al. (2012), 2/100 people reported adverse events with oral ivermectin (headache and an increase in pruritus) compared with 1/99 receiving permethrin (burning sensation). In Goldust et al. (2012), 3/121 people reported irritation with ivermectin compared with 6/121 receiving permethrin.

In studies that reported the use of ivermectin for crusted scabies, 3 studies reported either no side effects or that no adverse effects were observed (Huffam and Currie 1998, Larralde et al. 1999 and Alberici et al. 2000). Nofal (2009) reported that no major adverse effects occurred. One person complained of gastric upset and 2 people experienced a transient increase in pruritus. Paasch and Haustein (2000) reported that one-third of people experienced an increase in pruritus for 2 days and haematomas developed in 2 people with an increase in prothrombin time.

Other sources of safety information

The European summary of product characteristics for Stromectol 3 mg tablets (Merck Sharp & Dohme: personal communication December 2013) lists side effects observed when using ivermectin to treat other parasitic conditions, such as strongyloidiasis or microfilaraemia. These include transient hypereosinophilia, liver function abnormalities, haematuria, toxic epidermal necrolysis, Stevens–Johnson syndrome, encephalopathy and hypersensitivity reactions. However, some of these side effects, such as those related to microfilarial density, may be specific to these conditions. The summary of product characteristics states that when ivermectin is used to treat scabies, transient exacerbation of pruritus may occur at the beginning of treatment. It also states that safety in paediatric patients weighing less than 15 kg has not been established.

Barkwell and Shields (1997) reported an association with ivermectin and an increased risk of death among a group of elderly people with scabies in a long-term care facility in Canada. However, the authors of the Cochrane systematic review and various discussions in the literature have questioned the validity of this report. It is unclear whether the increased risk of death was caused by ivermectin, interactions with other scabicides (including lindane and permethrin) or other treatments such as psychoactive drugs. The authors of the Cochrane systematic review suggest that ivermectin has been used widely in the treatment of onchocerciasis (river blindness) and even with repeated doses serious adverse effects have been rare.

Between 1 July 1963 and 12 December 2011, 16 adverse drug reactions for ivermectin (in 6 adverse drug reaction reports and 4 fatal adverse drug reaction reports) were reported to the Medicines and Healthcare Products Regulatory Agency (MHRA). It is not known how many people took ivermectin, or for what indication. In addition, it is important to note that healthcare professionals are asked to report even if they only have a suspicion that the medicine may have caused the adverse drug reaction. The fact that a report has been submitted does not necessarily mean that the medicine has been proven to cause an adverse drug reaction.

Evidence review: economic issues

Cost effectiveness

No cost-effectiveness studies were identified.

Cost

Ivermectin is unlicensed in the UK and can be supplied from 'special order' manufacturers or specialist importing companies. No costs could be obtained from standard published sources. Informal sources suggest that the cost is around £160 for 20×3 mg tablets.

The NHS Electronic Drug Tariff (January) lists the cost of permethrin 5% cream as £6.96 for 30 g and the cost of malathion 0.5% aqueous liquid (Derbac-M) as £2.37 for 50 ml and £5.93 for 200 ml. The British National Formulary lists the cost of 25% benzyl benzoate emulsion as £2.50 for 500 ml.

Current drug usage

The current usage of oral ivermectin for the treatment of scabies is unknown.

Evidence strengths and limitations

A Cochrane systematic review has evaluated topical and systemic drugs for treating scabies. The review included 1 randomised controlled trial (RCT) that compared oral ivermectin with placebo, 5 RCTs that compared oral ivermectin with benzyl benzoate and 2 RCTs that compared oral ivermectin with permethrin. Since the publication of the Cochrane systematic review, 4 RCTs comparing the efficacy of oral ivermectin with permethrin have been published. All of these trials assessed ivermectin for the treatment of classical or uncomplicated scabies.

The RCTs included different treatment regimens and varying lengths of follow-up, which may explain some of the heterogeneity in the results of the different studies.

Three trials (Macotela-Ruíz and Peña-González 1993, Bachewar et al. 2009 and Chhaiya et al. 2012) assessed treatment failure after just 1 week of follow-up, which is not enough time to have confidence in the outcome. The European summary of product characteristics for Stromectol 3 mg tablets (Merck Sharp & Dohme: personal communication December 2013), states that, for classical scabies, recovery is considered definite only after 4 weeks have elapsed since treatment. Persistence of pruritus or scraping lesions does not justify a second treatment before this date. Administration of a second dose within 2 weeks after the initial dose should only be considered when new specific lesions occur or when parasitological examination is positive.

The authors of the Cochrane systematic review suggested that ivermectin may be slower in achieving cure than topical benzyl benzoate, and this may also be the case compared with permethrin.

The European summary of product characteristics for Stromectol 3 mg tablets (Merck Sharp & Dohme: personal communication December 2013) also states that the recommended dose for scabies is a single oral dose of ivermectin 200 micrograms/kg body weight. Most of the trials used this dose, but Glaziou et al. (1993) and Ly et al. (2009) used lower doses of 100 micrograms/kg and 150–200 micrograms/kg respectively.

The quality of relevant individual studies included in the Cochrane systematic review is summarised in table 8. The Cochrane review concluded that only 1 trial with ivermectin described both adequate randomisation sequence generation and adequate allocation concealment, and the majority of the reports described neither adequately. Blinding was absent or unclear in many of the trials. The same limitations can be applied to the 4 RCTs published since the Cochrane review. Most of the RCTs were conducted in countries with few healthcare resources, such as India, and it is unclear how applicable the findings will be to people in the UK with scabies. Most were also small trials (50–200 participants), which are too small to properly assess serious but rare potential adverse effects.

Table 8 Quality of trials included in the Cochrane systematic review

Trial	Allocation sequence generation	Allocation concealment	Blinding	Inclusion of randomised participants in the analysis
Macotela-Ruíz and Peña-González (1993)[a]	Unclear	Unclear	Participant and outcomes assessor	Adequate
Glaziou et al. (1993)[a]	Unclear	Unclear	Outcomes assessor	Adequate
Nnoruka and Agu (2001)[a]	Adequate	Unclear	Unclear	Adequate
Brooks and Grace (2002)[a]	Adequate	Unclear	Investigators	Inadequate

Bachewar et al. (2009)[a]	Adequate	Unclear	None	Inadequate
Ly et al. (2009)[a]	Adequate	Unclear	None	Adequate
Usha and Gopalakrishnan Nair (2000)[a]	Adequate	Adequate	None	Adequate
[a] Results extracted from the Cochrane systematic review.				

The quality of the 4 additional RCTs is described briefly below.

Chhaiya et al. (2012) was an open-label (unblinded) RCT. Randomisation was adequate and the method of allocation described suggests that this was concealed.

Goldust et al. (2012) was a single-blind (to the assessor) RCT. The randomisation procedure was not reported and it is unclear if allocation was concealed.

Saqib et al. (2012) states that it was a quasi-experimental study, but then goes on to state that participants were randomly divided into 2 groups. The randomisation procedure was not reported and it is unclear if allocation was concealed. The study was open-label (unblinded).

Sharma and Singal (2011) was a double-blind RCT that used both placebo topical applications and tablets. Randomisation was adequate and the method of allocation described suggests that this was concealed.

No RCTs of oral ivermectin for the treatment of crusted scabies were identified.

The results of uncontrolled trials and case series with 4 or more participants with crusted scabies that reported cure rates or treatment failures are included in this evidence summary. Multiple doses of oral ivermectin and/or ivermectin in combination with topical therapy were frequently administered in these small studies. The results of these studies should be interpreted with caution because of the potential for publication bias (publication of cases with good outcomes).

Summary for patients

A summary written for patients is available on the NICE website.

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- Broad internet search: 26 November 2013

  — <u>Google</u> scabies ivermectin OR stromectol OR mectizan OR ivomec filetype:pdf [sifted first 5 pages of results]

  — <u>Trip Database</u> ivermectin and scabies

MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy: 26 November 2013

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1 Scabies/ (2866)

2 Sarcoptes scabiei/ (589)

3 scabie$.tw. (3031)

4 1 or 2 or 3 (3792)

5 Ivermectin/ (4726)

6 (ivermectin or eqvalan or stromectol or mectizan or mk 933 or mk933 or ivomec).tw. (4293)

7 5 or 6 (5847)

8 4 and 7 (418)

9 limit 8 to english language (362)

10 animal/ not (animal/ and human/) (3970297)

11 9 not 10 (236)

Embase (via Ovid)

Database: Embase <1988 to 2013 November 25>

Search Strategy: 26 November 2013

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1 Scabies/ (3120)

2 Sarcoptes scabiei/ (791)

3 scabie$.tw. (2588)

4 1 or 2 or 3 (3773)

5 Ivermectin/ (7607)

6 (ivermectin or eqvalan or stromectol or mectizan or mk 933 or mk933 or ivomec).tw. (4879)

7 5 or 6 (8054)

8 4 and 7 (756)

9 limit 8 to english language (597)

10 animal/ not (animal/ and human/) (709419)

11 9 not 10 (550)

12 limit 11 to exclude medline journals (67)

Cochrane Central Register of Controlled Trials (CENTRAL)

ID Search Hits 26 November 2013

#1 "scabies":ti,ab,kw (Word variations have been searched) 82

#2 MeSH descriptor: [Scabies] explode all trees 37

#3 (ivermectin or eqvalan or stromectol or mectizan or mk 933 or mk933 or ivomec):ti,ab,kw (Word variations have been searched) 262

#4 MeSH descriptor: [Ivermectin] explode all trees 214

#5 #1 or #2 82

#6 #3 or #4 262

#7 #5 and #6 24

[#8 Limit to Trials 22]

CRD HTA, DARE and EED database

ID Search Hits 26 November 2013

#1 "scabies":ti,ab,kw (Word variations have been searched) 82

#2 MeSH descriptor: [Scabies] explode all trees 37

#3 (ivermectin or eqvalan or stromectol or mectizan or mk 933 or mk933 or ivomec):ti,ab,kw (Word variations have been searched) 262

#4 MeSH descriptor: [Ivermectin] explode all trees 214

#5 #1 or #2 82

#6 #3 or #4 262

#7 #5 and #6 24

[#8 Limit to Economic Evaluations 1]

Grey literature and ongoing trials

- NICE Evidence Services

- Health Canada – Clinical Trials Search

- metaRegister of Controlled Trials (mRCT)

- ClinicalTrials.gov

Manufacturers' websites

Merck (international)

Shalaks pharmaceuticals

Cipla Ltd

Evidence selection

This evidence summary included randomised controlled trials (RCTs) that investigated the efficacy of oral ivermectin for scabies. Because no RCTs were identified that had investigated the efficacy of oral ivermectin for crusted scabies, uncontrolled trials and

case series with 4 or more participants with crusted scabies that reported cure rates or treatment failures were included. There are also reports in the literature about using oral ivermectin to treat outbreaks of scabies in mass care settings, such as nursing homes. However, only 1 study met the inclusion criteria for the review.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

> This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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