Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ivermectin

Proprietary Product Name: Stromectol

Sponsor: Merck Sharp Dohme (Australia) Pty Ltd

First round evaluation: 28 September 2012
Second round evaluation: 20 February 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
APSGN	acute post-streptococcal glomerulonephritis
ARF	acute rheumatic fever.
BB	benzyl benzoate
BMV	corticosteroid betamethasone valerate.
CER	comparative effectiveness review
EU	European Union
HCW	healthcare worker
ITT	Intent to treat
PP	per protocol
RHD	rheumatic heart disease

1. Clinical rationale

Merck Sharp Dohme Australia Pty Ltd (MSDA) was approached by the National Aboriginal Community Controlled Health Organisation (NACCHO)[1] regarding the need for general practitioners in Australia to have better access to ivermectin for scabies. NACCHO endorses and supports MSDA's application to extend indication of ivermectin and in its independent capacity has also advised the PBAC of its keen interest in supporting appropriate use of ivermectin in scabies. The sponsors claim that the key issue driving this submission is not commercial benefit but is in response to the request by NACCHO in its independent capacity regarding the high clinical need and urgency of making Stromectol tablets available for the treatment of scabies and crusted scabies in the Aboriginal population.

1.1. Guidance

This submission is entirely literature-based as no clinical studies were conducted by the sponsor regarding use of Stromectol for treatment of scabies. The literature search strategy has been considered acceptable by the TGA to support the literature-based submission for proposed use of Stromectol for treatment of scabies. The TGA had requested that the sponsors include a Risk Management Plan (RMP) for pharmacovigilance in the submission and the sponsor has complied with this request.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

Scabies is a parasitic infection of the skin that is caused by the mite *Sarcoptes scabiei, var hominis.* Scabies is endemic in many tropical and subtropical areas, such as Africa, Egypt, Central and South America, northern and central Australia, the Caribbean Islands, India and Southeast Asia. In industrialised countries including Australia, scabies is observed primarily in sporadic individual cases and institutional outbreaks such as hospitals, nursing homes, prisons or kindergartens.

Scabies is currently endemic in remote northern and central Aboriginal communities where up to 50% of children may be infested. By the age of one, up to 60% of indigenous children will have been affected by scabies. Rates of crusted scabies (the most severe form of the disease) in these communities are amongst the highest and most virulent in the world.

Clinical infection with the scabies mite causes discomfort and often intense itching of the skin, particularly at night, with irritating papular or vesicular eruptions. Complications and death can also occur, usually as a result of secondary bacterial pyoderma, commonly caused by *Streptococcus pyogenes* or *Staphylococcus aureus*. Group A streptococcus is responsible for the continuing outbreaks of acute post-streptococcal glomerulonephritis (APSGN) and acute rheumatic fever (ARF) in remote communities. Treatment for scabies in these communities can require prolonged isolation in hospital with combination topical and oral anti-parasitic therapy. Despite this, re-infection is frequent and relapses have been documented with repeated episodes of scabies. Mortality of patients with crusted scabies in northern Australia, mostly from secondary sepsis, is up to 50% over 5 years.

The practical use of topical treatment for the community management of endemic scabies has some limitations. Environmental factors make total-body topical treatment impractical due to large number of people in each house, high heat and humidity, limited opportunities for privacy

[1]NACCHO represents over 140 aboriginal community-controlled health services in Australia and is managed by an elected aboriginal board of directors.

to apply the cream, and poor infrastructure for washing it off. Hence, rapid reinfestation may be common due to the high prevalence of scabies, overcrowding and frequent movement between households and communities. Another potential concern is the development of drug resistance when such long-running community disease control programs achieve only limited participation and disease reduction. Concerns regarding mite resistance to permethrin have recently been described in a number of Aboriginal communities in northern Australia. Thus it is possible that even if greater levels of treatment participation could be achieved, resistance to this treatment may undermine any potential impact on disease burden. These findings demonstrate an urgent need for a more suitable treatment for scabies to reduce the burden in endemic settings. The sponsors proposed that oral treatment with Ivermectin may help to address the above limitations of current antiscabetic treatment and may provide a more accepted and therefore more effective mass community treatment.

This submission is entirely literature-based as there have been no clinical studies conducted by the sponsor regarding use of Stromectol for treatment of scabies. Two systematic reviews were conducted respectively on the typical and crusted presentation of scabies to identify available evidence of the efficacy and safety of Ivermectin in the treatment of both forms of scabies.

The submission contained the following clinical information:

- Study 066 in healthy subjects to evaluate safety/ tolerability of supratherapeutic doses of ivermectin and effect of food on PKs of ivermectin.
- Literature based evidence to support use of ivermectin in 'typical scabies'
- Literature based evidence to support use of ivermectin in 'crusted scabies'
- Additional references provided as supportive evidence.

2.2. Paediatric data

There were no studies conducted or planned in the paediatric population with Stromectol for the proposed indication of treatment against scabies. However, there are literature reports where Stromectol has been widely used in children aged >5 years.

2.3. Good clinical practice (GCP)

Study 066 was carried out according to GCP guidelines.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

3.1.1. Summary of pharmacokinetics

Only one new study (066) was submitted in this dossier and no new data were submitted regarding the Absorption Distribution Metabolism Excretion (ADME) profile or other PK characteristics of ivermectin, which is already approved and marketed for other indications.

3.1.1.1. Physicochemical characteristics of the active substance

No new data submitted.

3.1.1.2. Pharmacokinetics in healthy subjects

3.1.1.2.1. Absorption

3.1.1.3. Sites and mechanisms of absorption

3.1.1.3.1. Bioavailability

3.1.1.4. Absolute bioavailability

No new data.

3.1.1.5. Bioavailability relative to an oral solution or micronised suspension

Not applicable.

3.1.1.6. Bioequivalence of clinical trial and market formulations

Not applicable.

3.1.1.7. Influence of food

In the Phase I Study 066 in healthy subjects, area under the concentration time curive from time 0 to infinity ($AUC_{0-\infty}$) was 2.57 (95% CI: 2.16, 3.05) times higher when ivermectin was administered with a standard high-fat meal compared to under fasting conditions.

3.1.1.8. Dose proportionality

In Study 066, dose proportionality was evaluated for single doses of 30 to 120 mg administered in the fasting condition. The AUC and peak plasma concentration (C_{max}) of ivermectin increase with increasing dose and appear generally dose proportional in this range. A high variability in absorption is apparent from examination of standard deviations and from the overall trends in AUC and C_{max} with increasing dose. Specifically, AUC and C_{max} do not appear to increase between the doses of 60 mg and 90 mg. However, a nearly proportional increase is seen with the 120 mg dose, indicating that absorption is not saturated in this range. The high variability in AUC is attributable to incomplete absorption of the drug in the fasted state. Comparison of the AUCs in fed and fasted subjects reveals that bioavailability of ivermectin in the fasted state is at most approximately 40%, allowing ample margin for variability in absorption.

Comments: The parallel design of the study may also have contributed to the variability in AUC and C_{max} observed across doses. Tmax and half-life were generally invariant across the dose range as would be expected from linear kinetics. The doses used in this study were up to 5 times the proposed dosage for treatment of scabies.

3.1.1.9. Bioavailability during multiple-dosing

In Study 066, the geometric mean ratio of AUC from time 0 to 60 h post dosing (AUC_{0-60hr}) of ivermectin on Study Day 7 to the AUC_{0-60hr} on Study Day 1 was calculated for assessing accumulation. The geometric mean ratios were 1.24 and 1.40 for the ivermectin 30 mg and 60 mg doses, respectively. This result suggests minimal accumulation of drug with Study Day 1, 4 and 7 dosing, consistent with a short half-life relative to the dosing interval. The geometric mean ratio : Study Day 7, last dose/ Study Day 1, first dose (95% confidence interval) was estimated to be 1.24 (0.80, 1.92) and 1.40 (0.91, 2.18) for the 30 mg level and the 60 mg level, respectively.

Comments: Overall results suggest that accumulation of ivermectin administered every fourth day is minimal which is consistent with half-life values being shorter than 1 day.

3.1.1.10. Effect of administration timing

Not applicable.

3.1.1.10.1. Distribution

No new data was submitted.

3.1.1.10.2. Metabolism

No new data was submitted.

3.1.1.10.3. Excretion

No new data was submitted.

3.1.1.10.4. Intra- and inter-individual variability of pharmacokinetics

No new data was submitted.

3.1.1.11. Pharmacokinetics in the target population

No PK studies were conducted in the target patient population.

3.1.1.12. Pharmacokinetics in other special populations

3.1.1.12.1. Pharmacokinetics in subjects with impaired hepatic function

Ivermectin has not been evaluated in patients with impaired hepatic function.

3.1.1.12.2. Pharmacokinetics in subjects with impaired renal function

Ivermectin has not been evaluated in patients with impaired renal function.

3.1.1.12.3. Pharmacokinetics according to age

No new data.

3.1.1.12.4. Pharmacokinetics related to genetic factors

No data submitted.

3.1.1.12.5. Pharmacokinetics {in other special population / according to other population characteristic}

No data submitted.

3.1.1.13. Pharmacokinetic interactions

3.1.1.13.1. Pharmacokinetic interactions demonstrated in human studies

No data submitted.

3.1.1.13.2. Clinical implications of in vitro findings

Not applicable.

3.2. Evaluator's overall conclusions on pharmacokinetics

Study 066 was designed primarily to evaluate the safety and tolerability of oral ivermectin to support its use for the treatment of head lice infestation and PK data was only collected as a secondary objective. Specifically, the study was designed to extend the kinetic understanding of this drug beyond the doses examined previously (up to 15 mg) and when administered in repeated doses for use against head lice and also to examine the effect of a high-fat meal on absorption. The design of the study was based on the anticipated dosage regimen for head lice (approximately 400 µg/kg) at the time the study was conducted. A 30 mg dose was chosen to span a range around this target dose but the actual range for the participants was 347 to 594 µg/kg. Doses of 60, 90, and 120 mg were included to establish a significant safety margin for administration of this drug. Doses of 30 and 60 mg were administered as 3 multiple doses on Study Days 1, 4 and 7 of their corresponding periods, which was the maximum frequency anticipated for head lice treatment and allowed evaluation of possible accumulation and safety

by Study Day 7. Additionally, the effect of a high fat meal on absorption of 30 mg was examined to evaluate the maximum potential food effect, since the interactions with food had not been studied previously.

Results from this study suggest that AUC and C_{max} of ivermectin increase with increasing dose and appear generally dose proportional in the range of 30 to 120 mg. However, interpretation was limited by high variability especially between doses 60-90 mg. Furthermore, it was shown that oral bioavailability of ivermectin increased almost 2.5 times following administration with a high fat meal compared to a fasting state. Following multiple dosing (3 times a week) with ivermectin, there was minimal accumulation which was consistent with the half-life of about 1 day.

Overall, the pharmacokinetic parameters were consistent with those previously established. However, proposed dose for scabies is 200 µg/kg which is already approved for use in onchocerciasis and this study did not provide any additional information on PKs at the proposed dose in treatment of scabies.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Only one Phase I study (066) in healthy subjects provided information on effects of ivermectin on central nervous system (CNS) toxicity and also provided safety/tolerability data at doses to be used for the proposed new indication. No other PD data was provided in this submission as ivermectin is already approved and marketed.

4.2. Summary of pharmacodynamics

4.2.1. Mechanism of action

No new data submitted.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

No new data.

4.2.2.2. Secondary pharmacodynamic effects

The Phase I Study 066 evaluated CNS toxicity and general safety/ tolerability of ivermectin 30 to 120mg (that is, up to 5 times the expected dose for the proposed new indication of treatment of scabies). Specific signs or symptoms of CNS toxicity were based on those determined in previous high-dose animal studies and observations of human overdose (emesis, mydriasis, and ataxia) which were also chosen as the safety endpoints in this study to be used for dose progression. Mydriasis was chosen as the endpoint for the primary hypothesis since, in addition to being identified as one of the main signs of toxicity, it can be accurately quantitated through pupillometry. Pupillometry is a simple, accurate and reproducible method to measure pupil diameter that was validated for use in this study.

The difference in pupil diameter change from baseline (Study Day 1 predose) at high light conditions on Study Day 7 between the groups receiving 30 mg ivermectin in the fasted state and placebo (pooled from Treatments A and B) was assessed using an Analysis of variance (ANOVA) model without considering gender effects. The 90% confidence interval (-0.239, -0.021) for the difference falls within the equivalence interval of (-1.0, 1.0), indicating that the ivermectin 30 mg regimen in the fasted state had equivalent mydriatic effect as compared with placebo according to prespecified criteria. Gender and food did not affect these results

significantly. In addition, examination of pupillometry results at the secondary time points (Study Days 1 and 4, high light and Study Days 1, 4, and 7, low light) and higher doses of ivermectin (60, 90 and 120 mg) showed no consistent trend indicative of a mydriatic effect when ivermectin is given at the specified regimens.

4.2.3. Time course of pharmacodynamic effects

No new data.

4.2.4. Relationship between drug concentration and pharmacodynamic effects

No new data.

4.2.5. Genetic, gender and age related differences in pharmacodynamic response

No new data.

4.2.6. Pharmacodynamic interactions

No new data.

4.3. Evaluator's overall conclusions on pharmacodynamics

No new data was provided on PDs of ivermectin, especially primary PD effects. The Phase I Study 066 evaluated effect of ivermectin (30-120 mg) on CNS toxicity in healthy subjects. No indication of CNS toxicity associated with oral ivermectin was observed for any of the doses administered in this study. This was most strongly supported by the absence of a mydriatic effect documented with pupillometry. The standard used was the difference in pupil size between baseline and the approximate time of C_{max} after the Study Day 7 dose. A conservative measure of a 1 mm difference between the ivermectin and placebo groups was considered significant. Comparison of pupil size to baseline was made after the third dose when maximum drug concentration was likely to be present if any accumulation occurred. Considering this criterion, the mydriatic effect following 30 mg ivermectin administration was equal to that observed with placebo. Escalation to a single dose of 120 mg (up to 2 mg/kg), 10 times the approved dose and 5 times the anticipated head lice dose, also produced no mydriatic effect. This supports the safety of ivermectin at the proposed dose and provides a significant margin of safety.

5. Dosage selection for the pivotal studies

Not applicable.

6. Efficacy

This was a literature-based submission.

[information redacted].

The references were presented to support evidence of efficacy in 'typical scabies' and 'crusted scabies' and will be discussed in the sections *Typical scabies* and *Crusted Scabies* below. *Additional references* will briefly discuss references submitted as 'additional information'.

6.1. Typical scabies

There were 16 randomised controlled studies and 24 observational studies to provide evidence for efficacy/ safety of ivermectin in treatment of typical scabies.

6.1.1. Randomised controlled studies

6.1.1.1. Studies which evaluated ivermectin

A prospective, randomized, comparative clinical trial compared efficacy, safety and cost effectiveness of two topical treatments [benzyl benzoate 25% lotion application for two consecutive nights; permethrin 5% cream applied and left overnight for one night] compared to a single oral dose of tablet ivermectin at 200 µg/kg in 103 patients with scabies in India **(Bachewar, 2009).** The participants were followed up for two weeks for cure rate (patients with no new lesions), adverse drug reaction (ADR) monitoring, and post intervention observation. The follow-up was stopped after two weeks. Majority (84%) of the participants were aged 12 to 41 years. Permethrin decreased pruritus by 76% at the end of one week and had significantly better cure rate than ivermectin (76%, 82% and 56% in BB, permethrin and ivermectin groups, respectively). However, at the end of two weeks treatment, cure rate in ivermectin group was 100% and similar to that in the permethrin group (96%) (Table 1). It was found that BB and ivermectin each consecutively for two weeks were most cost effective[2] regimens giving complete cure in four weeks, while ivermectin gave the same results in two weeks. Benzyl benzoate as first line intervention and ivermectin in the remaining gave best cost-effective results (Table 2).

Table 1. Participant response during the trial in each group. Bachewar, 2009

Participant response	*BB*	*P*	*I*
Recruited participants	35	34	34
Followed up at the end of two weeks	25	28	27
Cure rate at end of one week (%)	76	82.14	55.56
Cure rate at the end of two weeks (%)	92	96.43	100

BB - benzyl benzoate, P - permethrin, I - ivermectin

Table 2. Cost effectiveness analysis of the trial medicines at the end of one week. Bachewar, 2009.

Parameters	*BB*	*P*	*I*
Cost in INR for 100 participants	11 X 100 = 1100	60 X 100 = 6000	25 X 100 = 2500
Cure rate (%) (effectiveness)	76	82.14	55.56
Cost effectiveness	INR1100 for 76 participants	INR6000 for 82.14 participants	INR2500 for 55.56 participants
Cost to treat one case (INR)	14.47	73.04	45

BB - benzyl benzoate, P - permethrin, I - ivermectin

Cost effectiveness analysis of the trial medicines at the end of one week.

Parameters	*BB*	*P*	*I*
Cost in INR for 100 participants	1364	7071.6	3611
Cure rate (%) (effectiveness)	92	96.43	100
Cost effectiveness	INR1364 for 92 participants	INR7071.6 for 96.43 participants	INR3611 for 100 participants
Cost to treat one case (INR)	14.83	73.33	36.11

BB - benzyl benzoate, P - permethrin, I - ivermectin

[2]For cost-effectiveness analysis, treatment regimens were formulated hypothetically for comparison from Markov population tree for decision analysis.

Comments: The main limitation of the study was that the definition of cure rate was defined as no appearance of new lesions; this could have introduced a subjective bias and disappearance of lesions would have been a more appropriate definition for cure. Furthermore, the study was biased due to non-blinding, although it is accepted that blinding was difficult because the formulations were different (lotion, cream, and tablet).

The randomised, controlled, double-blind, double-dummy study **(Choulea, 1999)** involving 53 patients in Argentina compared efficacy and safety of ivermectin with that of lindane 1% topical application**.** Overall, 43 patients (81%) completed the study (ivermectin versus lindane: 19 versus 24). Clinical cure was defined as absence of lesions and pruritus. At Day 15, greater number of patients on ivermectin (n=14; 74%; 95% CI: 48.8%-90.8%) showed healing of their scabies compared to the lindane group (n=13 patients; 54%; 95% CI: 32.8%-74.4%). At 29 days, almost all patients were cured in both treatment groups: 18 patients (95%; 95% CI: 74.0%-99.9%) with ivermectin and 23 patients (96%; 95% CI: 78.9%, 99.9%) with lindane. Adverse effects from the treatments were few, mild, and transient. Results from laboratory tests showed no major abnormalities and no difference between treatments.

Comments: This well-conducted study showed similar efficacy and safety following single oral dose of Ivermectin (200ug/kg) or topical lindane 1% in 53 patients with scabies.

The randomised, controlled, open-label study compared efficacy of BB and ivermectin in 181 patients aged 5 to 65 years with confirmed diagnosis of scabies **(Ly, 2009).** The mean age of the patients was 16.5 years (range: 5-63), and 110 of the 181 patients (60.8%) were aged under 15 years. The mean disease duration was 5.2 weeks (range: 1-20). Superinfection was noted in 54 patients (29.8%) before randomization. The number of sites affected was: 5 5 in 102 patients (56.4%) and > 5 in the remainder. Overall, 128 index patients (70.7%) reported at least one other family member with scabies, and of these patients, 89% reported more than three family members affected. The baseline demographics and disease characteristics were similar in the 3 treatment groups. All eight patients who had clearly worsened clinically at Day 7 were in the IV group; no patient who received BB required a second course of treatment at Day 7. By Day 14, 19 patients were lost to follow-up: 8 in the BB 1 group and 11 in the IV group. Three additional patients were lost to follow-up by day 28 (i.e. 2 in the BBI group and 1 in the IV group). Failure to follow the treatment protocol was noted in 32 patients: 29 applied BB either excessively or insufficiently and 3 took an inadequate dose of IV but treatment compliance was significantly better in the IV group *(P* = 0.002). At Day 14, 86 of the 181 patients (47.5%) were cured. The cure rate was significantly ($p<10^{-6}$) higher in the BB2 group (68.8%) than the BB1 group (54.4%) or the IV group (24.6%). A comparison of the treatment groups showed that topical treatment (that is, BB1 and BB2 groups combined) was superior to oral IV *(*$p < 10^{-5}$). Also at Dday 28, the cure rate was higher in the BB2 group (95.8%) and the BB1 group (76.5%) than in the IV group (43.1 %), with $p < 10^{-5}$**.** An analysis of the subgroup of patients with parasitologically proven scabies showed that two applications of BB resulted in significantly (p = 0.029) higher rate of healing (66.7%, 14/21 patients) compared with one application (52.0%; 13/25), and Ivermectin (28.0%; 7/25).

Results were confirmed in a per-protocol analysis that excluded poorly compliant patients, those lost to follow up and those who had received less than 150 µg/kg of IV. The rates of healing at Day 14 were 84%, 62% and 29% in the BB2, BB1 and IV groups, respectively and those at Day 28 were 96%, 91% and 50%, respectively. Topical treatment was still significantly better than oral IV *(X2* = 24.3, $p < 10^{-5}$). The results of a multivariate logistic analysis performed on the data collected at Day 14, with the BB 1 group serving as the control group confirmed that the cure rate was highest in the BB2 group, followed by the BB1 group and then by the IV group. The OR for a cure in the BB2 group was 2.04 (95% CI: 0.89-4.66) and it was only 0.23 (95% CI: 0.10-0.50) in the IV group (Table 3). At Day 28, the 25 patients in the IV group and the 6 in the BB1 group who were not lost to follow-up and who were not cured received two consecutive

applications of BB, while the 2 patients in the BB2 group who were not cured were given IV. Two weeks later, all patients had been cured.

Given the clear difference in effectiveness between IV and both of the BB protocols and the significantly higher risk of superinfection during treatment in the IV group, the study was suspended for ethical reasons after the intermediate analysis.

Table 3. Cure rates at treatment days 14 and 28 in patients with scabies who received BB once or twice or IV. Dakar, Senegal. Ly, 2009

Treatment	No.	Day 14		Day 28	
		Cured No. (%)	*P*-value	Cured No. (%)	*P*-value
BB1[a]	68	37 (54.4)	$< 10^{-6}$	52 (76.5)	$< 10^{-5}$
BB2[b]	48	33 (68.8)		46 (95.8)	
IV group[c]	65	16 (24.6)		28 (43.1)	
Total	**181**	**86**		**126**	

BB, benzyl benzoate; IV, ivermectin.
[a] Group that received one application of benzyl benzoate.
[b] Group that received two applications of benzyl benzoate.
[c] Group that received ivermectin.

Results of multivariate logistic analysis of data collected 14 days after initiating treatment for scabies in randomized trial. Dakar, Senegal.

Variable	OR[a]	95% CI
Two applications of BB[b]	2.04	0.89–4.66
Oral IV[b]	0.23	0.10–0.50
Age > 15 years	1.21	0.57–2.56
Parasitology test positive	1.04	0.52–2.08
Compliant with treatment	2.27	1.02–5.03
No. of sites initially involved ≥ 6	0.83	0.21–3.19
Superinfection before randomization	1.28	0.61–2.69
No. of family members with scabies > 5	0.70	0.43–1.16

BB, benzyl benzoate; CI, confidence interval; IV, ivermectin; OR, odds ratio.
[a] Ratio of the odds of achieving a cure.

Comments: Overall, this study was well-conducted with well predefined statistical analysis in the ITT and PP populations. Results from this study failed to show efficacy of ivermectin over topical treatment with BB. However, it is important to note that majority of patients in this study (57%) had scabies in more than 5 sites and thus may likely have more severe disease in which ivermectin may not be as effective. Furthermore, role of resistance to ivermectin (due to its use in treatment of onchocerciasis in Senegal) was not explored and could have played a role in reduced efficacy of ivermectin observed in this study.

The randomised, controlled open-label study in 200 patients with scabies in India compared the efficacy of a single dose of ivermectin (200 µg/kg) with that of single overnight application of

lindane 1% **(Madan, 2001).** Improvement was graded from 100% (complete cure with no signs/symptoms of scabies) to 0% (no improvement/ further aggravation). Good improvement was seen in 17.52% of patients at 48 h with ivermectin compared to 7.14% of patients with lindane. Excellent improvement in signs and symptoms was seen in 36.1%, and 82.6% of patients in ivermectin group at two weeks and four weeks, respectively. Similar improvement was recorded in 22.3% and 44.4% of patients in lindane group at two weeks and four weeks, respectively. Exacerbation of signs and symptoms was noted in a total of two patients in the IV group and four patients in the lindane group (Table 4). There was a clear and significantly better result obtained with oral ivermectin . Good results with ivermectin were also seen in crusted scabies patients and the easier usage schedule may also lead to better patient compliance.

Table 4. Madan, 2001.

Extent of improvement during follow-up of patients treated with oral ivermectin.

No. of Cases	Time	Improvement					
		Negative (–)	Poor (0)	Slight (+)	Moderate (+)	Good (+)	Complete (+)
100	48 hrs.	None	2 (2.06%)	43 (44.32%)	35 (36.08%)	17 (17.52%)	None (3)*
97	2 weeks	2 (2.4%)	None (0%)	None (0%)	23 (27.71%)	28 (33.73%)	30(17)* (36.14%)
83	4 weeks	2 (2.8%)	None (0%)	None (0%)	4 (5.79%)	6 (8.6 %)	57(31)* (82.6 %)

*Lost to follow-up

Extent of improvement during follow-up of patients treated with 1% lindane lotion.

No. of Cases	Time	Improvement					
		Negative (–)	Poor (0)	Slight (+)	Moderate (+)	Good (+)	Complete (+)
100	48 hrs	6 (6.12%)	12 (12.24%)	53 (54.08%)	20 (20.4%)	7 (7.14%)	None(2)*
98	2 weeks	10 (11.76%)	6 (7.05%)	32 (37.64%)	10 (11.76%)	8 (9.41%)	19(15)* (22.35%)
85	4 weeks	4 (4.93%)	2 (2.46%)	10 (12.34%)	12 (14.81%)	17 (20.98%)	36(19)* (44.44%)

*Lost to follow-up

The randomised controlled study in 100 patients with scabies in Pakistan compared the efficacy and safety of single dose of ivermectin (200 ug/kg) with that of single overnight application of permethrin 5% **(Mushtaq, 2010).** Baseline demographics and disease characteristics were similar in the two treatment groups**.** Two weeks after the first dose of respective treatments, 24 (54.5%) subjects in the ivermectin group and 20 (47.6%) subjects in topical permethrin group were cured of disease (p=0.5) (Table 5).

Table 5. Characteristics of patients at baseline, first week and second week. Mushtaq, 2010

	Group A (Ivermectin) n (%)			Group B (Permethrin) n (%)		
Sex distribution						
Female	20 (45.5)			24 (54.5)		
Male	22 (52.4)			20 (47.6)		
Family History						
Present	42 (95.5)			38 (90.5)		
Absent	2 (4.5)			4 (9.5)		
Lesions at presentation	*1st week*	*2nd week*	*4th week*	*1st week*	*2nd week*	*4th week*
No lesion	0	24 (54.5)	11 (25)	0	20 (47.6)	17 (40.5)
Mild	0	10 (22.7)	9 (20.5)	1 (2.4)	17 (40.5)	5 (11.9)
Moderate	20 (45.5)	8 (18.2)	0	28 (66.7)	5 (11.9)	0
Severe	24 (55.5)	2 (4.5)	0	13 (31)	0	0
Nocturnal pruritus	*1st week*	*2nd week*		*1st week*	*2nd week*	
Mild	0	9 (20.5)	3 (6.8)	0	11 (26.2)	1 (2.4)
Moderate	16 (36)	16 (36.4)	0	18 (43)	7 (16.7)	0
Severe	28 (64)	1 (2.3)	0	24 (57)	0	0
Scraping for mite	*1st week*	*2nd week*		*1st week*	*2nd week*	
Not applicable	37 (84.1)	38 (86.4)	44 (100)	33 (78.6)	33 (78.6)	42 (100)
Positive	4 (9.1)	0	0	8 (19)	0	0
Negative	3 (6.8)	6 (13.6)	0	1 (2.4)	9 (21.4)	0

All patients with persistent lesions were given a second dose of both treatments at Week 2. Two weeks after the second treatment, greater number of subjects had persistent lesions in the ivermectin group compared with subjects in the permethrin group. Similarly, greater percentage of patients in ivermectin group still complained of nocturnal pruritus at fourth week of treatment, as compared to only one patient in the permethrin group though the difference was insignificant. At fourth week of follow-up, 35 (79.5%) patients in ivermectin group and 37 (88.1%) patients in permethrin group were cured of scabies, p=0.157. Regarding safety, only one patient in permethrin group had erythema and burning on second day of treatment whereas 4 (9.1%) patients in ivermectin group suffered from severe itching, 3 (6.8%) had secondary bacterial infections, while 1 patient (2.3%) complained of headache. Difference of side effects between two groups was statistically significant (p=0.05).

Comments: Ivermectin did not show greater efficacy than permethrin and was associated with significantly more AEs than permethrin (p=0.05). Only one patient had mild superficial burning as compared to 7 patients in ivermectin group who had secondary bacterial infection, headache and increase in pruritus.

The randomised, controlled study involving 58 Nigerian patients with scabies compared efficacy and safety of single oral dose of ivermectin (200 µg/kg body weight) with topical application of benzyl benzoate 25% for 72 h **(Nnoruka, 2001).** Ivermectin showed a rapid response in terms of reduced clinical scores compared with BB (Table 6).

Table 6. Nnoruka, 2001.

Age distribution of 58 patients with scabies.

Age (in years)	No. of patients	Frequency (%)
0–9	4	6.9
10–19	18	31
20–29	13	22.4
30–39	9	15.5
40–49	6	10.3
50–59	7	12.1
60–69	1	1.7
>70	0	0
Total	58	100

Clinical scores of the rash of 58 patients suffering scabies according to treatment group.

Name of drug	No. of patients	Day			
		0	7	14	30
Ivermectin	29	16.1	5.4	2.3	1.1
25% benzyl benzoate	29	16	10.3	6.1	3.5

At Day 7, nine (31 %) patients of those on ivermectin presented with complete disappearance of their lesions and pruritus. On Day 14, 19 (65.3%) patients from the group on ivermectin and 10 (34.5%) of those on benzyl benzoate were healed. By the thirtieth Day 27 (93.7%) of the patients on ivermectin were completely healed. Amongst the patients healed before Day 30 (whatever group), no relapse was observed. An analysis of variance with repeated measures showed a significant decrease of the score in the group on ivermectin *(*p = 0.004). None of the patients reported side effects for ivermectin whilst seven (24.1 %) patients belonging to the group on benzyl benzoate, described a mild to moderate increase of irritation and pruritus by Day 2 (Table 7).

Table 7. Nnoruka 2001. Response of puritus to ivermectin and 25% benzyl benzoate in 58 patients suffering from scbies. Grading was based n a subjective scale.

Name of drug	Response	Day		
		7 (%)	14 (%)	30 (%)
Ivermectin	Excellent	9 (31%)	19 (65.5%)	27 (93.1%)
	Good	10 (34.4%)	5 (17.2%)	1 (3.4%)
	Fair	5 (17.2%)	5 (6.9%)	1 (3.4%)
	Poor	5 (17.2%)	3 (10.2%)	0 (0%)
25% benzyl benzoate	Excellent	3 (10.2%)	10 (34.5%)	14 (48.3%)
	Good	7 (24.1%)	10 (10.3%)	4 (13.8%)
	Fair	8 (27.5%)	7 (24.1%)	5 (17.3%)
	Poor	11 (37.9%)	9 (37%)	7 (24.1%)

Repeat full blood count, serum urea, electrolytes, creatinine and liver function test were all within normal. The examination of skin scrapings after treatment did not show any eggs, larva or adult parasites. Complete clearance occurred within 7 days in more than half of the patients placed on ivermectin, whilst 5 (17.2%) of them complained of a transient increase in pruritus within 12 to 24h. The transient increase in itch and erythema may have been due to release of antigen by the destroyed mites. In addition, no laboratory abnormalities were detected amongst the patients placed on ivermectin within the study period. Results show that oral ivermectin is a more comfortable treatment for scabies than the local application of 25% benzyl benzoate. The group treated with benzyl benzoate had a low recovery rate of 48.5%. This rather low rate could be attributed to the reluctance of a population living under hot humid temperature to use a topical application according to the instructions and to keep the body unwashed for a long enough period.

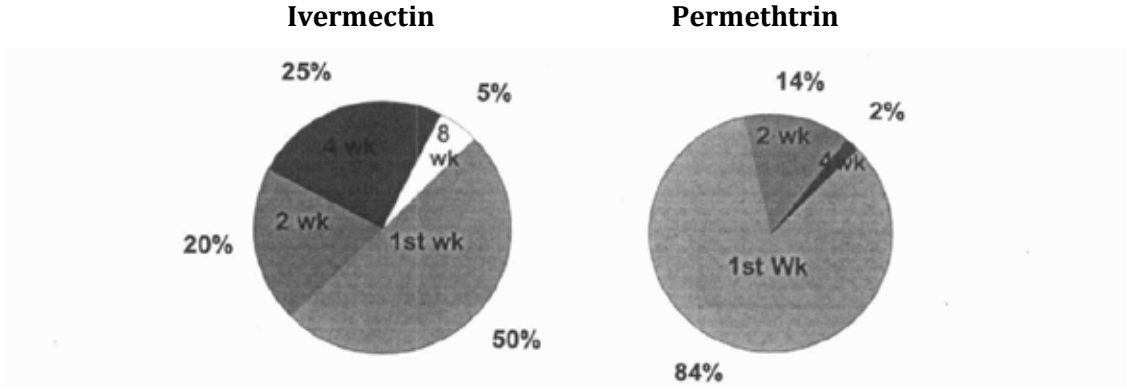
Comments: A single oral dose of ivermectin (200 µg/kg) showed much greater improvement compared to 72 h topical application with BB 25% (93% versus 44% showed complete clearance of lesions and pruritus by Day 30).

The randomised, controlled study involving 85 patients with scabies compared the efficacy and safety of single oral dose of ivermectin (200 µg/kg) with that of single application of permethrin 5% cream **(Usha, 2000).** Baseline demographics were similar in both groups. On follow-up, with a single dose, symptom improvement was observed by the first week in 20 patients (50%) in the ivermectin group and 35 patients (84.3%) in the permethrin group. By the second week, 28 patients (70%) in the ivermectin group and 44 patients (97.8%) in the permethrin group had symptom improvement and the non-responders (12 and 1, respectively) received a repeat therapy. By the fourth week, 38 (95%) patients had symptom improvement with ivermectin,

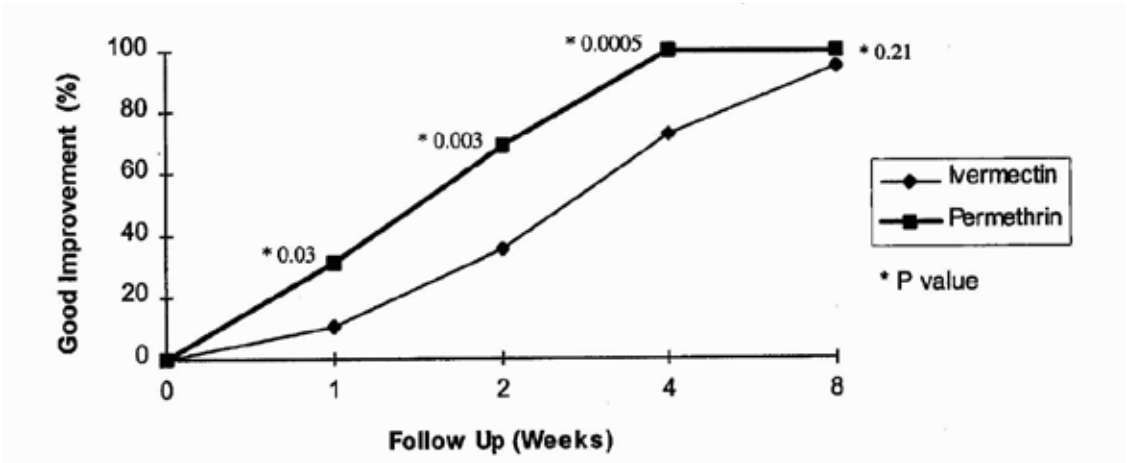
whereas all the patients were cured with permethrin. Two (5%) patients did not respond to 2 doses of ivermectin. They were crossed over to the permethrin group and were cured after a single application. Complete clearance of lesions (graded as good improvement) occurred earlier in permethrin-treated patients. All the patients were completely cured at the end of 8 weeks (Figure 1). There was no recurrence of scabies at the end of 2 months of follow-up in either group. A single dose of ivermectin provided a cure rate of 70%, which increased to 95% with 2 doses at a 2 week interval. A single application of permethrin was effective in 97.8% of patients. One (2.2%) patient responded to 2 applications at a 2-week interval. Permethrin-treated patients recovered earlier.

Figure 1. Usha, 2000.

Pie chart showing the response to ivermectin and permethrin.



Time course of good response to therapy with ivermectin and permethrin



Comments: Overall, a single application of permethrin was superior to a single oral dose of ivermectin. Two doses of ivermectin taken at a 2 week interval are as effective as a single application of permethrin. Both drugs were effective in preventing recurrences over a period of 2 months. The temporal dissociation in clinical response suggests that ivermectin may not be effective against all stages in the life cycle of the parasite. Therefore 2 doses of ivermectin, 1 to 2 weeks apart, may be the appropriate schedule in the treatment of scabies.

The objective of the randomised, controlled study **(Daneshpajooh, 2000)** was to compare the efficacy and safety of oral ivermectin with topical gamma benzene hexachloride (GBH) 1% in 58 patients with scabies. In the ivermectin group, patients received a single oral dose of the drug (200 µg/kg). In case of any signs of active disease, a second dose was administered one week later. All the patients in the GBH group received two topical applications of the drug, one week apart. The patients were visited after a period of 48 h , 1 week, 2 weeks and 4 weeks. Of the 37

patients treated with ivermectin, 27 (73%) required a second dose one week later. In the 21 patients treated with GBH, 18 (85.7%) received two applications of GBH and three cases (14.3%) were cured by an additional course of precipitated sulfur 6%. The mean time for the improvement of pruritus, the sense of well-being and healing of lesions, were all shorter with ivermectin than GBH and the differences were statistically significant. Although all of the patients treated with ivermectin or topical GBH were eventually cured, the cure was faster with ivermectin than topical treatment.

Comments: Only abstract was provided in the dossier;a complete study report or reference was not provided.

A placebo-controlled study conducted in Mexico **(Marcotela-Ruiz,** 1993) involving 55 patients with scabies demonstrated efficacy and safety of a single oral dose of ivermectin (200 µg/kg body weight); 26 (79.3%) patients were cured with ivermectin on their first follow-up visit. as compared to only 4 (16%) in the placebo group (p<0. 001). The overall cure rate was significantly (p<0. 001) higher for ivermectin (74%; 37/50) compared with placebo (16%; 4/26).

Comments: The study report was not presented in English and only a 5 –line summary was provided for evaluation.

6.1.1.2. Other randomised controlled studies that did not evaluate ivermectin

Amer, 1992: A randomised, controlled study in 150 patients with clinically diagnosed scabies which was confirmed microscopically by the detection of the mite from at least one body site evaluated the efficacy and safety of permethrin with that of other scabicides; lindane and clotamitron[3]. There were no reported systemic, neurologic or local irritations, or adverse effects to the medications used in the trial. Permethrin, as a scabicide, appeared to be more potent than lindane or crotamitron and also appeared to be more effective in infants and young children (Table 8). It may be successful in treating failures of other scabicides, especially lindane.

Table 8. Amer, 1992

Results of permethrin in 50 patients with scabies

	Age Group (years)						
	<10	*10–19*	*20–29*	*30–39*	*40–49*	*>50*	*Total*
Patients treated	14	—	7	16	10	3	50
Patients cured	14	—	7	16	10	2	49
% of patients cured	100	—	100	100	100	33.66	98

[3] Study treatment was applied, on in-patient basis, for two successive nights from neck-to-toe paying particular attention to common sites for the mite. Therapy was stopped after 2 days, at which time the patients took a bath with soap and water. Subjects were examined 1 h and 24 h after application of the medication for signs or reports of irritancy, and again at 14 days, and 28 days. Efficacy was assessed by taking photographs of the lesions and after day 28, patients were scored as either cured or treatment failures3. In addition, an attempt was made to recover live mites.

Results of Crotamiton in 50 patients with scabies

	Age Group (years)						
	<10	*10–19*	*20–29*	*30–39*	*40–49*	*>50*	*Total*
Patients treated	10	—	17	10	6	7	50
Patients cured	8	—	17	8	6	5	44
% of patients cured	80	—	100	80	100	71.4	88

Results of Lindane in 50 patients with scabies

	Age Group (years)						
	<10	*10–19*	*20–29*	*30–39*	*40–49*	*>50*	*Total*
Patients treated	3	10	10	10	7	10	50
Patients cured	0	8	9	8	6	8	37
% of patients cured	0	80	90	80	85.7	80	84

Comments: This study only provided evidence regarding efficacy/ safety of permethrin and failed to provide any information regarding ivermectin.

Bokhari, 2000 showed similar efficacy with lindane and permethrin with cure rates of 92% and 87.5%, respectively at Day 28.

Hansen, 1986 published results of a randomised, controlled, single-blind study which showed comparable efficacy and safety of single application of permethrin 5% cream or lindane 1% lotion in 104 patients with scabies (age 2-71years).

A multicentre, randomised, single-blind study **(Schultz, 1990)** involving 467 patients with scabies **(Table 9)** showed that a single 8 to 14 h application of permethrin cream was as effective as a single application of lindane lotion for the treatment of scabies**.** However pruritus resolved within 4 weeks in significantly more patients treated with permethrin than with lindane *(P* =0 .007) (Table 10).

Table 9. Schultz, 1990 Demographic and clinical characteristics

Characteristic	No. of Patients (%) Permethrin (N = 234)	Lindane (N = 233)
Age, y		
≤5	35 (15)	19 (8)
6-17	60 (26)	53 (23)
≥18	139 (60)	161 (69)
Male	144 (62)	153 (66)
Race		
White	108 (46)	118 (51)
Hispanic	120 (51)	106 (45)
Black	6 (3)	4 (2)
Other	0 (0)	5 (3)
No. of lesions		
<10	8 (3)	11 (5)
10-49	111 (47)	99 (42)
50-199	92 (40)	98 (42)
≥200	23 (10)	25 (11)
Mean	83	87
Median	49	50

Table 10. Schultz, 1990

Analysis of cure in patients treated for scabies with 5% permetrin cream or 1% lindane lotion.

Follow-up Interval, d	Patients Evaluated	No. Cured/No. Evaluated (%) Permethrin	Lindane	RR (95% CI)*	P†
14±3	All	74/193 (38)	79/213 (37)	1.05 (0.83-1.32)	.70
	Confirmed†	59/161 (37)	61/180 (34)	1.05 (0.80-1.37)	.72
28±7	All	181/199 (91)	177/205 (86)	1.05 (0.98-1.14)	.18
	Confirmed‡	151/165 (92)	152/173 (88)	1.04 (0.96-1.13)	.30

*RR indicates relative risk (of cure with permethrin vs lindane); CI, confidence interval.
†Cochran-Mantel-Haenzel Test, adjusting for center differences.
‡Microscopic confirmation of scabies.

Dermatologic adverse effects in patients treated for scabies with % permetrin cream or 1% lindane lotion.

Manifestation*	No. of Patients (%) Permethrin (N = 233)	Lindane (N = 232)	RR (95% CI)†	P‡
Burning/stinging	23 (9.9)	12 (5.2)	1.91 (0.99-3.69)	.08
Pruritus	15 (6.4)	17 (7.3)	0.88 (0.45-1.72)	.72
Erythema	5 (2.1)	3 (1.3)	1.66 (0.41-6.77)	.72
Tingling	4 (1.7)	5 (2.2)	0.80 (0.22-2.92)	.75
Rash	2 (0.9)	2 (0.9)	1.00 (0.14-7.02)	1.00
Other§	2 (0.9)	3 (1.3)	0.66 (0.11-3.89)	.68

*Defined as new manifestations, not present before therapy, or otherwise distinct from pretreatment manifestations.
†RR indicates relative risk (of manifestation occurring with permethrin vs lindane); CI, confidence interval.
‡Fisher's Exact Test (two-tailed).
§Includes one or two patients each with cutaneous "pain," "numbness," nonspecific papules, or "coolness," with equal distribution in both treatment groups.

A randomised, controlled, double-blind study in 99 patients with scabies in Iran **(Zargari, 2006)** showed that permethrin (5%) cream was found to be significantly more effective in the treatment of scabies in comparison with lindane (Table 11).

Table 11. Zargari, 2006. Demographic data of enrolled patients and their reponse to treatment.

Characteristics		Group A $n = 52$	Group B $n = 47$	p-value*
Sex distribution (%)	Male	28 (53.8)	27 (57.4)	0.840
	Female	24 (46.2)	20 (42.6)	
Age (in years)	Mean (SD)	27.9 (12.9)	32.7 (17.5)	0.172
	Median	28	29	
Effectively treated patients at week 2 (%)		44 (84.6)	23 (48.9)	<0.0001

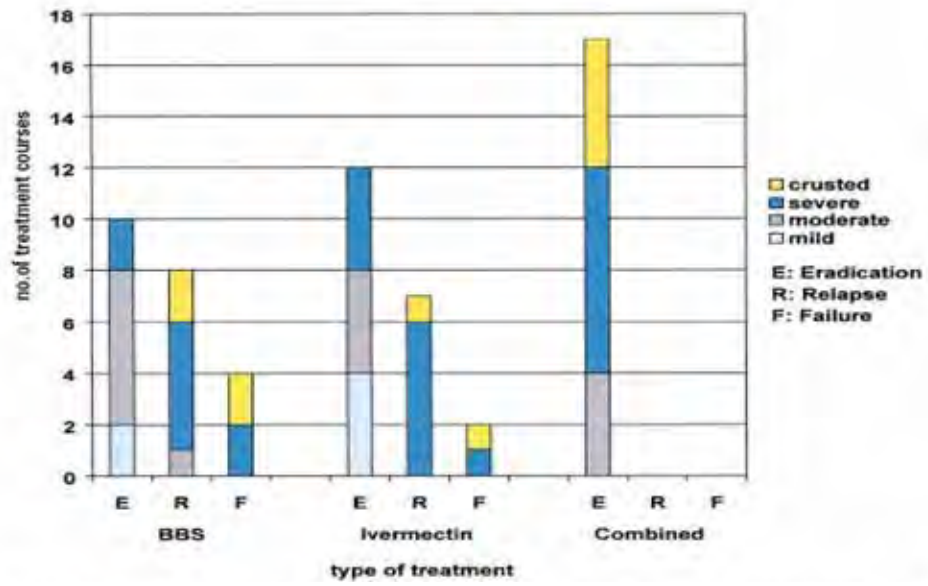
*Value corresponds to statistical difference between groups A and B by χ^2 test or Fisher's exact test, as appropriate.

6.1.2. Observational studies

6.1.2.1. Studies which evaluated ivermectin

A retrospective, open-label study **(Alberici, 2000)** involving 39 patients showed that treatment of Human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) associated scabies with a single dose of oral ivermectin alone was effective only in cases we classified as mild to moderate and that there were several relapses and treatment failures in crusted scabies. However, combination therapy with ivermectin and BBS was extremely effective. Hence, the authors suggest that combined treatment with ivermectin and BBS is a useful regimen to employ in the management of scabies, particularly the crusted variety, in patients with HIV infection/AIDS (Figure 2).

Figure 2. Alberici, 2000. Overall results. Relationship between severity score, type of treatment and Overall results. BBS, benzyl benzoate solution.



When elderly patients (mean age of 73 years) not responding to topical treatment of scabies were treated with a single oral dose of ivermectin (150–200 µg/kg of body weight), all rashes and symptoms had cleared within 5 days, and no further treatment was needed **(Barkwell, 1997).** However, in the next 6 months, 15 of the 47 who had received ivermectin died, compared with five of the age-matched and sex-matched cohort and the 3 fold increase in risk was statistically significant (Fisher's exact test, relative risk was 3·00; 95% CI 1·19–7·59; p=0·001). Although no definite pattern was found, those in the ivermectin group developed a sudden change in behaviour with lethargy, anorexia and listlessness which preceded death. In

the face of what appears to be a significant statistical association between use of ivermectin and increased risk of death, that ivermectin should not be used for treatment of scabies in the elderly.

Comments: The above observational study indicated increased risk of death associated with ivermectin in elderly, this needs to be confirmed in controlled studies due to confounding by an underlying medical condition or interaction with another treatment (such as lindane or psychoactive drugs) in the observational study. However, pending such a controlled study it would be prudent to exercise due caution when using ivermectin in elderly patients and this fact has been incorporated in the proposed PI.

An observational study in 43 Mexican patients (23 men and 20 women) ranging from 5 to 85 years of age evaluated efficacy and safety of 2 doses of oral ivermectin (200ug/kg body weight) separated by 1 week interval for treatment of scabies (19, 21 and 5 had mild, moderate and severe scabies, respectively) **(Conti Diaz, 1999).** Excellent results were achieved in 29 cases (76.34%), improvement in 6 (15.78%) and poor responses in 3 (7.88%). Tolerance was satisfactory-excellent in 32 patients (84.2%). Among the 5 patients with severe scabies, one had improvement, another one cured perfectly and the remaining 3 showed an unfavourable outcome.

Another observational study in 18 Mexican children (aged 14 months to 17 years), with scabies or cutaneous larva migrans also showed good efficacy/tolerability following treatment with ivermectin (150-200ug/kg) **(Dal Mar Saaz-de-Ocariz, 2002).** They included four cases of crusted scabies associated with immunosuppression and seven cases of common scabies, four of whom had associated clinical mental retardation, immunosuppression or hypomobility. A further seven patients had cutaneous larva migrans. Fifteen patients were cured with a single dose of ivermectin and three patients with crusted scabies required a second dose. None of our patients suffered significant adverse effects.

An open-label study of 19 patients[4] (13 males and six females; age range between 18 and 73 years; mean, 45.3 years) with scabies were treated with an oral dose of 200ug/kg ivermectin on days I and 8 **(Dourmishev, 1998a).** None of the 19 patients with scabies had evidence of scabies after the second dose of ivermectin. In seven patients, there was enhancement of pruritus 24 to 72 h after the first administration of ivermectin, while in 3 patients the skin manifestation, vesicle-pustular rash increased between the second and the fourth day. **Dourmishev, 1998** also reported successful cure of 3 patients with crusted scabies of the scalp and dermatomyositis following one or 2 oral doses (with 1 week interval) of ivermectin (200 µg/kg).

An observational study **(Elmogy, 1999)** evaluated the efficacy of a single oral dose of ivermectin (200 µg/kg) in 101 patients (aged 18-70 years; mean=34yrs; 30 men and 71 women) with scabies (at the start of the study, 25 (24.8%) had mild disease, 27 (26.7%) had moderate disease, and 49 (48.5%) had severe disease). Two weeks after the initiation of therapy, 89 cases (88.1%) were completely free of scabies. Three others had mild disease, negative skin scraping and were completely cured at the 4 week follow-up examination. The remaining nine patients had persistent itching and new lesions consistent with scabies; although their skin scraping tested negative. They were given a second dose and were also cured by the time of the 4 week follow-up visit. Tolerability was good with adverse events (AEs) reported in only 12 patients (11.88%) who experienced drowsiness (four patients), arthralgia and bone aches (two patients), dyspnea (three patients), headache (one patient), nausea (one patient) or blurring of vision (one patient). The side-effects occurred mainly during the initial

[4] Nineteen patients included 10 otherwise healthy outpatients with scabies, and 9 inpatients with scabies and another skin disease (dermatomyositis, 3; pemphigus, 2; bullous pemphigoid, I; pyoderma, I; HIV, I; Beh<;et's disease, I)

interview; were mild, transient, and easily tolerated by the patients, and resolved without treatment.

Oral ivermectin (200 µg/kg) was used to control a scabies outbreak involving 23 healthcare workers (who developed pruritus and/or skin lesions) after contact with a patient with classic scabies effectively in a limited-resource hospital in Lima, Peru **(Garcia, 2007).**

Heukelbach (2004) assessed the short-term and long-term impact of selective mass treatment[5] with ivermectin (200 µg/kg) in an economically depressed community (n=605 subjects) infected with ectoparasites and enteroparasites in Brazil. At baseline, 548 individuals (90.6% of the total population) were examined for parasitic skin diseases. At the time of first follow-up 505 people were examined (83.5% of total population); and at the time of the second follow-up, 535 people were examined (88.4% of the total population). The prevalence of scabies decreased at the time of first follow-up ($p < 0.01$) and remained stable for the next 9 months compared to baseline *(P* = 0.02).The prevalence of other parasitic diseases such as pediculosis and cutaneous larva migrans was also reduced following ivermectin treatment (Table 12).

Table 12. Heukelbach, 2004. Prevalence of parasitic skin diseases at baseline, 1 month after treatment and 9 months after treatment.

Disease	Baseline (*n* = 548)[a]		1 month after treatment (*n* = 505)[a]		9 months after treatment (*n* = 535)[a]	
	No. testing positive	Prevalence[b]	No. testing positive	Prevalence[b]	No. testing positive	Prevalence[b]
Pediculosis	154	28.1 (24.4–32.1)	107	21.2 (17.8–25.1)	72	13.5 (10.7–16.7)
Active pediculosis[c]	88	16.1 (13.1–19.5)	5	1.0 (0.4–2.4)	55	10.3 (7.9–13.2)
Scabies	21	3.8 (2.4–5.9)	5	1.0 (0.4–2.4)	8	1.5 (0.7–3.0)
Cutaneous larva migrans	4	0.7 (0.2–2.0)	0	0	0	0
Tungiasis	281	51.3 (47.0–55.5)	263	52.1 (47.6–56.5)	167	31.2 (27.3–35.4)

[a] Number of participants examined for parasitic skin diseases.
[b] Prevalences are shown as % (95% confidence interval).
[c] Presence of nymphs or adults or both.

[5] Selective mass treatment was performed as follows. The target population was defined as all individuals from households where at least one individual was found to be infected with at least one intestinal helminth or one ectoparasite species. All members of these households were treated with ivermectin (200 ug/kg; Revectina, Solvay Farma, Sao Paulo, Brazil), provided there were no contraindications.The dose was repeated after 10 days. Contraindications for administration of ivermectin were: being younger than 5 years, weighing < 15 kg, being pregnant or breastfeeding, or having renal or hepatic disease

Table 12. Heukelbach, 2004 (continued.Relative reduction in prevalence 9 months after selective mass treatment.

Disease	Relative reduction in prevalence (factor)
Hookworm disease	3.7
Ascariasis	2.4
Trichuriasis	1.8
Strongyloidiasis	16
Hymenolepiasis	1.2
Pediculosis	2.1
Active pediculosis	1.6
Scabies	2.5
Cutaneous larva migrans	NA
Tungiasis	1.6

NA = Not applicable.

A non-randomised, open-label comparison study (conducted in Islamabad, Pakistan) involving 30 patients (≥12 years of age) with scabies (diagnosed on the basis of clinical features, including history and clinical examination with typical lesions and sites of involvement) showed complete healing of lesions (100% cure rate) and relief of symptoms following treatment with ivermectin (two doses of 200µg/kg body weight separated by one week) and local treatment with permethrin 5%, (applied for 12 h and was repeated after one week). All patients completed therapy without any complication **(Khan, 2007).**

Leppard, et al (2000) evaluated the efficacy of ivermectin in the treatment of scabies in an institutional environment (prison in Tanzania). A single dose of ivermectin 150 µg/kg was given under supervision to 1153 prisoners following an outbreak of scabies. Sixteen prisoners had crusted scabies (1.4%), 802 had ordinary scabies (69.5%) and 196 had severe pyoderma, especially on the hands, buttocks and genitalia (24% of those with scabies). Overall, 30% of the prisoners were cured after 1 week, 88% after 4 weeks and 95.5% after 8 weeks. Of 16 prisoners with crusted scabies, seven (44%) still had scabies after 8 weeks. Those who were not cured were then treated with 1% lindane lotion topically (as were the prison staff that had scabies). This regimen eradicated scabies from the prison for the next 2 years.

Marcotela-Ruiz, 1996 also evaluated efficacy of oral ivermectin in treatment of scabies in an enclosed rural Mexican community but the report was in Spanish and no translation or even summary in English was provided making the data unevaluable.

The Japanese study **(Makigami, 2005)** evaluated the effectiveness of mass treatment with oral ivermectin of scabies outbreak in institutional settings (a nosocomial scabies outbreak in a close psychiatric ward). The index case was a man with steroid induced localised crusted scabies. Twenty-six patients were diagnosed with scabies, 4 of them had relapse of scabies, while no staff was infested. Despite frequent surveillance and treatment of symptomatic patients with 1% gamma-benzenehexachloride (y-BHC: Lindane), new cases were observed. Thus, all 69 patients in the ward were treated with ivermectin (200 µg/kg) simultaneously on Day 105 of the outbreak (the mass treatment). The mass treatment was implemented without any significant adverse events. Although two patients developed symptoms of scabies after the mass treatment, no patient in the ward had been diagnosed with scabies since the 98th day of the treatment. Overall, oral ivermectin was safe and effective for controlling scabies in institutional settings.

Comments: The study report was presented in Japanese and only the abstract was in English.

Meinking (1995) conducted an open-label study in which ivermectin was administered in a single oral dose of 200 µg/kg body weight to 11 otherwise healthy patients with scabies and to 11 patients with scabies who were also infected with the HIV (7 of who had AIDS). None of the 11 otherwise healthy patients had evidence of scabies four weeks after a single dose of ivermectin. Of the 11 HIV-infected patients, 2 had ≤10 scabies lesions before treatment, 3 had 11 to 49 lesions, 4 had ≥50 lesions and 2 had heavily crusted skin lesions. In eight of the patients the scabies was cured after a single dose of ivermectin. Two patients received a second dose two weeks after the first. Ten of the 11 patients with HIV infection (91 percent) had no evidence of scabies four weeks after their first treatment with ivermectin.

Millership (2002) reported that mass treatment with oral ivermectin (150-200 µg/kg body weight) was effective in 2 homes for the elderly mentally ill patients affected with scabies. The main advantages of the oral ivermectin therapy were convenience of administration, lack of side effects and the prompt control of spread. Although attempts at long-term control in both homes were unsuccessful, primarily caused by difficulties in, ensuring that all involved staff were properly treated, the post-ivermectin period was the first for many months without any residents with scabies rashes.

Offidani (1999) report six new cases of patients suffering from severe infestation with the mite sarcoptes scabiei, treated with single oral dose of ivermectin 200 µg/kg. No topical therapy was undertaken, except for topical treatment with emollient, as needed. The drug was very effective in all cases, easy to use, safe and particularly useful in those patients with secondary eczematisation and escoriations, for whom the topical treatments are irritant and less well tolerated.

Sullivan (1997) reported results of an effort to eradicate scabies in rural nursing home ward that had suffered from endemic scabies for at least 3 years, despite conventional topical therapies. Following the initial dermatological and general medical examination, all 33 demented elderly male patients were treated with, a single oral dose or ivermectin (200ug/kg). This dose was repeated at 2 weeks in all patients, irrespective of clinical examination. Further second weekly doses were to be given if active infestation was found on review. No application of topical scabicides occurred from 1 week prior to ivermectin therapy and for 6 weeks following treatment. Topical therapy over 6 weeks post-ivermectin therapy consisted exclusively of soap substitutes and 25% emulsifying ointment. Patients with no pruritus or scratching and no evidence of scabies infestation at 6 weeks were considered to be cured. All patients were free of scratching at 6 weeks and all other scabies-related rashes had completely resolved. There were no complaints nor was evidence of pruritus in any of the residents at 6 weeks and their skin well hydrated by the regular use of emollient. Based on their results, the authors have suggested an ivermectin regimen for patients with scabies in a setting of nursing homes or other difficult management settings (Table 13).

Table 13. Suggested ivermectin regimen for individuals with scabies in difficult management settings*. Sullivan, 1997

Ivermectin oral stat dose of 200 μg/kg
In crusted and Norwegian scabies consider concurrent topical 5% permethrin cream ± additional keratolytic
Reassess at 2 weeks and give second stat dose of 200 μg/kg if suspicion of active infestation
Subsequently, do second weekly reviews with further stat doses if evidence of active infestation[†]

* Treatment of contacts and environment should also be undertaken concurrently with conventional therapies. A several day leeway may be safe given the drug's pharmacology.
[†]Caution is recommended after several second weekly doses, as the safety of prolonged therapy has not been ascertained.

6.1.2.2. Studies which did not evaluate ivermectin

Five topical treatments for scabies (sulphur, lindane, benzyl benzoate, crotamitron and furacin) were compared for efficacy in 85 infants (aged 3 weeks to 1 year) with scabetic infestation **(Amer, 1981)** and preliminary results during the six month study period showed lindane to be the most effective, with furacin the least effective.

An open clinical study **(Haustein, 1987)** compared the efficacy and side effects of lindane (1 % and 0.3 %), benzyl benzoate (20% and 10 %) and permethrin (5% and 2.5 %) after two, three, and one application at bedtime, in the treatment of scabies in 114 adults and 80 children aged between 0 and 5 years. Treatment failures were registered after lindane in 3 adults and 2 children, whereas benzyl benzoate and permethrin cured all patients as assessed after a 3 week follow-up. Tolerability was better with permethrin.

An open-label study **(Kaur, 1980)** showed that treatment of scabies with Gamma Benzene Hexachloride [GBH] was more effective giving 97.9% cure rate with one application compared with Benzyl benzoate emulsion [BBE].

6.1.3. Review of all randomised controlled trials on treatments for scabies

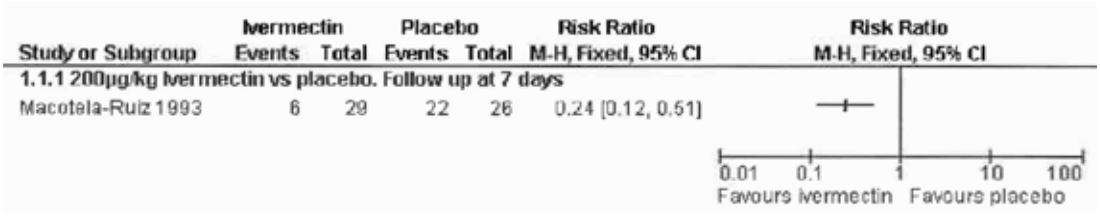
Strong et al (2010) have conducted a review of all randomised controlled trials evaluating ivermectin for treatment of scabies and included 22 trials of which 19 were conducted in resource-poor countries, although one, Schultz 1990, was a large multicentre trial involving eight centres (four sexually transmitted disease clinics, two dermatology clinics and two family practice clinics), with one of the family practice centres in Mexico and the others in the USA. Of the other three trials, one was carried out in the USA (Hansen 1986) and two in Italy (Amerio 2003; Bide 2006). Three trials included only adults (Chouda 1999; Amerio 2003: Bide 2006), six included only children (Maggi 1986; Schenone 1986; Taplin 1990; Avila-Romay 1991; Brooks 2002; Singalavanija 2003); and the other 13 included both adults and children. The total number of participants randomised in the 22 trials was 2676; all had a clinical diagnosis of scabies, with a subset of 903 identified as having their diagnosis confirmed parasitologically. The effectiveness of the following drugs was tested: topical benzyl benzoate; crotamitron; decamethrin; lindane; permethrin; synergized natural pyrethrins; sulfur; and oral ivermectin. Eighteen trials compared one drug with at least one other drug, one trial compared ivermectin against placebo, three trials compared different drug treatment regimens, and one trial compared two different vehicles for the same drug. Clinicians and drug companies recommended treatment of family members and close contacts at the same time as cases, to improve cure rates and reduce re-infection (Taplin 1986) but none of the trials tested this

hypothesis. However, close and family contacts in both ivermectin and control groups were treated in majority of the trials (16 of 22 trials). The oral dose of ivermectin varied from a 100 µg/kg bodyweight (Glaziou 1993) to 200 µg/kg bodyweight (Macotela-Ruiz 1993; Usha 2000; Madan 2001; Nnoruka 2001; Brooks 2002; Bachewar 2009). The Chouela 1999 and Ly 2009 trials used an ivermectin dose between 150 and 200 µg/kg bodyweight. Each trial gave a single dose and follow up ranged from seven days to one month.

The review's primary outcome measure (treatment failure) was reported in 21 of the 22 trials. Six of these 21 trials reported treatment failure in both clinically diagnosed cases and in microscopically confirmed cases (Schultz 1990; Taplin 1990; Amer 1992; Amerio 2003; Singalavanija 2003; Biele 2006); the other 13 trials reported treatment failure in clinically diagnosed cases that may or may not have been confirmed microscopically. Seven trials reported the secondary outcome measure (itch persistence) in addition to treatment failure (Hansen 1986; Schultz 1990; Taplin 1990; Brooks 2002; Amerio 2003; Singalavanija 2003; Biele 2006). Itch persistence alone was reported by Maggi 1986. Adverse events were reported as an outcome in all trials except Gulati 1978 and Maggi 1986.

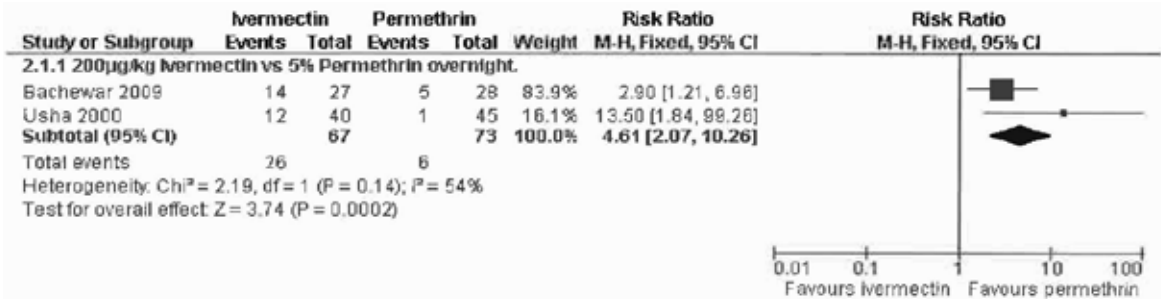
Only one trial assessed the effectiveness of ivermectin against placebo, while eight trials compared it with another drug. Marcola-Ruiz 1993 compared 200 µg/kg bodyweight oral ivermectin with placebo in 55 patients and reported fewer treatment failures in the ivermectin group at seven days (RR= 0.24; 95% CI 0.12 to 0.51) (Figure 3).

Figure 3. Strong, 2010. Forest plot comparison: Ivermectin versus placebo, outcome. Treatment failures in clinically diagnosed cases.



Trials involving 153 subjects evaluated efficacy/ safety of ivermectin (200 µg/kg) compared with topical application of 5% permethrin (Usha 2000 and Bachewar 2009). Usha 2000 reported more treatment failures in the ivermectin group at two weeks (RR 13.50, 95% CI 1.84 to 99.26; 85 participants), as did Bachewar 2009 at one week follow up (RR 2.90, 95% CI 1.21 to 6.96; 55 participants). Significant heterogeneity was not detected and the trials' combined estimate showed more treatment failures with ivermectin (RR 4.61, 95% CI: 2.07 to 10.26, fixed-effect model; 140 participants) (Figure 4).

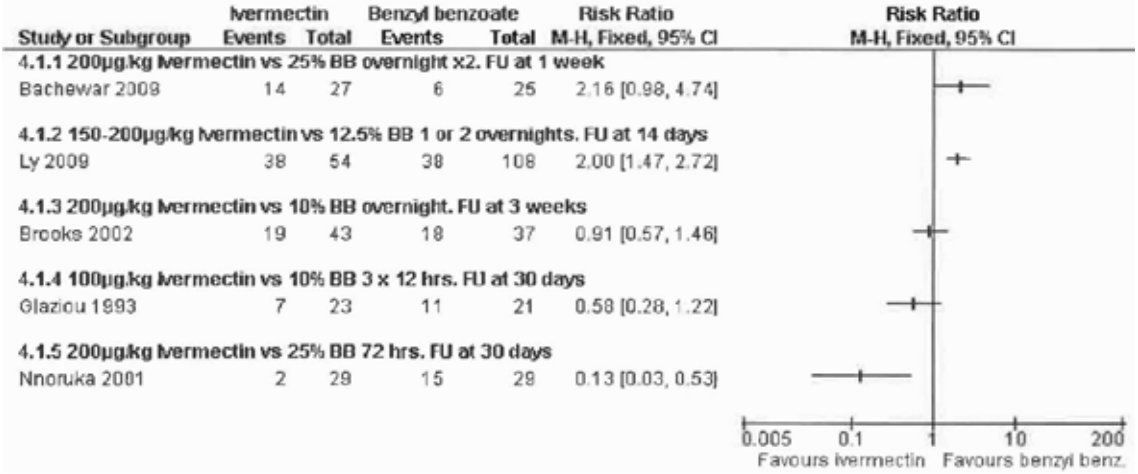
Figure 4. Strong, 2010, Forest plot comparison: Ivermectin versus permethrin, outcome. Treatment failure in clinically diagnosed cases.



Two trials involving 253 subjects compared lindane 1% with 150 µg/kg ivermectin (Chouela 1999) and 200 µg/kg ivermectin (Madan 2001). Chouela 1999 found no significant difference between the groups at 15 days (43 participants), while at four weeks Madan 2001 found that treatment failures were reduced in the ivermectin group (RR= 0.31; 95% CI: 0.18 to 0.54; 150 subjects). Heterogeneity was not detected and the trials' combined estimate showed a benefit of

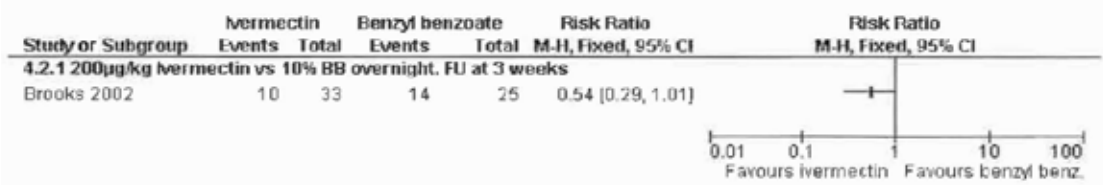
ivermectin over lindane (RR= 0.36; 95% CI 0.23 to 0.58, fixed-effect model; 193 participants) (Figure 5).

Figure 5. Strong, 2010, Ivermectin versus benzyl benzoate, outcome. Treatment failure in clinically diagnosed cases.



Five trials compared efficacy/ safety of ivermectin (150-200 µg/kg) with that of benzyl benzoate (10%-25%) in 462 subjects. No significant difference between the two groups was found in Bachewar 2009 at one week follow up (52 participants). After 14 days Ly 2009 found a significant difference in favour of benzyl benzoate compared with ivermectin (RR=2.00; 95% CI: 1.47 to 2.72; 162 participants). No significant difference between the two groups was found in Brooks 2002 at three weeks (80 participants) or by Glaziou 1993 at 30 days (44 participants). At 30 days Nnoruka 2001 found a significant difference in favour of ivermectin (RR=0.13; 95% CI: 0.03 to 0.53; 58 participants). Heterogeneity was detected between the trials (Chi^2 = 27.97, df =4, P < 0.000 1; r^2 = 86%) (Figure 6). The differences in drug regimen and length of follow up that exist between the five trials may explain this heterogeneity.

Figure 6. Strong, 2010. Ivermectin versus benzyl benzoate, outcome. Itch persistence.



Comments: Results of this review suggest that, of the topical treatments for scabies, permethrin is most effective and it also appeared to be more effective than oral ivermectin **(Usha, 2000; Bachewar, 1999**). Compared to topical lindane, efficacy of oral ivermectin was similar **(Choulea, 1999)** or better **(Madan, 2001).** Results of the 5 trials comparing oral ivermectin with topical application of BB (10-25%) were inconclusive with some studies showing reduced efficacy of ivermectin **(Ly, 2009)**, one showing greater efficacy **(Nnoruku, 2001)** and the other 3 trials showing similar efficacy of ivermectin and BB. However, one of the advantages of an oral antiscabetic treatment such as ivermectin over a topical one is ease of use, particularly in hot humid climates, when engaging in mass treatment, or when treating children.

6.2. Crusted scabies

6.2.1. Observational studies

A retrospective, open-label study **(Alberici, 2000)** involving 39 patients showed that treatment of HIV/AIDS-associated scabies with both benzyl benzoate and ivermectin alone were quite effective in mild to moderate scabies, but they were both associated with an unacceptable rate of relapse and failure in severe or crusted scabies. In contrast, combined treatment produced an optimal rate of success, without significant treatment-related side-effects.

Comments: Results from this small observational study suggest that combined treatment with ivermectin and BBS is a useful regimen in the management of severe crusted scabies, in patients with HIV infection/AIDS.

Del Mar Saez-de-Ocariz (2002) present their experience with 18 children (aged 14 months to 17 years) with scabies or cutaneous larva migrans who were successfully treated with ivermectin. They included four cases of crusted scabies associated with immunosuppression and seven cases of common scabies four of whom had associated clinical mental retardation, immunosuppression[6] or hypomobility. A further seven patients had cutaneous larva migrans. Overall, 15 patients were cured with a single dose of ivermectin and three patients with crusted scabies (and immunosuppression) required a second dose. Side-effects were uncommon with only patient 1 developing mild transient headache and dizziness of 4 h duration. None of our patients suffered significant adverse effects.

Comments: This small study provides some evidence to suggest that ivermectin may provide a safe, oral treatment option of children suffering from crusted scabies. There is concern regarding the safety of ivermectin use in children under 5 years of age or weighing less than 15 kg and this study did not specify how many children were under 5 years or <15kg.

Huffam, 1998 conducted an observational study in 22 aboriginal patients (12 male and 10 female aged 21 to 76 years; mean=42.8 years) in Northern Australia with crusted scabies[7] refractory to topical therapy. These patients were treated with 1 to 3 doses of ivermectin (200 μg/kg) at 1 week intervals in combination with topical scabicide and keratolytic therapy. A complete initial response was achieved in 8 of 20 (40%) patients, 9 of 20 (45%) had at least a partial response (1 of these possibly had a complete response but this was not confirmed) and 3 of 20 (15%) had minimal improvement after ivermectin therapy. Four of the eight patients with a complete initial response had recurrence of scabies, occurring 6 to 40 weeks after the last ivermectin dose and usually progressing to crusted scabies. Two of these were retreated, with again a complete response, but both had further recurrence 8 and 16 weeks after ivermectin. One of these had a third treatment course, but again developed recurrent severe crusted scabies. This last patient has had a total of 10 ivermectin doses over 12 months. Of the 25 treatment courses given to 20 patients, there was significantly better clinical response in those who received three doses of ivermectin (Table 14).

[6] Two of these patients were taking immunosuppressive therapy for idiopathic thrombocytopenic purpura and non-Hodgkin's lymphoma, respectively. The third patient had a selective IgG primary immunodeficiency with recurrent cutaneous infections. The fourth patient, with oedematous scarring vasculitic panniculitis, achieved clinical cure with only one dose, despite having crusted scabies.

[7] Crusted lesions involved all four limbs and the trunk, in the majority, and skin scrapings invariably showed numerous S. scabiei mites. Most had documented clinical scabies for over I year, the longest being for 12 years.

Table 14. Huffam, 1998. Number of doses of ivermectin received and clinical response.

Response	One Dose	Two Doses	Three Doses*
Complete	0	3	8
Partial	5	2	2
Minimal	3	2	0

*Complete response versus minimal or partial response was significantly greater for three doses than for one or two doses of ivermectin; P = 0.005, Fisher's exact test.

Leppard, et al (2000) evaluated the efficacy of ivermectin in the treatment of scabies in 1153 inmates of a prison in Tanzania. Thirty per cent of the prisoners were cured after 1 week, 88% after 4 weeks and 95.5% after 8 weeks. Of 16 prisoners with crusted scabies, seven (44%) still had scabies after 8 weeks. Those who were not cured were then treated with 1% lindane lotion topically (as was the prison staff that had scabies). This regimen eradicated scabies from the prison for the next 2 years.

Comments: Ivermectin was of limited value in those with crusted scabies with 44% of those with crusted scabies not responding after 8 weeks although they did respond to subsequent treatment with a topical scabicide (lindane). It is possible that some of these individuals may have been HIV positive but enzyme-linked immunosorbent assay testing for HIV was not available. All the previous reports of successful treatment of crusted scabies with ivermectin used multiple doses (each of 200 µg/kg instead of the 150 µg/kg used in this study) and combination therapy with oral ivermectin and a topical scabicide is more likely to be effective in treatment of crusted scabies.

Meinking (1995) conducted an open-label study in which ivermectin was administered in a single oral dose of 200 µg/kg body weight to 11 otherwise healthy patients with scabies and to 11 patients with scabies who were also infected with the human immunodeficiency virus (HIV) (7 of whom had the acquired immunodeficiency syndrome). All 11 patients in the group with scabies and HIV infection (9 men and 2 women; aged 28-48 years) completed the study. Two had mild cases of scabies, three had moderate disease, four had severe disease and two had crusted scabies. Overall, 8 of 11 (73%) of the patients seropositive for HIV were cured with a single dose of ivermectin. Two of the remaining three (18 %of the treatment group) required a second dose two weeks after the first treatment and were cured by the time of the four week follow-up evaluation. The last case was a therapeutic challenge. The patient, a 34 year old woman, was seriously ill with advanced AIDS, tuberculosis and extensive, heavily crusted scabies did however respond after 3 courses of ivermectin and topical scabicide therapy.

Comments: Results from this study suggests that a single oral dose of 200ug/kg of ivermectin cures most cases of scabies, but that crusted or other stubborn cases may require additional treatments in combination with topical scabicides. Furthermore, it appears that ivermectin may have no residual activity against scabies two months after a single dose.

Paasch, 2000 reported experience with repeated scabies infestation at 3 elderly residence homes. According to the clinical examination and microscopically identified mites, all 252 individuals of the population (IOP), that is, patients, staff and family members were divided into 2 groups: (a) healthy and infested IOP (n=240) and (b) 12 cases with crusted scabies. The first group was treated with external scabicides (allethrin and permethrin) and all others were hospitalised and treated with systemic ivermectin (with or without permethrin). The patients with crusted scabies received single oral dose of ivermectin (200 µg/kg) once (n=7) or twice (n=5) after an interval of 8 days. This ivermectin regimen in combination with permethrin 5% topical application in severe cases was associated with clearance of lesions (Table 15).

Table 15. Paasch, 2000. Standard and additional therapy applied.

Residence	Patients	Standard therapy	Additional therapy	Failure
I	117	Allethrin spray	Ivermectin once, 7 Ivermectin twice, 4	2
II	56	Allethrin spray	Ivermectin once, 3 Ivermectin twice, 1	0
III	79	Permethrin cream	Ivermectin once, 2 Ivermectin twice, 2	0
Total	252		Ivermectin once, 12 Ivermectin twice, 7	

Sullivan (1997) reported results of an effort to eradicate scabies in rural nursing home ward involving 33 demented elderly male patients that had suffered from endemic scabies for at least 3 years, despite conventional topical therapies.

Comments: Treatment of crusted scabies was not evaluated in this study.

Pham (2010) report a case of one patient with crusted (Norwegian) scabies who probably developed crusted scabies because of an abnormal immune response caused by etanercept therapy. The patient was treated with one dose of ivermectin 12 mg orally and one overnight application of topical permethrin 5% cream; both were repeated 1 week later. At a follow-up appointment 1 month later, the skin was completely normal.

Goyal, 2008 report their experience with a 67 year old woman with crusted scabies who responded to aggressive therapy with two doses of 200 µg/kg ivermectin, 2 weeks apart in combination with topical permethrin and keratolytics.

Guggisberg, 1996 report the case of a 42 year old man with symptomatic HIV infection who presented with widespread hyperkeratotic skin lesions diagnosed as Norwegian scabies and was treated successfully with combined topical treatment (permethrin 5% cream plus keratolytic agents) and two single oral doses of ivermectin (200 µg/kg) with an interval of 1 week between dosing.

Comments: Although the above 3 reports by **Pham (2010) Goyal (2008) and Guggisberg (1996)** have been presented under section on observational studies, they were actually only case reports involving a single patient.

Dia, 1999 report results of 11 patients with crusted scabies in Dakar, Senegal, 10 of whom were treated and responded to treatment with a single oral dose of ivermectin (200 µg/kg)**.**

Pau, 1998 describe the case of a 67 year old male patient with crusted (Norwegian) scabies not responding to repeated topical therapy. He was treated with a single dose of 100 µg/kg ivermectin repeated after 7 days and led to recovery after 30 days and no relapse was observed after 10 months.

Quadripur, 1997 report a case of a 76 year old female with diabetes mellitus and lindane resistant crusted scabies who was cured following treatment with oral ivermectin.

Comments: Two other references (Gourhant, 2007 and Picquaro-Cascis, 2002) did not provide an English translation and the other 3 studies described above only provided 4-5 line English summaries making these 5 reports unevaluable.

6.2.2. Case reports of crusted scabies

Anselmo, 1996 report 2 patients with group HIV infection with crusted scabies who were treated with single oral dose of 12 mg of ivermectin. The clinical picture resolved on the fifth day after treatment and no patients suffered any relapse of the dermatological picture after 100 days of follow-up.

Aubin, 1995 report 2 patients with extensive crusted scabies (a 48 year old woman with Down's syndrome and a 82 year old woman who had received systemic corticosteroids for 11

years for polymyalgia rheumatic) not responding to treatment with benzyl benzoate. Both the women received a single oral dose (12 mg) of ivermectin in combination with 3 percent topical ointment of salicylic acid and showed improvement in itching and healing of lesions within 5-6 days with no recurrence or side effects during 3 to 8 months of follow-up.

Bakos 2007 only described diagnosis of crusted scabies in female genitalia in a 26 year old patient with HIV but ivermectin treatment was not discussed in this report.

Balighi, 2006 reported a 56 year old male patient with vesiculobullous lesions confirmed with diagnosis of crusted scabies who responded to treatment with oral ivermectin and 80 mg of prednisone.

Comment: The dose of ivermectin used in this patient was not specified.

Bergman, 1999 reported a 37 year old woman with diagnosed with Human T lymphotropic virus type 1 (HTLV-l) infection and HTLV-l-associated myelopathy (HAM) who developed crusted scabies which failed to respond to multiple application of permethrin 5%. Hospitalisation and treatment with two oral doses of ivermectin (12 mg) in addition to topical scabicides led to eventual resolution of the eruption.

Bongiorno, 2009 reported a 47 year old immunocompetent male with crusted scabies of the glans penis. He received oral ivermectin 12 mg (200 µg/kg) and the concomitant application of topical crotamitron containing 30% benzyl benzoate. He experienced no adverse effects. The skin lesions and itching cleared completely 10 days after the treatment.

Cestari, 2000 reported oral treatment with ivermectin of crusted (Norwegian) scabies in two immunosuppressed patients[8]. There was resolution of symptoms and signs of the cutaneous parasitosis on administration of 18-36 mg ivermectin (total doses) in 2 and 3 week periods of treatment, with remission periods of 3 and 4 months, respectively.

Colsky, 1997 report a patient with Darier's disease[9] who developed severe crusted scabies and was treated with permethrin 5.0% cream on two successive days. However, following recurrence within 1 month, she was treated with permethrin 5.0% cream to her entire body on five successive days. In addition, she was given a single 18 mg (200 µg/kg) oral dose of ivermectin as an adjunctive scabicide. She had no evidence of scabies at follow-up 6 months after her second admission.

Corbett, 1996 reported 2 HIV patients with crusted scabies who responded to combined treatment with oral ivermectin (120 µg/kg and 200 µg/kg, respectively) and topical scabicides (malathion).

Cordoliani, 1996 reported an 80 year old woman with HTLV infection who had severe crusted scabies and responded to single oral dose of 9mg ivermectin (equivalent to 175 µg/kg) in combination with topical scabicides (benzyl benzoate 25%) and remained in remission during the 2 months of follow-up.

Currie, 1994 report a single case of severe crusted scabies which failed to respond to 2 single doses of ivermectin (200 µg/kg) given at an interval of 4 weeks. Combination treatment with ivermectin (200 µg/kg) with topical permethrin 5% as well as keratolytic therapy also failed to improve crusted scabies in a 59 year old Aboriginal male patient **(Currie, 1995).**

Currie, 2004 report clinical and *in vitro* evidence of ivermectin resistance in 2 patients with multiple recurrences of crusted scabies who had previously received 30 and 58 doses of ivermectin over 4 and 4.5 years, respectively.

[8] A 10 year old Black girl with HIV and a 15 year old White girl with Down's syndrome.
[9] Darier's disease is an inherited condition of defective keratinisation in which patients are predisposed to development of severe viral infections.

Del Guidece, 1996 report two cases of HIV infected patients (72 year old woman and 30 year old man) with crusted Norwegian scabies who responded to 1 or 2 oral doses of ivermectin (200 µg/kg).

Dourmishav 1998 report that 3 patients with crusted scabies of the scalp and dermatomyositis were successfully cured of crusted scabies with a twice oral dose of 200 mg/kg ivermectin within 8 days.

Fucha, 2007 report a 45 year old man with AIDS which highlighted the difficulties that may be encountered in diagnosing and treating crusted scabies in patients with psoriasis. Patient was then given permethrin 5% cream, which he applied 3 times a week for 2 weeks, and 1 dose of oral ivermectin 200 µg/kg which resulted in a marked decrease in crusting and scaling although the lesions reappeared after 4 months.

Galvany, 2010 report a rare case of a 76 year old man with bullous scabies who was treated with 2 doses of ivermectin (200 µg/kg [17 mg]) 10 days apart and of a topical preparation made up of 10% urea, 5% permethrin, 0.1% triamcinolone acetonide and 0.1% gentamicin, achieved resolution of all the lesions and the pruritus. The oral corticosteroids were withdrawn over the course of the following 3 weeks and at 6 months' follow-up the patient remained asymptomatic with no new lesions.

Gladstone, 2000 report a case of an 11 year old girl with recalcitrant crusted scabies despite repeated applications of topical scabicides. She had no history of corticosteroid use prior to onset of the eruption and no evidence of immunodeficiency. A combination of oral ivermectin (6 mg), topical lindane and keratolytics cleared the infestation.

Jaramilo-Ayerbe, 1998 reported a case of an 11 year old girl with crusted scabies who was treated with several regimens of topical permethrin and keratolytics but the patient's lesions failed to achieve any significant improvement. However 2 single oral doses of ivermectin (6 mg) given at interval of 3 weeks cleared the lesions and the patient was asymptomatic at 6 month follow-up.

Kartano, 2007 reported a 49 year old woman with Langerhans cell histiocytosis (LCH) with marked thrombocytopenia and a hyperkeratotic skin eruption which following analysis of skin scrapings confirmed the presence of scabies. Her crusted scabies was treated with a single oral dose of ivermectin (12 mg). No recurrence or AEs occurred during the 6 months of follow-up.

Kedia, 2010 reported a 35 year old apparently healthy man who developed crusted Norwegian scabies showed considerable improvement following treatment with single oral dose of ivermectin 12 mg which was repeated after week along with topical Gamma Benzene Hexachloride lotion (GBHC).

Klein, 1996 reported a 40 year old HIV-seropositive man who developed crusted scabies 4 times over a 9 month period. During admission for his fourth episode, he received two oral doses of ivermectin 12 mg given 1 week apart in addition to topical 5% Permethrin cream which led to a prompt clinical response with no evidence of relapse three months later. All previous episodes were only treated topically, together with measures to prevent re-infestation.

Larralde, 1999 reported 4 cases of crusted scabies in immunocompromised patients (13 and 14 year old boys with Down's syndrome and HIV positive 4 year old girl and 30 year old man) who responded to 2 oral doses of ivermectin (200 µg/kg) given 1 week apart.

Marliere, 1999 describe a case of a 2 year old boy with crusted scabies, induced by long-term application of a topical corticosteroid, who relapsed after topical scabicidal treatment and was then given a single oral dose of ivermectin (200 µg/kg) combined with local treatment (including keratolytics, emollients and antiseptic bath with diluted triclocarban). This resulted in total resolution of pruritus in 24 h and remarkable improvement of skin lesions in 72 h. Definitive healing occurred 1 week after ivermectin and there was no relapse up to 5 months of follow-up.

McLucas, 2007 reported a case of a 5 year old boy with IPEX syndrome[10] with crusted scabies who responded to repeated applications of permethrin 5% cream and a single oral dose of ivermectin 3mg.

Nakamura, 2006 reported a 71 year old man diagnosed as having crusted scabies with bullous pemphigoid-like eruptions and nail involvement who responded to oral ivermectin (two doses of 12 mg ivermectin with a 1 week interval) and topical lindane (1%γ-BHC in petrolatum) with 5% salicylic acid in plastibase as an additional treatment for the crusted lesions on his soles. He showed remarkable improvement in 2 weeks and his nails showed complete recovery after 7 weeks of occlusive dressing treatment with 1%γ-BHC and the patient showed no sign of a recurrence of scabies, 1.5 years later.

Obasanjo, 2001 provide guidelines to institute effective control measures to end the outbreak of scabies in HIV care units, and prevent future occurrences and mention that oral ivermectin has an important role in patients not responding to conventional therapy for crusted scabies.

O-Callaghan, 1999 report a case of a 94 year old man with crusted Norwegian scabies not responding to conventional therapy which showed dramatic improvement following 2 single oral doses of ivermectin (150 μg/kg) given 1 week apart; ivermectin treatment was not associated with any significant AEs.

Ohtaki, 2003 report 2 cases of crusted scabies in a 72 year old man and a 52 year old woman treated with corticosteroids who failed to respond to topical scabicidal therapy alone. Both patients were successfully treated with two doses of oral ivermectin (200 μg/kg) at a 7 day interval with concomitant topical use of crotamitron and keratolytic agents. However, the nail scabies failed to respond to these treatments and only responded to occlusive dressing of 1% BHC on all toenails for one month.

Patel, 1999 report two immunodeficient Aboriginal children, aged 4 and 12 years, with crusted scabies who were successfully treated with a single oral dose of ivermectin (200 mg/kg) following lack of response to topical therapy alone.

Pellizer, 1996 report 6 cases of crusted scabies in 6 male patients with AIDS (aged 32 to 39 years) who were treated with single oral dose of ivermectin (200 μg/kg) repeated after 2 weeks and showed clearing of lesions and symptoms associated with crusted scabies.

Perna, 2004 reported localised, genital Norwegian scabies in a 49 year old AIDS male patient who was treated with ivermectin 200 μg/kg per dose taken as 2 doses, 14 days apart and showed complete resolution of both pruritus and skin lesions.

Ruiz-Maldonado, 2006 report a case of a 2.5 month old infant whose crusted scabies responded to 2 oral doses of ivermectin (200 μg/kg) administered 14 days apart.

Sampathkumar, 2010 report a case of crusted scabies in a 35 year old following his renal transplantation that was treated with 2 oral doses of ivermectin (200 μg/kg) with a 1 week interval, along with topical 5% permethrin and permethrin soap bath and responded with complete clearing of lesions and symptoms.

Subramaniam, 2010 report a case of a 19 year old malnourished male patient diagnosed with crusted scabies and secondary bacterial infection who was treated successfully with oral ivermectin (3 oral doses of 12mg given at weekly intervals), topical permethrin (5% cream applied twice daily) and vancomycin.

Torrelo, 2000 report a case of a girl with crusted scabies and epidermolysis bullosa simplex that responded to oral treatment with ivermectin 3 mg.

[10]This syndrome is a disorder caused by defects in the forkhead box P3 (FOXP3) gene.1 Hallmarks of IPEX include the congenital absence of pancreatic islands of Langerhans resulting in neonatal type-1 diabetes, hypothyroidism, intermittent eosinophilia, elevated IgE levels, variable immunodeficiencies, and bowel dysmotility.

Van der Wal, 1999 report a case of a 13 year old girl with severe non-mutilating recessive dystrophic epidermolysis bullosa (EB) and crusted scabies who was successfully treated with two oral doses of ivermectin and one application of lindane ointment (Permethrin cream was not tolerated).

Vignesh, 2008 report a case of a HIV-positive 16 year old man with severe crusted Norwegian scabies initially misdiagnosed as a dermal fungal infection. The patient had extensive, generalised, thick, hyperkeratotic, crusting, yellowish papule lesions distributed on the entire body from his scalp to his toes; he was started with Ivermectin (6 mg) and topical Permethrin, which eventually resulted in complete resolution.

Comments: The published report states that ivermectin 6mg was given for 15 days which does not appear accurate as the usual dose of ivermectin is single oral doses given at weekly intervals.

Yonekura, 2006 report a case of a 63 year old man with adult T-cell leukemia/lymphoma (ATL) patient whose crusted scabies was successfully treated with two doses of oral ivermectin (200 μg/kg) 10 days apart and the concomitant topical application of crotamitron containing 30% benzyl benzoate.

Yoshinaga, 2010 report a case of non-immunosuppressed 15 year old female patient with crusted scabies cured with 2 oral doses of ivermectin (200 μg/kg) and topical 10% crotamitron.

6.2.3. Case series

Nofal, 2009 evaluated the response of crusted scabies to oral ivermectin in 8 Egyptian patients (5 women, 3 mean aged 25 to 78 years) with crusted scabies, diagnosed clinically and confirmed microscopically. Patients received a single oral dose of ivermectin (200 μg/kg) and re-examined at 2, 4, 6 and 8 weeks. A second dose of ivermectin was given in case of treatment failure at the end of the second week. A third dose of ivermectin, combined with permethrin 5% and salicylic acid 5% was given at the end of the fourth week for the non-responders to the second dose. Two patients were completely cured after a single dose of ivermectin, 4 patients required a second dose after a 2 week interval to achieve cure and 2 patients cleared from scabies after the combined therapy. No recurrence was reported at the end of 8 weeks. An inverse relation was observed between the response to ivermectin and the severity of immunosuppression, crust thickness and mite burden **(Table 16).**

Table 16. Nafol, 2009. Case series of ivermectin in treatment of crusted scabies. Summary of the studies patients.

Case	Age (year)	Sex	Duration	Pruritus	Underlying immunosuppression	Crust thickness	Infestation	Response to ivermectin
1	43	Female	2 months	Mild	Steroids for SS	Moderate	Mild	After 2 doses
2	41	Female	4 months	Moderate	Steroids for PV	Severe	Moderate	After 2 doses
3	55	Male	6 months	Mild	KS, HIV, Ch	Severe	Severe	After 3 doses + TT
4	25	Female	1 month	Moderate	Steroids for SJS	Mild	Mild	After single dose
5	32	Female	2 months	Moderate	Apparently healthy	Mild	Mild	After single dose
6	58	Male	5 months	Absent	KS, Ch	Moderate	Moderate	After 2 doses
7	78	Female	3 months	Moderate	Apparently healthy	Moderate	Moderate	After 2 doses
8	53	Male	3 months	Severe	Leukaemia, Ch	Severe	Severe	After 3 doses + TT

Ch, chemotherapy; KS, Kaposi sarcoma; PV, pemphigus vulgaris; SJS, Steven–Johnson syndrome; SS, systemic sclerosis; TT, topical therapy.

Comments: Results from this case series suggest that oral ivermectin is an effective alternative therapy for the treatment of crusted scabies although the response is variable and combination therapy with topical scabicides and keratolytics seems to be the best choice.

Roberts, 2005 describe the clinical and immunological features of crusted scabies in a prospectively ascertained cohort of 78 patients in the northern territory of Australia over a 10 year period. Demographics, risk factors and immunological parameters were retrospectively

compiled from their medical records and pathology databases. Children weighing less than 15 kg and pregnant and lactating women were excluded from the study. There were only two children, aged 1 month and 15 years. Disease was otherwise spread evenly across the adult years, with the mean age being 43 years and the oldest patient being 76 years of age. All but 2 patients were indigenous Australians from remote Aboriginal communities. High mite counts were demonstrated by light microscopy in 71% of patients **(Table 17).** Seventeen percent had a history of leprosy, 3 patients were seropositive for HTLV-I. Of note, no patient was infected with HIV. Overall 33 patients (42%) had no identifiable risk factor and except for their skin disease these individuals appeared healthy **(Table 18).** More than half the patients with crusted scabies had identifiable immunosuppressive risk factors. Eosinophilia and elevated IgE levels occurred in 58% and 96% of patients, respectively, with median IgE levels 17 times the upper limit of normal **(Table 19).**

Table17. Roberts, 2005. Case series of ivermectin in treatment of crusted scabies in 78 patients in Northern Australia. Demographics and death rates of people with crusted scabies.

Number of cases	78
Mean age	43
Year of presentation (range)	1991-2000
High mite count confirmed	71%
Definite immunosuppressive risk factor	26%
Possible immunosuppressive risk factor	60%
Indigenous	97%
Annual death rate prior to 1997[a]	4.3%
Annual death rate from 1997	1.6%

[a] Rates of death directly attributable to crusted scabies are shown before and after the routine use of ivermectin during 1996. This difference is significant $p=0.02$, Fisher Exact test.

Table 18. Roberts, 2005. Potential risk factors leading to immunosuppressed state in patients with crusted scabies.

Immunosuppressive risk factor	Frequency
Heavy ethanol use	17
Past leprosy	13
Heavy kava use	8
Type 2 diabetes mellitus[a]	8
Malnutrition	5
Hepatic cirrhosis	5
Renal transplant immunosuppression[a]	4
Systemic lupus erythematosus[a]	3
Chronic hepatitis B infection	3
Renal dialysis[a]	2
Hypothyroidism	2
Mixed connective tissue disease[a]	2
Syphilis	2
Behcet's disease[a]	1
Scleroderma[a]	1
Chronic Myelogenous Leukemia[a]	1
Chronic petrol inhalation	1
Sturge-Weber Syndrome[a]	1
HTLV-I infection	3
HIV infection	0
No risk factor identified	33 (42%)[b]

Some patients had more than one risk factor.
[a] Definite immunosuppressive risk factor as described in Table 1.
[b] Percentage of patients without an identifiable risk factor.

Table 19. Roberts, 2005. Markers of immune function in patients with crusted scabies.

Immune parameter	Normal range[a]	Frequency of cases outside[b] normal range (%)	Number tested	Range	Median
IgG	6.3-13.5 g/l	96	56	6-64	33
IgA	0.5-3.12 g/l	64	56	0.8-33	3.9
IgM	0.52-3.34 g/l	11	56	0.37-4	1.3
IgE	0-100 mcg/l	96	52	1.34-217 260	1700
Eosinophils	$0.04\text{-}0.7\times10^9$/l	58	59	0.02-13	1.6
C3[c]	0.86-1.84	29	58	0.39-1.55	1.04
C4[c]	0.2-0.59	45	58	0.09-0.48	0.21
C3 and C4 low		22			
CD4[c]	$0.41\text{-}2.21\times10^9$/l	13	40	0.30-3.2	0.61
CD8	$0.17\text{-}1.33\times10^9$/l	3	40	0.18-3.4	0.56
ANA titre	1:80-1:320	28			
ANA titre	>1:320	13			

The annual rate of death in the years prior 1997 was 4.3% (8 patients died out of 31 over 6 years) and fell to 1.1% (3 patients died out of 47 over 4 years) in the years from 1997 onward (Table 17). This substantial difference in death rate corresponds to the commencement of the use of multiple dose ivermectin in the treatment of all patients with crusted scabies since mid 1996, together with a protocol for early empirical broad spectrum antibiotic cover for suspected secondary sepsis. An intensive ivermectin treatment regimen was used: a five dose regimen with doses (200 µg/kg) on Days 1, 2, 8, 9 and 15 with an additional two doses on Days 22 and 29 for the most severe cases; this was used in combination with topical scabicides and keratolytic therapy.

Comments: This is the largest reported case series of crusted scabies. The authors attribute the significant decrease in mortality in crusted scabies over the period of this study to the more intensive ivermectin use together with a protocol for early use of antibiotics in suspected secondary bacterial sepsis. However, this study lacked any definite efficacy endpoints such as cure rates in terms of clearing of lesions and symptoms of crusted scabies in these patients.

Ndiaye, 1999 evaluated 30 patients with crusted scabies at the dermatological clinic in Dakar (Senegal) between January 1993 and June 1997. Seventeen of these patients were male and 13 were female. Six were children aged 5 to 15 years and 24 were adults aged 18 to 70 years. The infection presented as an extensive scaly or crusted eruption with symmetrical lesions affecting the hands, feet, knees, elbows and ears in particular and scalp involvement was reported in 25 patients and 27 of 30 patients had moderate or severe pruritus. Diagnosis was confirmed by examination of hyperkeratotic material under the microscope which showed numerous mites and eggs. The two most common etiological factors were autoimmune diseases (6 cases, 4 of whom were receiving no steroid or other immunosuppressive treatment at the time of onset of crusted scabies) and malnutrition (5 of the 6 children in the study). The other associated conditions identified were: physical debilitation (4 cases), HIV infection (3), mental disability-Downs's syndrome (3) and long term use of topical steroids (2). Two patients were immunocompetent and 5 patients died shortly after diagnosis, before any underlying conditions could be identified.

Seven patients were cured with benzyl benzoate. Seven others, all adults, received a single oral dose of ivermectin (200 µg/kg) and topical kerotolytic drugs. Ivermectin was ineffective in 1 case and an improvement was observed in another case, although a complete cure was achieved only after a second dose. The other patients were all cured and showed no signs of scabies one month after ivermectin treatment. A recurrence was observed in 3 patients a few months later however, suggesting that these patients were reinfected. No side effects were reported in any of the patients treated with ivermectin.

Comments: The actual publication was not in English and only summary (in English) was provided for review. Overall results from this case series in 30 patients with crusted scabies showed efficacy in 6 of the 7 patients treated with ivermectin although it was difficult to interpret results.

There were 13 other foreign references to support use of ivermectin in crusted scabies but 6 of these publications were unevaluable as English translations or even summary in English was not provided **(Clyti, 2010; Ducki, 2004; Illes, 2010; Mara, 2004; Ram-Wolff, 2008 and Rodriguez-Gomez, 2006)**. The other 7 publications had short 3-4 line summaries in English which suggested efficacy/safety of ivermectin (200 µg/kg) administered as 1 to 3 doses at 7-14 day intervals in patients with crusted scabies **(Alvaro, 2003; Angelo, 2004; Cornolli, 2003; Fernandez-Tamayo, 2006; Hernandez, 2010; Luz, 1999 and Mijelshon, 2000).**

6.3. Additional references

There were another 155 additional references provided in the sponsor's submission. Of these about 11 were not provided in the dossier; majority of the others were related to generalised publications regarding scabies, epidemiology of skin diseases and so on which were not directly relevant to this submission of ivermectin for treatment of scabies. All the other relevant publications which have not already been covered in earlier sections of this evaluation report are discussed in this section.

Comments: The evaluators seek clarification from the sponsors regarding the following:-

- The article by Chosidow, 2006[11] was not provided and in fact an earlier publication by the same author (Chosidow, 2000) was repeated in its place.
- The publication by Coyne, 1997 was identical to the publication by Bredal, 1997.

Alexander, 1998: Alexander, 1998 presented an analysis of deaths in a part of Papua New Guinea where demographic surveillance was part of a randomised community-based trial of ivermectin plus diethylcarbamazine (DEC) versus DEC alone for lymphatic filariasis (Bockarie, 1998). There was no evidence of an increased death rate associated with ivermectin treatment (400 µg/kg) with similar results in an analysis restricted to those aged at least 60 years at first treatment **(Table 20).**

Table 20. Alexander, 1998. Death rates following treatment with ivermectin plus diethylcarbamazine or diethylcarbamazine alone.

Treatment[a]	No. of deaths/ person-years of surveillance[b]	Rate ratio[c]	*P*
All treated persons			
Ivermectin plus DEC	28/3259 (0·0086)	0·74 (0·45–1·20)	0·22
DEC alone	39/3344 (0·0117)		
Age ≥60 years			
Ivermectin plus DEC	6/132 (0·045)	0·54 (0·21–1·37)	0·20
DEC alone	17/202 (0·084)		

[a]DEC=diethylcarbamazine.
[b]Death rate in parentheses.
[c]95% confidence interval in parentheses.

Badiaga, 2008 conducted a randomised, double-blind, placebo-controlled trial from January 2006 to April 2006 in two homeless shelters in the city of Marseille, France involving 82 patients with pruritus who were randomised to receive either ivermectin 24 mg (n=42) or placebo (n=40). On Day 14, pruritus was reported by significantly more subjects in the placebo

[11]Clinical Practice- Scabies; NEJM, 2006; 354 (18): 1718-27

group than those in the ivermectin group for both the per-protocol (PP) population (91.42% versus 68.57%, P=0.014) and the intention-to-treat (ITT) population (92.5% versus 73.80%, p= 0.038). However, this significant difference was not observed at Day 28. Overall, single dose of oral ivermectin had a transient beneficial effect on the reduction of the prevalence of pruritus in the homeless population.

Comments: This study only showed transient improvement in patients with pruritus; however, diagnosis of scabies was not confirmed in any of these patients and this study failed to provide any information relevant to this submission.

Bredal, 1997 evaluated several scabies outbreaks occurred in a psychogeriatric nursing home between 1994 and 1996. All 220 residents were treated with ivermectin in August, 1996 and the authors looked at mortality over the past 3 years, comparing the 6 months after ivermectin treatment with the 30 months before. Age and medical conditions were much the same for the group of residents within this period. The mortality rate in the month after treatment did not differ significantly from that before (Kruskal-Wallis test). The odds ratio was 1.33 (95% CI: 0.91-1.94). Ivermectin has been used extensively and has been associated with a low frequency of side-effects.

Bockarie, 2000 report striking reduction in village-specific prevalence of scabies from 87.1% to 26% following a single-dose mass treatment with ivermectin which was comparable to the outcome of a mass topical treatment program using 5% permethrin cream in an Australian aboriginal community over a 25 month period (Carapetis et al.. 1997). These findings suggest that semi-annual single-dose treatment with ivermectin may be more effective than topical treatment with permethrin for controlling scabies infection at the community level.

Buffet, 2003 reviewed the literature with an evidence-based medicine method and attempted to provide guidance on the treatment of choice for common scabies in an otherwise healthy patient and also defined the role of systemic ivermectin. Among local treatments, studies are heterogeneous according to products, countries, group of treated patients, with or without contact subjects and the method of treatment application. There are very few high proof-level controlled studies. In France, a combination of benzyl benzoate 10% and sulfiram 2% is used most commonly. The most studied product is the cream permethrin 5%, available in the USA, United Kingdom (UK) and Australia. Its efficacy seems slightly superior to lindane and less toxic. It is more efficient than crotamitron. There is no study comparing benzyl benzoate and permethrin. Concerning systemic ivermectin, five controlled studies showed its efficiency in common scabies. But its relative efficiency over local treatment has not been established. A few open studies showed its efficacy in institutional epidemic, profuse scabies and in HIV positive patients. Indication of ivermectin seems proved in common scabies and probably for HIV-positive patients. It remains to be determined if it should be prescribed as first line of therapy, requires 2 or 3 doses, be associated or not with local treatment. Ivermectin is probably useful in institutional epidemic and therapeutic attitude remains to be defined. Ivermectin seems to have little or no risk. Treatment must be adapted case-by-case, according to feasibility. It is still important to treat contacts and modality of this treatment remains to be specified.

Cook, 2003 have conducted a review of the clinical literature describing the use of ivermectin in cases of treatment-resistant scabies infestations; this was through a MEDLINE search (1966–July 2001) and the Cochrane Database. A limited number of case reports and case series describes successful intervention with ivermectin use in patients. Table 21 summarises some of the available case series and reports associated with treatment-resistant scabies infestations. These reports show that ivermectin was effective in completely resolving scabies infestations that were not effectively cleared by standard topical therapies. Of note, the populations described include patients who are presumed to be at high risk for scabies infestation: the elderly, immunosuppressed, and those with Down syndrome, who have failed prior therapy.

Table 21. Cook, 2003. Summary of Resistant Scabies treated with Ivermectin.

Reference	N	Patient Population	Treatment Used	Results	Comments
Dourmishev et al. (1998)[11]	3	immunosuppressed; 1 treatment-resistant	IVER 200 µg/kg × 2 (q1wk — 1 pt. received only 1 dose)	CR in 100% at 8 d	
Guggisberg et al. (1998)[10]	1	HIV+; Norwegian scabies; treatment-resistant	IVER 200 µg/kg, PERM 5% × 2 (q1wk)	CR at 6 d	pt. had crusted lesions
Huffam et al. (1998)[4]	20	treatment-resistant	IVER 200 µg/kg × 1–3 doses (q2wk)	CR in 15% after 2 doses; CR in 40% after 3 doses	all pts. had crusted lesions; complicated by reinfestation
Dannaoui et al. (1999)[2]	7	after nursing home outbreak recurrence	IVER 12 mg x 2 (q2wk)	CR in 84% (6/7 pts.); 1 failure at 7 wk	given to remainder of nursing home population — contained outbreak
Larralde et al. (1999)[5]	4	2 Down syndrome (treatment-resistant), 2 HIV+	IVER 200 µg/kg × 2 (q1wk to HIV pts., q2wk to others)	CR in 100% at 2 wk (Down syndrome pts.) and at 6 mo (HIV+ pts.)	all pts. had crusted lesions
Offidani et al. (1999)[12]	6	treatment-resistant	IVER 200 µg/kg × 1 (× 2 q1wk for 1 pt.)	CR in 100% at 4 wk	

CR = complete response; IVER = ivermectin; PERM = permethrin.

Diazgranados, 1997 report no increase in mortality in a Colombian study, where ivermectin has been commonly prescribed for geriatric patients since 1989, some of whom received treatment for several years. The clinical histories of 47 patients, aged 65 years or more (average age 74.7 years) were randomly selected and were followed up for at least 6 months after administration of their first dose of ivermectin (at least 200 µg/kg, and in some cases higher). Among 47 patients there was only one death during the 6 month observation period. Many of the patients continued to take ivermectin for months or years after their first dose and no deaths have been reported.

Guldbakke, 2004 have written a clinical review on 'Crusted Scabies' and mention that Ivermectin has been used successfully in crusted scabies both as monotherapy or in combination with topical scabicides and has also been employed in children. The therapy may be effective after a 200 µg/kg single dose but multiple doses are usually required to achieve cure. Most patients need 2 or 3 single doses separated by intervals of 1 or 2 weeks; but even on this regimen, recurrence 6 or more weeks after completing treatment is common.

Haas, 2001 report one patient who was treated with two doses of ivermectin at one week intervals and local keratolytic ointment with good subsequent clearing of the disease.

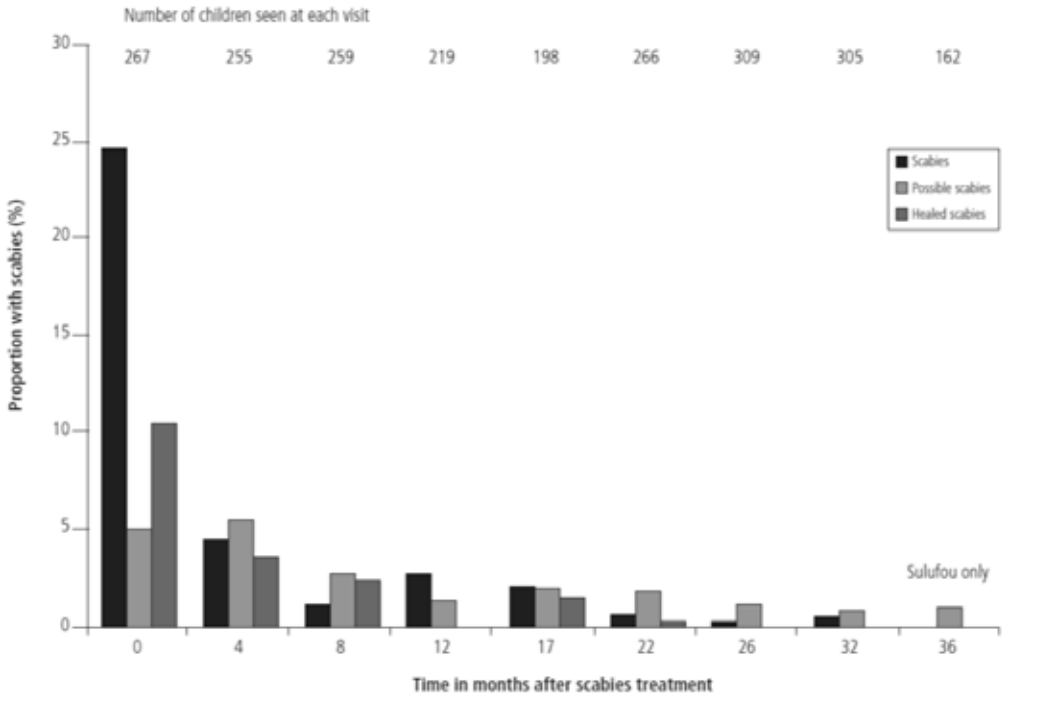
Kar, 1994 report 2 cases of microfilarial infection and concomitant scabies in Orissa, India who were treated with ivermectin (25-100 µg/kg) which cleared the scabies although the lesions reappeared after 3 months.

La Vincente, 2009 conducted an observational study of households in two scabies-endemic Aboriginal communities in northern Australia wherein permethrin treatment was provided for all householders upon identification of scabies within a household during home visit. Very low levels of treatment uptake were reported among household contacts of these children (193/440, 44%). Household contacts who themselves had scabies were more likely to use the treatment than those contacts who did not have scabies (OR 2.4; 95%CI 1.1, 5.4), whilst males (OR 0.6, 95%CI 0.42, 0.95) and individuals from high-scabies-burden households (OR 0.2, 95%CI 0.08, 0.77) were less likely to use the treatment. Among 185 susceptible individuals, there were 17 confirmed or probable new diagnoses of scabies recorded in the subsequent 4 weeks (9.2%). The odds of remaining scabies-free was almost 6 times greater among individuals belonging to a household where all people reported treatment uptake (OR 5.9; 95%CI 1.3, 27.2, p = 0.02).

Comments: These findings indicated an urgent need for a more suitable treatment for scabies to reduce the burden in endemic settings but the role of ivermectin was not investigated in this study.

Lawrence, 2005 assessed the effects of a 3 year program aimed at controlling scabies on five small lagoon islands in the Solomon Islands by monitoring scabies, skin sores, streptococcal skin contamination, 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 evident scabies. Prevalence of scabies dropped from 25% to less than 1% ($p < 0.001$) (Figure 7); prevalence of sores from 40% to 21% ($p < 0.001$); streptococcal contamination of the fingers in those with and without sores decreased significantly ($p = 0.02$ and 0.047, respectively) and anti-DNase B levels decreased ($p = 0.002$). Both the proportion of children with haematuria and its mean level fell ($p = 0.002$ and $p < 0.001$, respectively). No adverse effects of the treatments were seen. Overall, the results show that ivermectin is an effective and practical agent in the control of scabies and that control reduces the occurrence of streptococcal skin disease and possible signs of renal damage in children. Integrating community-based control of scabies and streptococcal skin disease with planned programs for controlling filariasis and intestinal nematodes could be both practical and produce great health benefits.

Figure 7. Lawrence, 2005. Number of children with scabies by approximate months after treatmenta.



[a] The fall in the proportion of children with scabies is significant ($P < 0.001$). As treatment began 4 months earlier on Sulufou, the results at 36 months refer only to Sulufou children, about half the total.

Otaki, 2005 reported use of oral ivermectin (2 doses at 200 µg/kg given with a 1 week interval) in 74 patients with scabies. Majority of the patients responded to treatment with only 9 cases (12.2%) not cured; recurrence was observed 9 cases (12.2%) in 4 months (mostly in elderly patients).

Scott, 2011 report the European guidelines for the management of scabies and some of the main points are: Permethrin cream 5% (once for 8-14 h) is effective, well-tolerated but expensive (level of evidence Ib; Grade A recommendation[12]). Benzyl benzoate lotion (10 to 25%) is also cheap and effective but requires application on more than one day (2 to 3 applications)(level of evidence III; Grade B recommendation). Ivermectin is not licensed in most countries but can be given orally as a repeated dose (200 µg/kg), 2 weeks apart in patients weighing more than 15 kg. Comparisons of ivermectin with lindane and benzyl benzoate gave conflicting results with regard to efficacy (level of evidence Ib; Grade A recommendation). Although Ivermectin has been associated with deaths when given to debilitated patients, this has not been borne out in the more recent studies. There are no controlled trials of topical ivermectin. Sulfur (6-33%) is the oldest antiscabetic in use and comes in various preparations. It appears to be effective, is very cheap and safe but stains clothing and requires application on three successive days (level of evidence Ib; Grade A recommendation). Topical treatment of crusted scabies (seen in immunocompromised persons, for example AIDS patients and those confined to long-term institutions)is with several applications of permethrin 5% cream to the entire skin including the head which may be alternated with keratolytic therapysuch as emollients or bathing. Combinations of topical treatments with oral agents such as ivermectin have been used in some outbreaks (level of evidence III; Grade B recommendation).

Wong, 2001 conducted a prospective, longitudinal screening, intervention and follow-up study assessing all children aged 5 years and under in one of the largest Aboriginal communities in the Northern Territory, total population, approximately 2,200 (95% Indigenous). The main outcome measures were a decrease in prevalence of scabies, infected scabies and non-scabies pyoderma over seven months. The number of children aged 5 years and under screened initially and at the three follow-up screenings ranged from 201 to 242 (more than 98% of those eligible on each occasion). The prevalence of scabies, infected scabies and non-scabies pyoderma before intervention were 35%, 12% and 11%, respectively. At 6 weeks post intervention these had decreased to 3%, 1% and 4%, respectively; low prevalence were maintained at four and seven months.

Comments: The details regarding interventions (treatments), especially ivermectin used for scabies were not specified in the report.

6.4. Evaluator's conclusions on clinical efficacy of ivermectin for treatment of scabies

The clinical evidence for efficacy of ivermectin in treatment of 'typical scabies' which was presented in this submission is summarised in the Table 22 below.

Table 22. Summary of type of evidence to support efficacy of ivermectin in typical scabies

Type of evidence (NHMRC level)	References submitted
Systematic review of all relevant Randomised Controlled Trials (RCTs) (Level I)	Strong, 2010
Individual properly designed	Bachewar, 2009; Choulea, 1999; Ly 2009;

[12] Grades of recommendation from Phillip et al: Grade A= Consistent Level 1 studies or a systematic review of meta-analyses; Grade B=Consistent Level II study or a single level I study or Consistent Level III studies; Grade C= Consistent level IV studies or extrapolations from Level II or III evidence; Grade D= Level 5 evidence (expert opinions) or inconsistent Level I to IV evidence.

Type of evidence (NHMRC level)	References submitted
RCTs (level II)	Madan, 2001; Mushtaq, 2010; Nnoruka 2001; Usha, 2000)
Non-randomised CTs (Level III-1)	None
Cohort or case-control analytic studies (Level III-2)	Various observational, open-label studies
Case series with historical control (Level III-3)	None
Case reports (Level IV)	None

The efficacy and safety of ivermectin in the classic (non-crusted) presentation of scabies relative to placebo and/or traditional local treatments was evaluated in a systematic literature review on 4044 published cases of typical scabies. The diagnosis of scabies was confirmed clinically and/or parasitologically (by microscopic examination) in most of the cases. There were 8 evaluable RCTs which showed ambiguous results for efficacy of ivermectin in treatment of typical scabies (Level II evidence). Of the topical treatments for scabies, permethrin is most effective and it also appeared to be more effective than oral ivermectin **(Usha, 2000; Bachewar, 1999**). Compared to topical lindane, efficacy of oral ivermectin was similar **(Choulea, 1999)** or better **(Madan, 2001).** Results of the 5 trials comparing oral ivermectin with topical application of BB (10-25%) were inconclusive with some studies showing reduced efficacy of ivermectin **(Ly, 2009)**, one showing greater efficacy **(Nnoruku, 2001)** and the other 3 trials showing similar efficacy of ivermectin and BB (see Table 23 below).

Table23. Main results of the evaluable RCTs for ivermectin in treatment of typical scabies

Reference	Nos of subjects	Main results
Bachewar, 2009	103	Cure rate defined as no new lesions: IV versus permethrin 5%=100% versus 96% after 2 weeks.
Choulea, 1999	53	Cure rate defined as clearance of symptoms and lesions: IV versus Lindane 1%= 75% versus 96% after 4 weeks, but IV showed faster onset of action.
Ly 2009	181	Cure rate was 43%, 77% and 96% with IV, BB1 and BB2 after 4 weeks.
Madan, 2001	200	Cure rate was IV versus Lindane= 82.6% versus 44% after 4 weeks
Mushtaq, 2010	100	Cure rate IV versus permethrin 5%= 79.5% versus 88.1% at 4 weeks and AEs more common with ivermectin.
Nnoruka,	58	Cure rate at 4 weeks: IV versus BB25%= 93.7% versus

Reference	Nos of subjects	Main results
2001		48.5%
Usha 2000	85	Cure rate at 4 weeks: IV versus permethrin 5%= 95% versus 100%.
Marcotela-Ruiz, 1993	55	Cure rate was 74% and 16% with ivermectin and placebo, respectively; but no study report provided in English.

There were many observational studies which demonstrated efficacy of oral ivermectin in treatment of typical scabies especially following failure of topical therapy or in mass community treatment programs (Level III evidence; refer *Observational studies section* of this report).

Although no controlled clinical trials have been published that evaluate the appropriate ivermectin dosing regimen to treat scabies, cohort reports and case series have been published that suggest possible dosing regimens (Level III evidence). Suggested treatments have ranged from a single 200 µg/kg dose up to 3 doses, each separated by 1–2 weeks. Severe infestation thus may require more aggressive therapy. Also, for long-term-care facility or hospital patients, reinfestation can be a significant problem, as it increases the risk of spread to other patients. Thus, for treatment-resistant scabies, it appears prudent to administer a second dose 1–2 weeks after the initial treatment. Further data are needed to define the dosing strategy optimal for safety and efficacy.

Majority of the evaluated patients with typical scabies in this submission were treated with ivermectin following failure of topical scabicidal treatment. Few controlled studies have been done to compare the effectiveness of topical treatments for scabies on the market. As a result, treatment recommendations vary from one country to another and the selection of a drug is often based on the personal preference of the physician, local availability and cost, rather than on medical evidence. For example, the low cost of benzyl benzoate cream or lotion (10% or 25%) means it is commonly used as the first line drug in developing countries, whereas permethrin cream (5%) is the standard treatment in the USA, UK and Australia. Other topical treatments in use are monosulfiram (25%), malathion (0·5%), lindane (0·3–1%), crotamitron (10%) and sulphur in petrolatum (2–10%). The inconclusive results of the randomised controlled trials (RCTs) comparing ivermectin to topical antiscabetic agents indicate that the submitted data is not adequate to justify use of ivermectin as first line therapy in patients with typical scabies. However ivermectin would provide a potentially useful therapeutic alternative for patients in whom standard topical therapies do not prove safe or effective or is contraindicated due to skin irritation/eczematisation and so on.

The clinical evidence to support efficacy of ivermectin in crusted scabies provided in this submission is summarised in Table 24 below.

Table 24. Summary of type of evidence to support efficacy of ivermectin in crusted scabies

Type of evidence (NHMRC level)	References submitted
Systematic review of all relevant RCTs (Level I)	None
Individual properly designed RCTs (level II)	None
Non-randomised CTs (Level III-1)	None

Type of evidence (NHMRC level)	References submitted
Cohort or case-control analytic studies (Level III-2)	Observational, open-label studies
Case series with historical control (Level III-3)	Roberts, 2005
Case reports (Level IV)	Various

The efficacy and safety of ivermectin in crusted scabies was evaluated in a systematic literature review on 260 published cases of crusted scabies. The mean age and age range of this cohort was 41.7 years (range: 2-94 years) and 78% of all patients were managed in a clinic setting following confirmation of high mite count. The majority of patients (70%) received ivermectin after proving refractory to classical topical treatments. With a few exceptions, the dose of ivermectin in this review was 200 µg/kg of body weight. At least 72% of cases were treated with combination ivermectin and topical scabicide. In the large Australian cohort studies from the review, all patients were administered topical keratolytic therapy in keeping with Australian clinical protocols. In published studies in patients with crusted scabies, ivermectin was shown to have an overall clinical efficacy response of 87% on cure rates. The majority of patients presenting with mild to severe forms of crusted scabies were adequately managed with one to two oral doses of 200 µg/kg ivermectin although 1-2 doses may not be adequate in treating very severe cases of crusted scabies. However, it should be noted that interpretation of efficacy of ivermectin in crusted scabies was confounded by publication bias.

Oral ivermectin has demonstrated success in the community management of endemic scabies [Lawrence, 2005; Heukelbach, 2004; Bockarie, 2000) and also showed a good tolerability profile. Ivermectin is also effective against other parasitic infestations that can occur in high-scabies burden settings, such as strongyloidiasis which is endemic in many Australian Aboriginal communities. Ivermectin is not currently approved for the mass community management of scabies in Australia. Hence, oral ivermectin may help to address the urgent need for a more practical and feasible treatment for community management of endemic scabies.

7. Clinical safety

7.1. Studies providing evaluable safety data

Safety results were only presented for the Phase I Study 066 in healthy subjects. The sponsors have not conducted any Phase II-III studies investigating safety of ivermectin in treatment of scabies.

7.1.1. Clinical pharmacology studies

In the Phase I Study 066 in healthy subjects oral ivermectin administered in multiple doses of 30 or 60 mg (in the fasted state) given 3 times a week or in single doses of 30 mg (in the fed state) or 90 or 120 mg (in the fasted state) was generally well tolerated. There was no evidence of mydriatic effect or other neurological toxicity after oral administration of ivermectin.

Of the 51 subjects who received ivermectin, 12 subjects (24%) reported at least 1 clinical AE. This rate was similar to that observed in the placebo group (6 subjects, 35%). All clinical AEs were transient and mild and no AEs recurred with repeated dosing or dose escalation. No AEs were reported in the subjects who received 120 mg of ivermectin which is almost 10 times the proposed dose of 200 µg/kg for treatment of scabies. None of the subjects discontinued due to clinical AEs. None of the clinical adverse experiences was serious. No subjects died during the study (Table 25).

Table 25. Study 066. Clinical Adverse Experience Summary

Clinical adverse experiences	Placebo (N=17)		Ivermectin 30 mg (N=15)		Ivermectin 60 mg (N=12)		Ivermectin 90 mg (N=12)		Ivermectin 120 mg (N=12)	
Number (%) of subjects:	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
With one or more adverse experiences	6	(35.3)	5	(33.3)	5	(41.7)	2	(16.7)	0	(0.0)
With no adverse experience	11	(64.7)	10	(66.7)	7	(58.3)	10	(83.3)	12	(100)
With drug-related adverse experiences†	3	(17.6)	1	(6.7)	4	(33.3)	2	(16.7)	0	(0.0)
With serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a drug-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.

The most common type of clinical AEs occurred in the nervous system and psychiatric disorder body system. Six (6) of the 51 subjects in the ivermectin-treated groups (5 headache, 1 anxiety, 1 dizziness) and 3 of the 17 subjects in the placebo groups (2 headache, 1 dizziness) experienced nervous system adverse experiences. The most commonly reported clinical AE was headache, occurring in 5 ivermectin-treated subjects (10%) and 2 placebo-treated subjects (12%). The next most frequently reported AEs were nausea, dizziness, and rash, each occurring in 1 ivermectin-treated subject (2%) and 1 placebo-treated subject (6%) (Table 26). Three (3) of 51 subjects in the ivermectin-treated groups (1 fecal abnormality, 1 nausea, 1 vomiting) and 1 of 17 subjects in the placebo groups (1 nausea) experienced gastrointestinal AEs. AEs of special concern included emesis, ataxia, and mydriasis. The AE of vomiting occurred in a subject administered 60 mg of ivermectin on Study Day 4[13]. No occurrences of ataxia or mydriasis were reported. Seven (7) ivermectin-treated subjects (14%) had drug-related clinical AEs. This rate is similar to that seen in the placebo group (3 subjects, 18%). The most frequently reported drug-related AEs was headache, occurring in 4 ivermectin-treated subjects (8%) and 2 placebo-treated subjects (12%) (Table 27).

[13] On Study Day 4, a subject who had received 60 mg of ivermectin and experienced mild nausea and vomiting lasting 2 minutes. The investigator rated this event as probably not related to study drug.

Table 26. Study 066. Number (%) of subjects with a specific clinical adverse experiences (incidence >0% in one or more treatment groups) by Body System

	Placebo (N=17)		Ivermectin 30 mg (N=15)		Ivermectin 60 mg (N=12)		Ivermectin 90 mg (N=12)		Ivermectin 120 mg (N=12)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with one or more adverse experiences	6	(35.3)	5	(33.3)	5	(41.7)	2	(16.7)	0	(0.0)
Subjects with no adverse experience	11	(64.7)	10	(66.7)	7	(58.3)	10	(83.3)	12	(100)
Body as a Whole/Site Unspecified	**0**	**(0.0)**	**2**	**(13.3)**	**1**	**(8.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Fever	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)
Flu-like illness	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Pain, abdominal	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)
Digestive System	**1**	**(5.9)**	**1**	**(6.7)**	**1**	**(8.3)**	**1**	**(8.3)**	**0**	**(0.0)**
Dry mouth	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)
Fecal abnormality	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	1	(5.9)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Musculoskeletal System	**1**	**(5.9)**	**2**	**(13.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Pain, back	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pain, leg	1	(5.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stiffness	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous System and Psychiatric Disorder	**3**	**(17.6)**	**1**	**(6.7)**	**4**	**(33.3)**	**1**	**(8.3)**	**0**	**(0.0)**
Anxiety	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Dizziness	1	(5.9)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Headache	2	(11.8)	1	(6.7)	3	(25.0)	1	(8.3)	0	(0.0)
Skin and Skin Appendage	**1**	**(5.9)**	**0**	**(0.0)**	**1**	**(8.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Rash	1	(5.9)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Urogenital System	**0**	**(0.0)**	**1**	**(6.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Urolithiasis	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)

Although a subject may have had 2 or more adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
All body systems are listed in which at least 1 subject had an adverse experience.

Table 27. Study 066 Number (%) of subjects with specific clinical adverse experiences (incidence >0% in one or more treatment groups) by Body System (drug related)

	Placebo (N=17)		Ivermectin 30 mg (N=15)		Ivermectin 60 mg (N=12)		Ivermectin 90 mg (N=12)		Ivermectin 120 mg (N=12)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with one or more drug-related[†] adverse experiences	3	(17.6)	1	(6.7)	4	(33.3)	2	(16.7)	0	(0.0)
Subjects with no drug-related adverse experience	14	(82.4)	14	(93.3)	8	(66.7)	10	(83.3)	12	(100)
Body as a Whole/Site Unspecified	**0**	**(0.0)**	**1**	**(6.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Pain, abdominal	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)
Digestive System	**1**	**(5.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(8.3)**	**0**	**(0.0)**
Dry mouth	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)
Nausea	1	(5.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous System and Psychiatric Disorder	**2**	**(11.8)**	**0**	**(0.0)**	**4**	**(33.3)**	**1**	**(8.3)**	**0**	**(0.0)**
Anxiety	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Dizziness	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)
Headache	2	(11.8)	0	(0.0)	3	(25.0)	1	(8.3)	0	(0.0)

[†] Determined by the investigator to be possibly, probably, or definitely drug related.
Although a subject may have had 2 or more drug-related adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
All body systems are listed in which at least 1 subject had a drug-related adverse experience.

Two (2) subjects experienced laboratory AEs and both of these subjects were in the 30 mg ivermectin group.[14] There were no adverse experiences detected through pupillometry, neurological examinations, vital signs, 12-lead electrocardiogram (ECGs) or physical examinations.

[14] One was increased alanine transaminase (ALT) to approximately 2.5 times normal and elevated gamma-glutamyl transferase (GGT) to approximately 4 times normal (possibly related to study drug) and the other subject reported hematuria (which was considered as not related to study drug). Another subject (AN 0017), a 38-year-old male on placebo treatment, developed increased AST and ALT levels (up to 2 times normal) during the study period

7.1.2. Safety of ivermectin for treatment of scabies based on published literature

In the review of 22 randomised controlled trials evaluating ivermectin for treatment of scabies **(Strong, 2010),** no major safety concerns were detected. Three of 43 participants in the ivermectin group in the Usha 2000 trial reported aggravation of symptoms. No AEs were reported in Bachewar 2009. Choulea 1999 reported AEs in 4/26 participants in the ivermectin group (headache, hypotension, abdominal pain, and vomiting) and in 6/37 participants in the lindane group (headache). Madan 2001 reported an AE in 1/100 participants in the ivermectin group (severe headache); there were none in the lindane group.

Brooks 2002 reported AEs in 4/43 participants in the ivermectin group (pustular rash, cellulitis) and in 12/ 37 participants in the benzyl benzoate group (burning or stinging, dermatitis). Glaziou 1993 and Nnoruka 2001 reported AEs only in the benzyl benzoate group: 5/21 participants (mild increase in pruritus) in Glaziou 1993; and 7/29 participants (pruritus and irritation) in Nnoruka 2001. Ly 2009 reported AEs in 7/65 participants in the ivermectin group (abdominal pain, diarrhoea) and in 30/116 participants in the benzyl benzoate groups. Bachewar 2009 reported no AEs. Serious adverse events leading to death or permanent disability were not reported in any of the trials.

Comments: In this review of 22 randomised controlled trials evaluating ivermectin for treatment of scabies, no major safety concerns were detected and the AEs profile of ivermectin use in treatment of scabies appears to be similar to that observed for other indications for which it is approved.

7.2. Postmarketing experience

The sponsors have provided 1 year Periodic Safety Update Report (PSUR) for ivermectin which is a worldwide document that summarises safety data from worldwide sources, between 15 April 2010 to 14 April 2011. This report is in the format proposed by the International Conference on Harmonization.[15] [information redacted] an estimated 1,423,010 patient treatment courses for the reporting period of this PSUR. There were no patients exposed to ivermectin in Marketing Authorisation Holder (MAH) sponsored clinical trials.

During the reporting period of this PSUR, 111 spontaneous individual case safety reports (ICSRs) (63 serious) and 4 study ICSRs meeting PSUR criteria were received. All time until the cut-off date of this PSUR, 2,045 spontaneous ICSRs (1,625 serious) and 127 study ICSRs meeting PSUR criteria were received. During the reporting period of this PSUR, there were safety related updates to the CCDS (Company Core Data Sheet) for ivermectin. Updates were made to the *Dosage and Administration* section.

During the reporting period of this PSUR, 10 ICSRs (6 spontaneous, 4 study) of overdose were identified for ivermectin, from Health care professionals (HCPs). Five of the 10 reports also included adverse drug reactions (ADRs) of medication errors.

During the reporting period of this PSUR, 4 ICSRs (2 initial reports, 2 follow-up reports) of exposure during pregnancy were received (outcome was known for only 1 patient who had a normal pregnancy and delivery).

During the reporting period of this PSUR, there were 24 ICSRs of use in the elderly identified for ivermectin from HCPs 57 reports received containing serious, unlisted ICSRs received from HCPs. Of these 57 ICSRs, 35 patients were reported to have either confirmed concurrent or "suspected" loiasis infection at the time of therapy with ivermectin and are not discussed. Only

[15]Harmonized Tripartite Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, November 6, 1996 (ICH E2C). <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/Step4/E2C_R1__Guideline.pdf>

6 were significant of which 4 were related to hallucinations, delirium, coma, or related to CNS, other 2 were hepatic and dysphagia. Table 28 lists all the ICSRs reported during this PSUR. The AE reports received cumulatively till April 2010 are summarised in Table 29.

Table 28. PSUR 15 April 2010 to 14 April 2011. By System organ Class. Ivermectin. Spontaneous reports by HCPs.

System Organ Class	Total Reports N (%)	Reports with Serious ADRs			Reports with Non-serious ADRs		
		Total N (%)	Listed N (%)	Unlisted N (%)	Total N (%)	Listed N (%)	Unlisted N (%)
Blood and lymphatic system disorders	1 (1)	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Cardiac disorders	2 (2)	1 (2)	0 (0)	1 (2)	1 (2)	0 (0)	1 (2)
Congenital, familial and genetic disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ear and labyrinth disorders	7 (6)	7 (11)	7 (15)	0 (0)	0 (0)	0 (0)	0 (0)
Endocrine disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorders	12 (11)	11 (17)	6 (13)	5 (9)	1 (2)	0 (0)	1 (2)
Gastrointestinal disorders	18 (16)	11 (17)	6 (13)	5 (9)	8 (14)	6 (25)	2 (5)
General disorders and administration site conditions	47 (42)	33 (52)	28 (61)	18 (33)	14 (24)	3 (13)	11 (26)
Hepatobiliary disorders	7 (6)	3 (5)	1 (2)	2 (4)	4 (7)	3 (13)	1 (2)
Immune system disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	6 (5)	4 (6)	0 (0)	4 (7)	2 (3)	0 (0)	2 (5)
Injury, poisoning and procedural complications	10 (9)	6 (10)	6 (13)	0 (0)	6 (10)	0 (0)	6 (14)
Investigations	18 (16)	6 (10)	2 (4)	4 (7)	12 (21)	4 (17)	9 (21)
Metabolism and nutrition disorders	2 (2)	1 (2)	0 (0)	1 (2)	1 (2)	1 (4)	0 (0)
Musculoskeletal and connective tissue disorders	16 (14)	14 (22)	4 (9)	10 (18)	2 (3)	0 (0)	2 (5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	44 (40)	41 (65)	18 (39)	34 (62)	4 (7)	4 (17)	0 (0)
Pregnancy, puerperium and perinatal conditions	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	10 (9)	8 (13)	0 (0)	8 (15)	2 (3)	0 (0)	2 (5)
Renal and urinary disorders	14 (13)	10 (16)	2 (4)	8 (15)	4 (7)	1 (4)	4 (10)
Reproductive system and breast disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	7 (6)	3 (5)	0 (0)	3 (5)	4 (7)	0 (0)	4 (10)
Skin and subcutaneous tissue disorders	16 (14)	6 (10)	6 (13)	1 (2)	10 (17)	3 (13)	7 (17)
Social circumstances	2 (2)	2 (3)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
Surgical and medical procedures	7 (6)	0 (0)	0 (0)	0 (0)	7 (12)	0 (0)	7 (17)
Vascular disorders	8 (7)	5 (8)	1 (2)	4 (7)	3 (5)	1 (4)	2 (5)
DISTINCT NUMBER OF REPORTS	**111**	**63**	**46**	**55**	**58**	**24**	**42**

*A single patient report may include serious and non-serious, listed and unlisted ADRs in one or more SOCs. Therefore, the sum of reports (or ADRs) from all SOCs, or the sum of serious and non-serious, listed and unlisted reports (or ADRs), can be greater than the total distinct number of reports received.

Table 29: PSUR April 2010 to April 2011. Spontaneous reports from HCP by System Organ Class. Ivermectin.

System Organ Class	Number of Reports Received From 15-Apr-2010 to 14-Apr-2011			Number of Reports Received Cumulative to 14-Apr-2010		
	Total (Serious and Non-Serious) N (%)	Reports with Serious ADRs N (%)	Reports with Non-Serious ADRs N (%)	Total (Serious and Non-Serious) N (%)	Reports with Serious ADRs N (%)	Reports with Non-Serious ADRs N (%)
Blood and lymphatic system disorders	1 (1)	1 (2)	0 (0)	51 (3)	32 (2)	19 (3)
Cardiac disorders	2 (2)	1 (2)	1 (2)	58 (3)	53 (3)	6 (1)
Congenital, familial and genetic disorders	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	1 (<1)
Ear and labyrinth disorders	7 (6)	7 (11)	0 (0)	274 (14)	264 (17)	10 (2)
Endocrine disorders	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)
Eye disorders	12 (11)	11 (17)	1 (2)	712 (37)	692 (44)	22 (4)
Gastrointestinal disorders	18 (16)	11 (17)	8 (14)	520 (27)	414 (27)	111 (20)
General disorders and administration site conditions	47 (42)	33 (52)	14 (24)	1286 (66)	1136 (73)	173 (32)
Hepatobiliary disorders	7 (6)	3 (5)	4 (7)	55 (3)	31 (2)	24 (4)
Immune system disorders	0 (0)	0 (0)	0 (0)	6 (<1)	4 (<1)	2 (<1)
Infections and infestations	6 (5)	4 (6)	2 (3)	140 (7)	124 (8)	19 (3)
Injury, poisoning and procedural complications	10 (9)	6 (10)	6 (10)	132 (7)	53 (3)	88 (16)
Investigations	18 (16)	6 (10)	12 (21)	110 (6)	70 (4)	41 (8)
Metabolism and nutrition disorders	2 (2)	1 (2)	1 (2)	138 (7)	119 (8)	22 (4)
Musculoskeletal and connective tissue disorders	16 (14)	14 (22)	2 (3)	562 (29)	527 (34)	37 (7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	0 (0)	0 (0)	5 (<1)	5 (<1)	0 (0)
Nervous system disorders	44 (40)	41 (65)	4 (7)	1073 (55)	1000 (64)	91 (17)
Pregnancy, puerperium and perinatal conditions	0 (0)	0 (0)	0 (0)	9 (<1)	7 (<1)	3 (1)
Psychiatric disorders	10 (9)	8 (13)	2 (3)	281 (15)	262 (17)	20 (4)
Renal and urinary disorders	14 (13)	10 (16)	4 (7)	213 (11)	200 (13)	14 (3)
Reproductive system and breast disorders	0 (0)	0 (0)	0 (0)	23 (1)	12 (1)	12 (2)
Respiratory, thoracic and mediastinal disorders	7 (6)	3 (5)	4 (7)	126 (7)	115 (7)	13 (2)
Skin and subcutaneous tissue disorders	16 (14)	6 (10)	10 (17)	401 (21)	280 (18)	127 (23)
Social circumstances	2 (2)	2 (3)	0 (0)	29 (1)	28 (2)	1 (<1)
Surgical and medical procedures	7 (6)	0 (0)	7 (12)	27 (1)	4 (<1)	23 (4)
Vascular disorders	8 (7)	5 (8)	3 (5)	125 (6)	115 (7)	11 (2)
TOTAL REPORTS RECEIVED	**111**	**63**	**58**	**1,934**	**1,562**	**543**

Overall, the 4 System Organ Classes (SOCs) with the largest number of ICSRs were: General disorders and administration site conditions (47, 42%), Nervous system disorders (44, 40%) and Gastrointestinal disorders and Investigations [both SOCs with 18 reports (16%)]. Of the serious reports, the SOCs with the greatest number of reports were Nervous system disorders (41), General disorders and administration site conditions (33) and Musculoskeletal and connective tissue disorders (14). In the Nervous system disorders SOC, the most frequently reported serious ADRs were headache (15), depressed level of consciousness (15), coma (14). The most frequently reported serious ADRs in the General disorders and administration site conditions SOC were gait disturbance (15), asthenia (21) and pyrexia (11) and in the Musculoskeletal and connective tissue disorders back pain (8) and myalgia (4) were the most frequently reported serious ADRs. Of these serious ADRs, headache, asthenia, pyrexia and myalgia are listed in the CCDS for ivermectin.

During the reporting period of this PSUR, 7 initial ICSRs with a fatal outcome identified for ivermectin were received from HCPs. Indication for usage included: Acarodermatitis (4 reports), Loiasis (1 report), and *Strongyloides stercoralis* infection (2 reports). One report was received from the Mectizan Donation Program from Congo. Two reports were from a postmarketing surveillance program from Japan. Four were spontaneous reports from Japan.

7.2.1. Safety in elderly

The Worldwide Adverse Experience System (WAES) database was searched for all spontaneous reports by age for 65 years and over and 64 years and younger for patients on therapy with ivermectin for this PSUR reporting period. Reports where age of the patient was not reported were not included. There were 24 reports containing 52 events in patients 65 years and older and 66 spontaneous reports containing 257 events in patients 64 years and younger. Patients in the 65 years and older group ranged from 67 years to 96 years of age with 54% of the reports from the age group of 80 to 89 years. Patients in the 64 years and younger group ranged from 7 years of age to 62 years of age with 33% of the reports from patients 25 to 34 years of age. The patients in the 65 years and older group were predominantly male (58%). Patients in the 64 years and younger group were also predominantly male (58%). Of the 24 reports in the 65 years and older group, 83% of the reports were from Japan compared to 26% in the 64 years and younger group. Reports in the 64 years and younger group were primarily from the Congo (47 %) and Japan (26%). There were 30 and 209 serious events in the 65 years and older and 64 years and younger age groups, respectively. The 5 most frequent serious e vents for each age group were depressed/ altered level of consciousness (Tables 30 and 31). Of the 24 reports in the 65 years and older group, 21 reports (88%) were identified with treatment indication of ' acarodermatitis' or 'scabies infestation'. Of the remaining 3 reports, 1 was identified with treatment indication for 'onchocerciasis'' and 2 reports where an indication was not reported.

With regards to safety profile of ivermectin for the reviewed treatment indications of onchocerciasis, intestinal strongyloidiasis and lymphatic filariasis, no new safety issues have been identified.

Table 30. PSUR April 2010 to April 2011. Five most common concurrent conditions in patients 64 years of age and younger and 65 years of age and older for PSUR period.

65 Years and Older		64 Years and Younger	
Concurrent Conditions	**N**	**Concurrent Conditions**	**N**
Dementia	3	Loiasis	31
Asthma	2	Hospitalization	5
Cerebral Infarction	2	Malaria	5
Loiasis	2	Constipation	3
Acarodermatitis	1	Chronic Alcoholism	2

Table 31. Five most frequent serious events in patients 64 years of age and younger and 65 years of age and older for PSUR period.

65 Years and Older		64 Years and Younger	
Event	**N (%)**	**Event**	**N (%)**
Depressed Level of Consciousness**	3 (6%)	Asthenia*	20 (10)
Altered State of Consciousness**	2 (4%)	Headache*	15 (7%)
Asthenia*	1 (2%)	Gait Disturbance**	14 (7%)
Blister	1 (2%)	Coma**	13 (6%)
Blood Creatinine Increased	1 (2%)	Depressed Level of Consciousness**	12 (5)
All others	44	*All others*	135
Totals	*52*	*Totals*	*209*

* Listed in CCDS for ivermectin
**Listed in CCDS for patients with *Loa loa* treated with ivermectin

Shimizuhira, 2009 investigated the safety and number of doses of oral ivermectin required for the treatment of scabies in 40 elderly hospitalised Japanese patients (8 males, 32 females, average 83.0 years, age range 65-97 years). Patients also received topical benzyl benzoate.

During or after treatment, 5 patients showed blood chemistry abnormalities (increased lactate dehydrogenase (LDH) in 3 patients, increased alanine transaminase (ALT) in 2), but all abnormal values returned to normal ranges without treatment. Two patients died of causes related to pre existing disease: colon cancer (1) and heart failure (1). Two patients given ivermectin had previous minor liver disorders but showed no abnormal effects on liver function test (LFT) values. Because of the life cycle of Sarcoptes scabiei, it was believed that ≥2 doses separated by a 1 week interval would be required; however, only 71% (27/38) of cases of scabies were cured after 2 doses. Five patients required 3 doses and 6 patients required more than 3 doses.

7.3. Safety issues with the potential for major regulatory impact

No new data.

7.4. Other safety issues

7.4.1. Safety in special populations

No new data.

7.5. Safety related to drug-drug interactions and other interactions

No new data submitted.

7.6. Evaluator's overall conclusions on clinical safety

The sponsors have only provided one new study (066) in 40 healthy subjects which showed good tolerability and no safety concerns at doses ranging from 30 to 120mg, that is, up to 10 times the proposed dose of 200 µg/kg for treatment of scabies. The PSUR (providing safety data from April 2010 to April 2011) did not identify any new safety concerns for ivermectin.

Ivermectin has been used extensively to treat 6 million people in 30 countries for onchocerciasis caused by the filarial worm *Onchocerca* volvulus. Ivermectin also has proven effective for the human diseases, loiasis, strongyloidiasis, bancroftian filariasis and cutaneous larva migrans. Several studies have now evaluated ivermectin for human scabies. There were no significant safety concerns reported with the use of ivermectin in any of the scabies studies to date, except for one report of fatal complications in patients from a long-term care facility (Barkwell, 1997) but these were not confirmed in other studies (Alexander, 1998; Bredal, 1997; Diazgranados, 1997).

7.7. First round benefit-risk assessment

7.7.1. First round assessment of benefits

The benefits of ivermectin in the proposed usage are:

- Ease of administration as only 1 or 2 single oral doses were effective in curing typical scabies in most patients.
- Oral ivermectin can also be given safely for treatment of scabies with secondary eczematisation, erosions or ulcers where topical therapies such as permethrin, lindane and benzyl benzoate can cause serious cutaneous and systemic side effects in addition to the problem of compliance.
- Ivermectin being an efficacious and well tolerated oral treatment has the opportunity to provide a more accepted and therefore more effective mass community treatment.

- It does not have the developing resistance issues associated with the classic treatment and has the opportunity to provide a more complete and effective solution than currently exists with the classic treatments Permethrin 5% and Benzyl Benzoate 25% alone.
- Improved compliance, reduction in the need for hospitalization and a more cost-effective option compared to permethrin which is used commonly in Australia.
- Crusted scabies which is more common in immunocompromised patients responds better to combination treatment with oral ivermectin, topical scabicides and keratolytic therapy. With an increasing number of patients taking immunosuppressive medications, crusted scabies can be expected to increase in prevalence and oral ivermectin can help provide a safe and effective treatment option in these difficult cases.
- Oral ivermectin at the proposed dose of 200 μg/kg was safe and well-tolerated with no major safety issues. Study 066 in healthy subjects evaluated single oral doses up to 10 times the proposed dose and showed no major safety concerns. Furthermore, oral ivermectin has been used worldwide in more than 6 million subjects with no serious AEs.
- In developing countries, ivermectin has been used to control scabies in the community, and to reduce associated morbidity (Lawrence, 2005; Bockarie, 2000; Heukelbach, 2004). In addition, the simultaneous elimination of the most common intestinal nematodes and of other ectoparasites benefits patients in developing countries who are typically poly-parasitised (Huekelbach, 2004 and 2003).

7.7.2. First round assessment of risks

The risks of ivermectin in the proposed usage are:

- Evidence to support use of oral ivermectin as first line of treatment for typical or crusted scabies is not adequate.
- In 'typical scabies', relative efficacy of ivermectin compared to other topical scabicidal treatments showed mixed results with better or similar cure rates compared with lindane; however, permethrin and BB appeared to show similar or greater cure rates than ivermectin The clinical trials so far have lacked statistical power, so the results must be confirmed.
- In crusted scabies, majority of patients who responded to oral ivermectin were also treated with topical scabicides and/or keratolytic therapy.
- Increased risk of mortality following ivermectin treatment in elderly patients reported by Barkwell (1997); however, these risks were not confirmed in other reports (Alexander, 1998; Bredal, 1997; Diazgranados, 1997)
- Optimal dosage schemes of ivermectin and the risk of recurrence needs further attention with the aim of establishing standardised protocols.
- So far, resistance to oral ivermectin has been reported in two cases. These patients had received 30–58 doses of the drug over 4 years, indicating that resistance can be induced by repetitive treatment (Currie, 2004).

7.7.3. First round assessment of benefit-risk balance

Topical application of active substances has been the mainstay of treatment of scabies, although oral Ivermectin is being increasingly used but it is approved for scabies in very few countries. However, there is extensive experience with ivermectin for treatment of other parasitic diseases such as onchocerciasis and strongolydosis for which it has approval in Australia too.

In Australia, the standard treatment of human scabies is topical application of the pyrethroid drug permethrin in a concentration of 5% massaged into the entire area of the skin from the hairline to the feet, including the palms of the hands and soles of the feet and under the

fingernails and toenails. Treatment of crusted scabies using permethrin or other topical anti-parasitic alone is more protracted and associated with a high failure rate and many studies have shown efficacy of ivermectin in these treatment-resistant cases. .

The practicality of topical treatment for the community management of endemic scabies has been questioned due to factors such as large number of people in each house, high heat and humidity, limited opportunities for privacy to apply the cream and poor infrastructure for washing it off. Another concern is the potential for the development of drug resistance when such long-running community disease control programs achieve only limited participation and disease reduction and concerns regarding mite resistance to permethrin have recently been described in a number of Aboriginal communities in northern Australia. Hence, ivermectin may help to address the urgent need for a more suitable treatment for scabies to reduce the burden in endemic settings.

Scabies can be a difficult and complex condition to treat. Patients who have repeated infestations require extended treatment courses and could potentially promote the spread of disease to others. Buffet, 2003 reviewed the literature with an evidence-based medicine method and attempted to provide guidance on the treatment of choice for common scabies in an otherwise healthy patient and also defined the role of systemic ivermectin. Among local treatments, studies are heterogeneous according to products, countries, group of treated patients, with or without contact subjects and the method of treatment application. There are very few high proof-level controlled studies. In France, a combination of benzyl benzoate 10% and sulfiram 2% is used most. The most studied product is the cream permethrin 5%, available in the USA, UK and Australia. Its efficacy seems slightly superior to lindane and less toxic. It is more efficient than crotamitron. Concerning systemic ivermectin, 8 evaluable RCTs in this submission showed evidence for some efficacy in typical scabies but its relative efficiency over topical treatment has not been established. More data are required to justify use of ivermectin in the management of initial scabies infestation but it provides a useful alternative in cases in which standard therapies do not prove safe or effective. The obvious advantages of ivermectin in the treatment of scabies in adults and particularly for children are its ease of use as well as the avoidance of skin irritation with the application of topical scabicides which may be a particular problem in skin that is fissured and secondarily eczematized.

A few open studies showed its efficacy in institutional epidemic, crusted scabies and in HIV positive patients. It is judged to be particularly useful in institutional outbreaks of scabies, for the treatment of crusted scabies and in immunocompromised patients (Alberici, 2000; Leppard, 2000; Millership, 2002; Patel, 1999; Corbett, 1996). There is clinical evidence level III-2 (observational, open-label studies), III-3 (Case series) and IV (case reports) to support use of ivermectin in treatment of crusted scabies. It should be noted that interpretation of efficacy of ivermectin in crusted scabies was confounded by publication bias. However, the majority of evaluated patients had failed prior treatment and had received combined treatment with topical scabicides as well as keratolytic therapy. Hence, for crusted scabies, oral ivermectin provides a safe and effective therapeutic option following failure of prior therapy and is especially effective when used in combination with topical scabicidal and/or keratolytic therapy.

Ivermectin has been available since the mid 1980s and millions of individuals have been treated with it for onchocerciasis and lymphatic filariasis control programs in Africa and South America. Ivermectin seems to have little or no risk. Hence, ivermectin appears to be a safe and effective alternative for patients with treatment-resistant scabies but larger, controlled trials are required before it can be recommended in the general population or as first line of therapy due to lack of adequate evidence. However, due to considerable benefits of oral ivermectin and its good tolerability profile, it provides a good therapeutic option following failure of topical therapy or in patients in whom topical application is unsuitable or contraindicated.

Based on the evidence provided in this submission, oral ivermectin may be approved for treatment of typical and crusted scabies (confirmed with a clinical and/or parasitological

diagnosis) following failure of topical treatment or in patients in whom standard topical therapy does not prove safe or effective or is contraindicated due to skin irritation/eczematisation.

However, the benefit-risk balance of ivermectin is unfavourable given the proposed generalised usage for '*treatment of scabies*' but would become favourable if the changes recommended in *First Round Recommendation Regarding Authorisation* are adopted.

7.8. First round recommendation regarding authorisation

It is recommended that ivermectin cannot be approved for the proposed generalised indication of 'treatment of scabies'. However, due to the benefits associated with oral ivermectin therapy and its good tolerability and safety profile, it could be approved for an alternative indication as suggested.[16] Approval would be subject to incorporation of changes suggested and also satisfactory response to questions raised from this evaluation report.

8. Clinical questions

8.1. Pharmacokinetics

Nil.

8.2. Pharmacodynamics

Nil.

8.3. Efficacy

1. The reference- Gulzar, 2007 comparing topical 1% lindane cream and oral ivermectin in management of scabies was not provided in the dossier. Instead a reference by the same author on treatment of melisma with glycolic acid peel was presented which was not relevant to this submission. Could the sponsors please provide the correct reference.
2. The evaluator seeks clarification from the sponsors regarding the following in the '*Additional references*' section in the dossier:
   - The article by Chosidow, 2006[17] was not provided and in fact an earlier publication by the same author (Chosidow, 2000) was repeated in its place.
   - The publication by Coyne, 1997 was in fact identical to the publication by Bredal, 1997.

[16] Proposed Indications:
Stromectol (ivermectin) is indicated for the treatment of onchocerciasis, intestinal strongyloidiasis (anguillulosis) and human sarcoptic scabies.
Evaluator Comments: Clinical evidence for these two forms of scabies I (typical and crusted) was very different. There are some RCTs and review/met analyses based on RCTs (level IB evidence) for the indication of 'typical scabies', but these provided ambiguous results and there was no conclusive evidence to support use of ivermectin as first line of treatment for scabies. For 'crusted scabies' there are only case reports or case series (level IIIb evidence). Treatment is justified only when diagnosis of scabies is confirmed with a clinical and/or parasitological diagnosis. Hence a blanket generalised indication that ivermectin can be used for all forms of scabies is not justified and this needs to be clarified in the 'Indications' section of the proposed PI. Hence, it is recommended that the 'Indications' section of the proposed PI be replaced with the following:-
"Ivermectin is indicated for treatment of human sarcoptic scabies when prior topical treatment has failed or is contraindicated in a patient. Treatment is only 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 alone"
[17] Clinical Practice- Scabies; NEJM, 2006; 354 (18): 1718-27

8.4. Safety

Nil.

9. Second round evaluation of clinical data submitted in response to questions

9.1. Efficacy

The sponsor submitted the two articles as requested.

The first of these, Gulzar (2007), was an abstract that compared the efficacy of 1% lindane cream and oral ivermectin (both administered as 2 doses 1 week apart) in patients diagnosed with scabies on the basis of history (nocturnal itch), dermatological examination (papules, vesicles, burrows) and parasitological examination under the microscope. A total of 100 patients were selected by "convenient sampling" and then randomised to treatment. Cure criteria were absence of nocturnal itch, papules, burrows, vesicles and mite/ova on microscopy. Results were presented for 89 patients (1% lindane n=44; ivermectin n=45), with the remaining 11 patients having been "dropped later on". Oral ivermectin was reported to be significantly more effective than 1% lindane cream with complete cure rates of 69% versus 57% at Day 8; 91% versus 86% at Day 15; and 100% versus 89% at Day 30. Pvalues were reported as 0.00 for all three comparisons. Deficiencies in the abstract include absence of information about the randomisation process; statistical methods; patient demographics; details of the clinical manifestations of scabies (crusted/non-crusted) and its prior treatments; the dose of ivermectin; reasons for drop-outs; and adverse events. The study also appears to have been open label as there was no mention of double dummy treatment.

The second article was listed as a general reference article and therefore not intended by the sponsor to be evaluated for efficacy or safety. Indeed the article did not provide any additional efficacy or safety data pertinent to ivermectin but did provide valuable insights into the treatment options available to clinicians and the various factors that determine the choice of treatment.

The sponsor confirmed that Coyne, 1997 and Bredal, 1997 represent letters to the editor from different authors in response to the same issue of deaths associated with the use of ivermectin in the elderly reported by Barkwell 1997. This is response is acceptable.

9.2. Other

In addition to its response to the specific questions raised about the PI (details of which are beyond the scope of this AusPAR), the sponsor proposed that the *Indication* be amended and presented in a bullet format so as to allow a distinction between treatment with ivermectin in typical and crusted scabies, as follows:

Stromectol (ivermectin) is indicated for the treatment of:

- *Onchocerciasis and intestinal strongylodiasis (anguillulosis).*
- *Crusted scabies in conjunction with topical therapy*
- *Human sarcoptic scabies when prior topical treatment has failed or is contraindicated.*

Treatment is only 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 alone.

The sponsor submitted a *Clinical Justification* in support of the use of ivermectin as initial treatment of crusted scabies when given in combination with standard topical treatment. No new analyses of existing data were submitted to support the change, and so their justification essentially relies on consideration of the seriousness of crusted scabies and the potential risks of its ineffective treatment as follows:

- There is a high failure rate when treating crusted scabies with permethrin or other single agent anti-parasitic agents;
- An effective treatment regimen is needed in order to reduce the potential for secondary bacterial complications with *Staphylococcus aureus* and *Streptococcus py*ogenes. This is particularly pertinent in an Australian setting in which there are such high rates of acute rheumatic fever and acute post-Streptococcal glomerulonephritis among the indigenous community in central Australia;
- Crusted scabies is associated with increased morbidity and mortality, and delaying combination treatment with ivermectin and topical therapy may be deleterious to the patient; and
- Ivermectin has a recognised safety profile from extensive use of the product and is generally well tolerated.

Comment from the first round evaluator was specifically sought on this issue and is reproduced below:

The evaluator stated that:

"based on the evidence provided in the submission, it is recommended that the following indication may be approved for ivermectin:

Ivermectin is indicated for the treatment of human sarcoptic scabies when prior topical treatment has failed or is contraindicated. Treatment is only 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 alone.

The sponsor appeared to have adapted the above in their amended proposed indication of ivermectin in scabies.

The majority of publications submitted to support the use of ivermectin in crusted scabies involved use of oral ivermectin in combination with topical scabicidal therapy and/or keratolytic therapy. Furthermore, there are doubts regarding the bioavailability of ivermectin at the site of lesions due to crusting of lesion suggesting that oral ivermectin in combination with topical scabicidal and/or keratolytic therapy maybe an acceptable and more effective first line treatment for crusted scabies. Considering the risk associated with inadequate treatment of crusted scabies, we would suggest there is enough evidence to support first line use of ivermectin in combination with topical therapy in crusted scabies. However, it is important to note that the approval for the amended indication should be subject to incorporation of changes suggested in section 11 of our report."

9.3. Second round benefit-risk assessment

9.3.1. Second round assessment of benefits

The benefits remain as stated in the First Round Evaluation.

9.3.2. Second round assessment of risks

The risks remain as stated the First Round Evaluation.

9.3.3. Second round assessment of benefit-risk balance

Subject to the resolution of outstanding issues raised in this report, the benefit-risk balance for the amended proposed use of ivermectin is acceptable.

9.4. Second round recommendation regarding authorisation

Subject to the resolution of outstanding issues from this report, it is recommended that the application to vary the registration of ivermectin (Stromectol) by way of the following extended indications be approved:

> *Stromectol (ivermectin) is indicated for the treatment of:*
>
> *Onchocerciasis and intestinal strongylodiasis (anguillulosis).*
>
> *Crusted scabies in conjunction with topical therapy*
>
> *Human sarcoptic scabies when prior topical treatment has failed or is contraindicated.*
>
> *Treatment is only 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 alone.*

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