



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ivermectin

Proprietary Product Name: Stromectol

Sponsor: Merck Sharp Dohme (Australia) Pty Ltd

October 2013

TGA Health Safety
Regulation

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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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

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extensions of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	15 July 2013
<i>Active ingredient:</i>	Ivermectin
<i>Product name:</i>	Stromectol
<i>Sponsor's name and address:</i>	Merck Sharp Dohme (Australia) Pty Ltd Locked Bag 2234, North Ryde NSW 2113
<i>Dose form:</i>	Tablet
<i>Strength:</i>	3 mg
<i>Container:</i>	Blister pack
<i>Pack size:</i>	4's
<i>Approved therapeutic use:</i>	<i>Stromectol (ivermectin) is indicated for the treatment of:</i>

- *Onchocerciasis and intestinal strongyloidiasis (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.

Route of administration: Oral (PO)

Dosage: The dose for treatment of scabies is 200 µg/kg body weight. Two doses are recommended (with interval of 7 to 14 days) for treatment of typical scabies and for mild crusted scabies (in combination with a topical scabicide). At least 3 doses are recommended for treatment of moderate to severe crusted scabies.

ARTG number: 181338

Product background

Ivermectin is a broad-spectrum anthelmintic agent that has been used since the 1980s in the treatment of human parasitic infections. It is derived from the avermectins, a class of highly active broad-spectrum antiparasitic agents isolated from fermentation broths of *Streptomyces avermitilis* and is structurally similar to the macrolide antibiotics but has no antibacterial effect.

Ivermectin disrupts the function of a class of ligand-gated chloride ion channels causing persistent opening of the channels. This interaction is well studied in nematodes, with both γ -aminobutyric acid and glutamate-gated channels identified as targets.¹ However, the target of this drug in the scabies mite has yet to be identified; only a pH gated chloride channel that is sensitive to Ivermectin has been described.² It has been postulated that ivermectin causes excessive release of the neurotransmitter γ -aminobutyric acid (GABA) in the peripheral nervous system of the parasite resulting in its death. Ivermectin has no effect on mammalian GABA-mediated central nervous activity because it does not cross the blood-brain barrier in mammals.

Stromectol is approved for use in the treatment of onchocerciasis and strongyloidiasis in many countries³. However, there has not been a global initiative to register the scabies indication; registration has been on the basis of local clinical need. Merck Sharp & Dohme (Australia) Pty Ltd was approached by the National Aboriginal Community Controlled Health Organisation to make oral ivermectin available for use in scabies to address an urgent clinical need for a more suitable treatment in the Indigenous population.

It should be noted that although the sponsor had originally proposed that the extension of indication for ivermectin be simply *for the treatment of human sarcoptic scabies*, when

¹Geary TG. Ivermectin 20 years on: maturation of a wonder drug. *Trends Parasitol* 2005; **21**: 530-2.

²Mounsey K E, et al. Molecular characterisation of a pH-gated chloride channel from *Sarcoptes scabiei*. *Invert Neurosci* 2007; **7**: 149-56.

³The currently in Australia approved indication is: *Stromectol (ivermectin) is indicated for the treatment of onchocerciasis and intestinal strongyloidiasis.*

responding to the TGA's consolidated questions at the end of the first round evaluation, the sponsor asked that the proposed indications be changed to

“Stromectol (ivermectin) is indicated for the treatment of:

- Onchocerciasis and intestinal strongyloidiasis (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 change in proposed indications was unsolicited and made without the sponsor having seen the first round Clinical Evaluation Report (CER). The sponsor considered that the revised proposed indications were a better reflection of the data that had been submitted and the request was accompanied by a clinical justification. This is covered in greater detail in the second round clinical evaluation (see below and Attachment 2).

No new formulations or dosage strengths were proposed by the sponsor.

Scabies is caused by infestation with the mite *Sarcoptes Scabiei* var. *hominis*, a human pathogen that is spread by close physical contact between infected persons. Typically there is an itchy, excoriated but nonspecific rash on the trunk associated with scaly burrows on the fingers and wrists. Papular lesions and nodules (in the axillae and groin) may also be present. Scratching in response to the inflammation and itching of scabies infestation can result in impetigo. A minority of patients develop crusted scabies, a severe form of scabies characterised by crusted lesions affecting the palms and soles, and thickened and dystrophic nails. In such hosts, a compromised immune response (due to underlying conditions such as Human immunodeficiency virus (HIV), haematological malignancy and immunosuppressive treatments) fails to contain the disease and results in fulminant hyper-infestation. In Central Australia crusted scabies has been associated with human T-cell lymphotropic virus (HTLV-I) infection, although the majority of cases have no obvious immune problems.⁴

Infestation with *Sarcoptes Scabiei* is endemic in some Indigenous communities. The disease burden is summarised by the Australian Indigenous Health InfoNet⁵ which notes:

- the prevalence of scabies in remote central and northern Indigenous communities has been estimated at up to 50% in children⁶ and up to 25% in adults⁷
- the East Arnhem Regional Healthy Skin Program reported that more than 70% of children presented in 2002-2005 with scabies, almost all before they reached 2 years of age⁸;
- a study of a remote community in the Northern Territory (NT) of Australia in 2007 found that 82% of children presented with pyoderma in their first year of life and 87%

⁴Centre for Disease Control, Department of Health and Families, Northern Territory (2010). [Guidelines for Community Control of Scabies, Skin Sores and Crusted Scabies in the Northern Territory](#). 2nd edition. ePublication accessed at <www.nt.gov.au/health/cdc>.

⁵<<http://www.healthinfonet.ecu.edu.au>>

⁶Hengge UR, et al. Scabies: a ubiquitous neglected skin disease. *The Lancet Infectious Diseases* 2006; 6(12): 769-779.

⁷Carapetis JR, et al. Success of a scabies control program in an Australian Aboriginal community. *Pediatric Infectious Disease Journal* 1997; 16(5): 494-499.

⁸Lucas DB, et al. Disease burden and health-care clinic attendances for young children in remote Aboriginal communities of northern Australia. *Bulletin of the World Health Organization* 2008; 86(4): 275-281.

in their first two years⁹; and the impetigo in Indigenous communities commonly involves group A streptococcus, which is responsible for continuing outbreaks of post-streptococcal glomerulonephritis and acute rheumatic fever.^{10,11}

In Australia the current TGA approved treatments for scabies comprise topical products only. These treatments are 5% permethrin lotion and cream, and 25% benzyl benzoate lotion, with permethrin being standard treatment. 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. Long running community disease control programs have achieved only limited participation and disease reduction and concerns regarding mite resistance to permethrin have been described in a number of Aboriginal communities in northern Australia.¹²

The Australian electronic Therapeutic Guidelines (eTGs) recommend ivermectin 200 µg/kg in combination with topical scabicides and keratolytics (such as salicylic acid 5% to 10% in sorbolene cream, or lactic acid 5% plus urea 10% in sorbolene cream) for the treatment of crusted scabies, with regimens ranging from 2 single doses given a week apart in less severe cases to single doses on Days 1, 2, 8, 9 and 15 (that is, 5 single doses), with 2 further doses on Days 22 and 29 for extremely severe cases. The eTGs also state that oral ivermectin may be required if topical treatment of typical scabies has failed, with prescribers having first considered the possibility of a wrong diagnosis, an unidentified source of re-infestation, inadequate contact tracing or noncompliance with instructions. The Australian Medicines Handbook lists ivermectin as an accepted treatment for crusted scabies and scabies resistant to conventional treatments.

Regulatory status

Stromectol was first approved for marketing in Australia in 1996 as 6 mg tablets indicated for the treatment of onchocerciasis and intestinal strongyloidiasis. In 1999, 3 mg tablets were registered as replacement for the 6 mg tablets.

Currently, Stromectol® tablets are registered and approved for use *in the treatment of onchocerciasis and strongyloidiasis* in many countries globally. However, there has not been a global initiative to register the scabies indication. It has been registered for this indication on the basis of local clinical need within each specific country. For its use in the treatment of scabies, Stromectol® tablets are approved in the countries as listed in Table 1.

⁹McMeniman E, et al. Skin disease in the first two years of life in Aboriginal children in East Arnhem Land. *Australasian Journal of Dermatology* 2011; 52(4): 270-273

¹⁰Currie BJ, Carapetis JR. Skin infections and infestations in Aboriginal communities in northern Australia. *Australasian Journal of Dermatology* 2000; 41(3): 139-145.

¹¹ McDonald M, Currie BJ, Carapetis JR. Acute rheumatic fever: a chink in the chain that links the heart to the throat? *Lancet Infectious Diseases* 2004; 4(4): 240-245.

¹²Currie BJ, et al. First documentation of in vivo and in vitro Ivermectin resistance in *Sarcoptes scabiei*. *Clinical Infectious Diseases* 2004; 39: e8-12.

Table 1. World Wide Regulatory Status of Stromectol tablets use in scabies/crusted scabies.

Country:	Scabies Indication Approved:	Date of Approval of Scabies Indication:
EU (France, The Netherlands)	<i>Treatment of human sarcoptic scabies. Treatment is justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.</i>	10 December 2002
Japan	<i>Scabies - Regarding scabies, patients with definite diagnosis or patients with symptoms of scabies who have an opportunity to come into contact with these patients with definite diagnosis should be treated.</i>	21 August 2006
New Zealand	<i>Treatment of human sarcoptic scabies after prior treatment has failed. Treatment is justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.</i>	2005/2006

As can be noticed from the above table, New Zealand is the only country wherein Stromectol® tablets are approved for use as a second line treatment of human sarcoptic scabies.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

This was a literature based submission and the details of the references quoted have been listed in Attachment 2 under *References*.

Introduction

Clinical rationale

Merck Sharp Dohme Australia Pty Ltd (MSDA) was approached by the National Aboriginal Community Controlled Health Organisation (NACCHO)¹³ 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 Pharmaceutical Benefits Advisory Committee (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.

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 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.

Guidance

This submission is entirely literature based as no clinical studies were conducted by the sponsor regarding use of Stromectol for the treatment of scabies.

The literature search strategy was 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.

¹³NACCHO represents over 140 aboriginal community-controlled health services in Australia and is managed by an elected aboriginal board of directors.

Scope of the clinical dossier

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 suprathreshold doses of ivermectin and effect of food on PKs of ivermectin.
- Literature based evidence to support use of ivermectin in 'typical scabies' (37 publications)
- Literature based evidence to support use of ivermectin in 'crusted scabies' (45 publications)
- Additional references provided as supportive evidence.

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.

Good clinical practice (GCP)

Study 066 was carried out according to GCP guidelines.

Pharmacokinetics

Studies providing pharmacokinetic (PK) data

Only one new study (066) was submitted by the sponsor 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.

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, the 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.

Pharmacodynamics

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.

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.

Efficacy

The submitted published 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'.

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

The clinical evidence for efficacy of ivermectin in treatment of 'typical scabies' presented in this submission is summarised in the Table 2 below.

Table 2. 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 RCTs (level II)	Bachewar, 2009; Choulea, 1999; Ly 2009; 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.^{14,15} Compared to topical lindane, efficacy of oral ivermectin was similar¹⁶ or better¹⁷. Results of the 5 trials comparing oral ivermectin with topical application of BB (10-25%) were inconclusive with some studies showing reduced efficacy of ivermectin¹⁸, one showing greater efficacy¹⁹ and the other 3 trials showing similar efficacy of ivermectin and BB (see Table 3 below).

Table 3. Main results of the evaluable RCTs for ivermectin in treatment of typical scabies

Reference	Number 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%

¹⁴Usha V, et al. A comparative study of oral Ivermectin and topical permethrin cream in the treatment of scabies. American Academy of Dermatology, 2000; 42(2)(Part1): 236-240.

¹⁵Bachewar N P, et al. Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and Ivermectin in patients of scabies. Indian J Pharmacol, Feb 2009; 41(1): 9-14.

¹⁶Choulea E N, et al. Equivalent therapeutic efficacy and safety of Ivermectin and lindane in the treatment of human scabies. Archives of Dermatology, 1999; 135(6): 651-655.

¹⁷Madan V, et al. Oral Ivermectin in scabies patients: A comparison with 1% topical lindane lotion. Journal of Dermatology, 2001; 28(9): 481-484

¹⁸Ly F, et al. Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial. Bull World Health Organ, 2009; 87: 424-430

¹⁹Nnoruka E N, et al. Successful treatment of scabies with oral Ivermectin in Nigeria. Tropical Doctor, 2001; 31(1): 15-18.

Reference	Number of subjects	Main results
		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, 2001	58	Cure rate at 4 weeks: IV versus BB25%= 93.7% versus 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.

The majority of the evaluated patients with typical scabies in this submission were treated with ivermectin following failure of topical scabicide 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%), crotamiton (10%) and sulphur in petrolatum (2–10%). The inconclusive results of the randomised controlled trials (RCTs) comparing ivermectin to topical antiscabietic 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 4 below.

Table 4. 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
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^{20, 21, 22} 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.

²⁰Lawrence G, et al. Control of scabies, skin sores and haematuria in children in the Solomon Islands: Another role for Ivermectin. *Bulletin of the World Health Organization*, 2005; 83(1): 34-42.

²¹ Heukelbach J, et al. Selective mass treatment with ivermectin to control intestinal helminthia. *Bulletin of the World Health Organization*, 2004; 82(8): 563-71.

Heukelbach J, Winter B, Wilcke T, et al. Selective mass treatment with ivermectin to control intestinal helminthiasis and parasitic skin diseases in a severely affected population. *Bull World Health Organ* 2004; 82: 563-71.

²²Bockarie M J et al. Treatment with ivermectin reduces the high prevalence of scabies in a village in Papua New Guinea. *Acta Tropica*, 2000; 75: 127-130.

Safety

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.

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.²³ During the reporting period of this Periodic Safety Update Report (PSUR), the total drug distribution figures for ivermectin. There has been 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 ICSR 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 ICSR 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 ICSR of use in the elderly identified for ivermectin from HCPs 57 reports received containing serious, unlisted ICSR received from HCPs. Of these 57 ICSR, 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 6 were significant of which 4 were related to hallucinations, delirium, coma, or related to CNS, other 2 were hepatic and dysphagia. Table 5 lists all the ICSR reported during this PSUR. The AE reports received cumulatively till April 2010 are summarised in Table 6.

²³Harmonized 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>

Table 5. PSUR 15 April 2010 to 14 April 2011. By System organ Class. Ivermectin. Spontaneous reports by Health Care Professionals (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 SOC's. Therefore, the sum of reports (or ADRs) from all SOC's, 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 6. PSUR April 2010 to April 2011. Spontaneous reports from Health care Professionals (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.

Safety issues with the potential for major regulatory impact

No new data submitted.

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 120 mg, 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 facility²⁴ but these were not confirmed in other studies.^{25, 26, 27}

First round clinical summary and conclusions

First round benefit-risk assessment

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 eczematization, 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

²⁴Barkwell R, et al. Deaths associated with Ivermectin treatment of scabies. *The Lancet*, 1997; 349: 1144.

²⁵Alexander N D E, et al. Absence of Ivermectin associated excess deaths (letter). *Trans R Soc Trop Med Hyg*, 1998; 92: 342.

²⁶Bredal, W P. Deaths associated with Ivermectin for scabies. *Lancet*, 1997; 350 (9072), p. 216.

²⁷Diazgranados, J A, Costa, J.L. Deaths after Ivermectin treatment. *Lancet*, 1997; 349 (9066): p. 1698.

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.²¹

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 scabicial 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)²⁴; however, these risks were not confirmed in other reports.^{25,26,27}
- 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.¹⁰

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 strongyloidosis 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, 2003²⁸ 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 sulfur 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 crotamiton. 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.^{29, 30, 31, 32, 33} 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 scabicial 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

²⁸ Buffet M, et al. Current treatment for scabies. *Fundamental & Clinical Pharmacology*, 2003; 17: 217-225.

²⁹ Alberici F, et al. Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies. *British Journal of Dermatology*, 2000

³⁰ Leppard B, et al. The use of Ivermectin in controlling an outbreak of scabies in a prison. *British Journal of Dermatology*, 2000; 143(3): 520-523.

³¹ Millership S, et al. Use of Ivermectin, given orally, to control scabies in homes for the elderly mentally ill. *Communicable Disease and Public Health / PHLS*, 2002; 5(2): 144-146.

³² Atel A, et al. Crusted scabies in two immunocompromised children: Successful treatment with oral Ivermectin. *Australasian Journal of Dermatology*, 1999. 40(1): 37-40.

³³ Corbett E L, et al. Crusted ("Norwegian") scabies in a specialist HIV unit: Successful use of Ivermectin and failure to prevent nosocomial transmission. *Genitourinary Medicine*, 1996; 72(2): 115-117.

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 below (*First Round Recommendation Regarding Authorisation*) are adopted.

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.

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 was 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"

Approval would be subject to incorporation of changes suggested and also satisfactory response to questions raised from this evaluation report.

List of questions

Pharmacokinetics

Nil.

Pharmacodynamics

Nil.

Efficacy

1. The reference Gulzar, 2007³⁴ 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, 2006³⁵ was not provided and in fact an earlier publication by the same author (Chosidow, 2000)³⁶ was repeated in its place.
 - The publication by Coyne, 1997³⁷ was in fact identical to the publication by Bredal, 1997.

Safety

Nil.

Second round evaluation of clinical data submitted in response to questions**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. P values 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.

³⁴ Gulzar et al. *Comparison between effectiveness of topical 1% lindane cream and oral Ivermectin in the management of scabies*. Medical Forum Monthly, 2007; **18**(10): 7-12.

³⁵ Clinical Practice- Scabies; NEJM, 2006; 354 (18): 1718-27

³⁶ Chosidow O. *Scabies and pediculosis*. Lancet, 2000; **355**(March): 819-26.

³⁷ Coyne P. *Deaths associated with ivermectin*. Lancet, 1997; **350**: 215-6.

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 1997²⁴. This response is acceptable.

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 strongyloidiasis (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 pyogenes*. 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 scabicide 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 scabicial 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.”

Second round clinical summary and conclusions

Second round benefit-risk assessment

Second round assessment of benefits

The benefits remain as stated in the First Round Evaluation.

Second round assessment of risks

The risks remain as stated the First Round Evaluation.

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 was considered to be acceptable.

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 strongyloidiasis (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.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Sponsor's summary of the risk management plan

Although an indication for treatment of scabies with ivermectin in Australia would be available to all patients and not just the Aboriginal population, the risk of death seen with scabies where scabies is approved for use, occur in elderly, primarily debilitated patients

using multiple mediations for multiple chronic diseases. Therefore, risk of death, while not causally associated with ivermectin use, is most likely to occur in this population, and as a result, requires routine pharmacovigilance.

Safety specification

The sponsor has not identified any Ongoing Safety Concerns associated with ivermectin (see evaluator's discussion in Table 7 below).

Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance. The evaluator has no objection to the routine pharmacovigilance activities described however the safety specification remains subject to clinical and nonclinical evaluation and this will inform the appropriateness of the pharmacovigilance plan (see evaluator's discussion in Table 7 below).

Risk minimisation activities

The sponsor proposed routine risk minimisation activities (see evaluator's discussion in Table 7 below).

Table 7. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>The recommended doses for the other indications are presented in a tabulated format according to weight in the PI however the dosage recommendations for the proposed indication are not. The sponsor should provide a justification for this discrepancy in the context of minimising the risk of medication error.</p>	<p>The sponsor has proposed to add a dosage recommendation table to be consistent with dosage information for other indications for ivermectin.</p>	<p>This was considered to be acceptable.</p>
<p>The RMP should include comprehensive and careful consideration of the Important risks and the associated pharmacovigilance and risk minimisation activities however the sponsor has not identified any Ongoing Safety Concerns associated with ivermectin. Generally speaking this is highly unusual. Nevertheless the safety specification remains subject to evaluation by the clinical and nonclinical evaluators and their comments on the appropriateness of the sponsor's conclusion was awaited.</p>	<p>The sponsor will re-evaluate important identified and potential risks for inclusion in the revised RMP.</p>	<p>The evaluator was unable to comment on the appropriateness or acceptability of the "revised RMP" until it is provided to the TGA.</p>
<p><i>Section 1.5.2 Details of Important Identified and Potential Risks</i> (RMP p12) states: "Although there are Important potential risks common to ivermectin irrespective of indication (for example, Stevens-Johnson syndrome), these occur rarely and are currently monitored through routine pharmacovigilance." The sponsor should elaborate on the "potential risks common to ivermectin" and provide a substantive justification to why these are not included in the summary of Ongoing Safety Concerns irrespective of whether routine pharmacovigilance alone is proposed.</p>	<p>The sponsor will better describe the risks observed with ivermectin in all indications, and will re-evaluate the Important identified and potential risks for inclusion in the revised RMP. Proper justification will be provided for routine pharmacovigilance.</p>	<p>The evaluator was unable to comment on the appropriateness or acceptability of the "revised RMP" until it is provided to the TGA.</p>
<p>At the very least, the evaluator considered that the following should be added as Important missing information given they are populations for</p>	<p>The sponsor will include this important missing information and risk minimisation</p>	<p>The evaluator was unable to comment on the appropriateness or acceptability</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>which safety data is limited/missing:</p> <p>Use in pregnancy</p> <p>Use in lactation</p> <p>Use in paediatrics (<5years, <15kg)</p> <p>Use in impaired renal or hepatic function</p> <p>Any safety concern should also include consideration of the pharmacovigilance and risk minimisation plan for each and this should be detailed in an update to the RMP.</p>	<p>plan in the revised RMP</p>	<p>of the "revised RMP" until it is provided to the TGA.</p>
<p>The sponsor should also clarify in their responses whether a European Union (EU) RMP exists for this product and if so, the differences between the EU RMP and the Australian (AU) RMP should be provided.</p>	<p>There is no EU RMP for ivermectin.</p>	<p>This was considered to be acceptable.</p>
<p>The sponsor has concluded that there is no need for additional risk minimisation activities. The appropriateness of this conclusion is largely dependent on the sufficiency of the safety specification as determined by the clinical and nonclinical evaluators. Presumably routine risk minimisation activities (that is, product labelling) apply however statements in the PI are not currently linked to specific safety concerns which is unusual. If safety concerns are adopted, such as those suggested previously, then this section of the RMP will need to be updated to include consideration of each, even if only routine risk minimisation is proposed.</p>	<p>The sponsor will re-evaluate the Important identified and potential risks, and any associated risk minimization activities. The sponsor will also better clarify risk minimization activities as they pertain to each risk.</p>	<p>The evaluator was unable to comment on the appropriateness or acceptability of the "revised RMP" until it is provided to the TGA.</p>
<p>The Australian Poisons Information Centre telephone number should be included in the <i>Overdosage</i> section of the draft PI.</p>	<p>The phone number for the Australian Poisons Information Centre has been added to the Overdosage section of the draft PI.</p>	<p>This was considered to be acceptable.</p>

Summary of recommendations

It was considered that the sponsor's response to the TGA request for information has NOT adequately addressed all of the issues identified in the RMP evaluation report (see *Outstanding issues* below).

Outstanding issues

Issues in relation to the RMP

Much of the sponsor's response to the TGA's request for information refers to creating a "revised RMP" however the sponsor had not indicated when this will be provided to the TGA for evaluation. It was recommended to the Delegate that approval be subject to the sponsor providing a RMP acceptable to the TGA, if this application is successful.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

OMA Clinical Evaluation Report

It was noted that the clinical evaluator has also recommended an amended indication.

Suggested wording for conditions of registration

RMP

The sponsor has indicated that they plan on providing a "revised RMP" addressing the outstanding issues in the RMP evaluation report. If this application is successful, it is recommended that the provision of a RMP satisfactory to the TGA is imposed as a condition of registration.

PSUR

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

The submission contained a draft RMP and clinical data comprising one pharmacokinetic (PK) study (066) and a literature based review of efficacy and safety of ivermectin in the treatment of typical scabies (37 publications) and crusted scabies (45 publications). The literature search used by the sponsor was agreed with the TGA.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacokinetics

Study 066 was designed primarily to evaluate the safety and tolerability of oral ivermectin in support of its use for the treatment of head lice infestation (at an anticipated dosage regimen of approximately 400 µg/kg) and PK data were only collected as a secondary objective. This study did not provide any additional information on PKs at the proposed dose for the treatment of scabies. The results were consistent with those previously established, suggesting 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.

Efficacy

The published clinical data submitted in support of the efficacy of ivermectin in the treatment of scabies is summarised by National Health and Medical Research Council (NHMRC) level of evidence in the CER (Attachment 2).

Typical scabies

The evidence submitted in support of the efficacy of ivermectin in typical scabies comprised 9 published randomised controlled trials (RCTs) in which oral ivermectin was compared mainly to topical therapies in approximately 800 patients; a Cochrane systematic review³⁸ which assessed almost all of the aforementioned RCTs; and many observational studies comprising several thousands of patients.

Only 7 of the publications that reported RCTs were fully evaluable (of the remaining two, one was an abstract and the other simply contained a 5 line summary in English). Collectively, the 7 evaluable RCTs were considered to give ambiguous results for the efficacy of ivermectin in comparison with established topical therapies. Oral ivermectin appeared to be less effective than topical 5% permethrin.^{39,40} Compared to topical 1%

³⁸Strong M, Johnstone P. Interventions for treating scabies (Review). The Cochrane Collaboration. 2010

³⁹Usha V, et al. *A comparative study of oral Ivermectin and topical permethrin cream in the treatment of scabies*. American Academy of Dermatology, 2000; **42**(2)(Part1): 236-240.

⁴⁰Bachewar N P, et al. *Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and Ivermectin in patients of scabies*. Indian J Pharmacol, Feb 2009; **41**(1): 9-14.

lindane, efficacy of oral ivermectin was similar⁴¹ or better⁴². Results of the 5 trials comparing oral ivermectin with 10-25% benzyl benzoate were inconclusive with some studies showing reduced efficacy of ivermectin⁴³, one showing greater efficacy⁴⁴ and the other 3 trials showing similar efficacy. Cure rates amongst patients receiving ivermectin ranged from 43% to 95% across these studies.

Many observational studies demonstrated efficacy of ivermectin in treatment of typical scabies, especially following failure of topical therapy or in mass community treatment programs.

Crusted scabies

The evidence submitted in support of the efficacy of ivermectin in crusted scabies consisted of published case series and reports involving 260 cases, 78% of which were managed in a clinic setting following confirmation of high mite count. With a few exceptions, the dose of ivermectin used was 200 µg/kg and at least 72% of cases were treated with combination ivermectin and topical scabicide (including those from larger Australian cohort studies). The overall cure rate was reported by the sponsor to be 87%. Although the evaluator questioned how the overall cure rate was derived, it was noted that the majority of patients were adequately managed with one to two oral doses of ivermectin.

The evaluator noted the potential confounding of publication bias on the estimates of efficacy of ivermectin derived from the data set. In addition, a number of key articles lacked essential information to allow the results to be appraised in greater detail.

Safety

The most comprehensively reported safety data came from the PK study conducted in healthy volunteers (Study 066). In this study oral ivermectin administered in multiple doses of up to 60 mg given 3 times a week or in single doses of up to 120 mg (which is approximately 10 times the proposed dose of 200 µg/kg for treatment of scabies) was generally well tolerated, with no evidence of mydriatic effect or other neurological toxicity. The most commonly reported clinical AE was headache, which occurred in equal proportions of ivermectin and placebo treated subjects. Other AEs, reported in single subjects in each group, were nausea, dizziness and rash. No serious AEs were reported in the study.

The clinical evaluator found there were no significant safety concerns reported with the use of ivermectin in any of the published scabies studies, except for one report of fatal complications in elderly patients from a long-term care facility.²⁴ However, Barkwell's findings were not confirmed in subsequent studies, some of which used even higher doses of ivermectin.

Overall, the adverse event profile for ivermectin use in treatment of scabies appeared to be similar to that observed for other indications for which it is approved. In the published randomised clinical trials the main adverse events were headache, abdominal pain, mild diarrhoea and rash. Post marketing data were also provided in the form of a PSUR, covering the period April 2010 to April 2011. During the reporting period an estimated 1,423,010 patient treatment courses were administered for all indications. The most

⁴¹Chouela E N, et al. *Equivalent therapeutic efficacy and safety of Ivermectin and lindane in the treatment of human scabies*. Archives of Dermatology, 1999; **135**(6): 651-655.

⁴²Madan V, et al. *Oral Ivermectin in scabies patients: A comparison with 1% topical lindane lotion*. Journal of Dermatology, 2001; **28**(9): 481-484.

⁴³Ly F, et al. *Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial*. Bull World Health Organ, 2009; **87**: 424-430.

⁴⁴Nnoruka E N, et al. *Successful treatment of scabies with oral Ivermectin in Nigeria*. Tropical Doctor, 2001; **31**(1): 15-18.

common serious adverse drug reactions (ADRs) were asthenia (n=21), headache (n=15), gait disturbance (n=15), depressed level of consciousness (n=15), coma (n=14), pyrexia (n=11), back pain (n=8) and myalgia (n=4). In patients aged >65 years, the most commonly reported serious AEs recorded during the reporting period were depressed level of conscious (n=3), altered state of consciousness (n=2) and single cases of asthenia, blister and blood creatinine increased.

Risk management plan

The RMP evaluator noted the sponsor had proposed routine pharmacovigilance activities for ivermectin, with no additional risk minimisation activities. Although the sponsor acknowledged that potential risks such as Stevens-Johnson Syndrome were relevant to all treatment indications for ivermectin, it had not identified any Ongoing Safety Concerns. The RMP evaluator asked the sponsor to elaborate on the “potential risks common to ivermectin” and provide a substantive justification as to why these are not included in the summary of Ongoing Safety Concerns. It was felt that at the very least, the following Important missing information should be included in the RMP:

- Use in pregnancy;
- Use in lactation;
- Use in paediatrics (<5 years, <15kg); and
- Use in impaired renal or hepatic Function.

In the sponsor’s response, it was indicated that they plan on providing a “revised RMP” addressing the outstanding issues in the RMP evaluation report. However, at the time of writing this Overview the revised RMP has not been submitted. The sponsor was asked to submit and negotiate a final version of the RMP with the OPR that is compliant with the recommendations of the RMP evaluator. Implementation of the final agreed version of the RMP will be imposed as a condition of registration in the event of product approval.

Risk-benefit analysis

Delegate considerations

There is an undoubted public health need for effective treatments for scabies in the Indigenous community where scabies underlies 50-70% of streptococcal skin infections (Centre for Disease Control, NT 2010). Control of scabies is critical to controlling streptococcal skin infection and its sequelae.

Efficacy

The assessment of the efficacy of ivermectin in scabies is somewhat problematic, firstly because there was an exclusive reliance on published papers that were of variable quality with regard to the reporting of the design, conduct and execution of the trials, and secondly because almost all of the RCTs were open label, which introduces observation bias. Quality assessment of the publications was an integral part of the Cochrane systematic review conducted by Strong 2010³⁸, which revealed some limitations of the data (and, therefore, potential risks of bias) beyond those identified by the clinical evaluator for the main randomised clinical trials. The Cochrane review also highlighted that certain information pivotal to the critical appraisal of the data were lacking in these publications. These findings include:

- unclear methods used to generate randomisation sequences^{45,46,47}
- unclear allocation concealment^{40, 45, 43, 46, 42, 44}
- ambiguity regarding the extent of blinding⁴⁵; the article described only the participants as being blinded but also reported the trial to be double blind with double dummy administration of treatments);
- high rates of loss to follow-up (Bachewar 1999⁴⁰ with 22% loss to follow-up; and Madan 2001⁴² with 25% loss to follow-up). For both these studies, this was compounded by the absence of an ITT analysis of efficacy; and
- further to the above point, only Ly 2009⁴³, Nnoruka 2001⁴⁴, Usha 2000³⁹ and Macoleta-Ruiz 1993⁴⁶ included patients lost to follow up as non responders.

In light of this additional information, the key characteristics and efficacy outcomes for the main RCTs conducted in patients with typical scabies have been re-presented by this Delegate in Table 8, below. Table 8 includes results from the study conducted by Macoleta-Ruiz 1993⁴⁸, largely on the strength of additional information obtained from the authors during the Cochrane review. The study reported by Daneshpajoo 2000⁴⁹ was excluded from the Cochrane review because it was not clear if it was randomised and, thus, no further information was available beyond that contained in the abstract. Consequently, that study does not appear in the table. The results for the ivermectin treatment groups are shaded in grey for ease of identification. From the table, it can be appreciated that:

- whilst most of these studies used the proposed ivermectin dose of 200 µg/kg, a number of differing regimens were used, including: a single dose only⁴⁶; a repeat dose at 7 days in the case of treatment failure at that time point⁴⁰; a repeat dose at 14 days in the case of treatment failure^{41,39, 44, 50}; and repeated doses at both 7 and 14 days in the case of treatment failure at each of those time points⁴³. Of note, Madan 2001⁴⁷ did not specifically mention whether there were repeated treatments in the event of treatment failure. However, it seems that patients must have received multiple treatments otherwise the marked increase in cure rates from week 2 to week 4 would be implausible. Indeed, at one point in the text the authors mentioned “*after three days of drug intake*”;
- in almost all RCTs the patients had not received any antiscabetic treatment in the 4 weeks prior to study entry;
- the definition of cure ranged from an absence of clinical symptoms and signs (although in one study⁴¹ patients were considered cured even if they continued to experience mild pruritus and mild lesions) through to a complete absence of both clinical symptoms and signs and parasites on microscopy.^{39,50} However, within the limitations of the varying treatment regimens, definitions of cure and analysis populations, by week 4 the cure rates were reasonably consistent across the main efficacy studies, with the exception of Ly 2009¹⁸ who reported a cure rate of only 43% at 4 weeks (intent-to-treat (ITT) analysis), despite patients who had not responded to treatment

⁴⁵Chouela E N, et al. *Equivalent therapeutic efficacy and safety of Ivermectin and lindane in the treatment of human scabies*. Archives of Dermatology, 1999; **135**(6): 651-655.

⁴⁶ Macotela-Ruiz E, et al. *The treatment of scabies with oral Ivermectin*. Gaceta medica de Mexico, 1993; **129**(3): 201-205.

⁴⁷ Madan V, et al. *Oral Ivermectin in scabies patients: A comparison with 1% topical lindane lotion*. Journal of Dermatology, 2001; **28**(9): 481-484.

⁴⁸Macotela-Ruiz E, et al. *Treatment of scabies with oral Ivermectin in an enclosed rural community*. Dermatologia Revista Mexicana, 1996; **40**(3): 179-184.

⁴⁹Danesh Pajoo M. *The comparison of oral Ivermectin and topical Gamma Benzene Hexachloride 1% in treatment of Scabies*. Iranian Journal of Dermatology, 2000; **3**(10)

⁵⁰ Mushtaq A. Comparison of efficacy and safety of oral Ivermectin with topical permethrin in treatment of scabies Journal of Pakistan Association of Dermatologists 2010; **20**: 227-231.

at Weeks 1 and 2 being re-treated at those time points. It is of interest to note that, in this study, diagnosis was made by trained healthcare workers. Also, 61% of trial participants had negative microscopy on entering the trial. The authors justified the inclusion of such patients on the basis that the sensitivity of the test is known to be less than 50%⁵¹ and suggested the low rate of positive parasitology may have been a result of the high frequency (30%) of bacterial superinfection of the lesions. Of note, it was reported that the effectiveness of treatment was similar in parasitologically positive and negative patients with each of the treatments. Another possible explanation for the low response rate is that more than 52% patients in the ivermectin group had what the authors considered to be severe disease (≥ 6 affected sites). In comparison, Usha 2000³⁹ who reported that only 12.5% patients in their ivermectin group had severe disease observed a cure rate of 95% at 4 weeks on ITT analysis; and

- as identified by the clinical evaluator, a single dose of ivermectin was superior to placebo in a single small study involving 55 patients; a single dose of ivermectin was consistently less effective than permethrin but with repeated dosing had similar cure rates to permethrin; and no conclusion could be drawn with regard to comparisons with benzyl benzoate because of inconsistent results across the studies.

The bulk of the evidence submitted for typical scabies was actually obtained from observational studies comprising several thousands of patients. These publications, in which the majority of the evaluated patients were treated with ivermectin following failure of topical scabies treatment, provide supportive evidence of efficacy.

The Delegate agreed with the clinical evaluator that, notwithstanding the conclusions of Strong 2010³⁸ that ivermectin appeared to be an effective oral treatment, the limitations of the publications and the inconclusive results of the RCTs comparing ivermectin to topical antiscabetic agents do not justify the 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 have been ineffective or are contraindicated due to skin irritation/ eczematization. This proposed usage is consistent with the current accepted clinical practice in Australia as reflected in the eTGs. This is also the position adopted by the sponsor in relation to its revised proposed indications.

There is no doubt the evidence available to support the use of ivermectin in crusted scabies is of quite a different nature, having been generated mainly in small case series and case reports, with a clear potential for publication bias and obvious limitations for generalising results from individual experience. The sponsor has, however, mounted an argument as to why ivermectin should be used for crusted scabies as a first line oral agent in combination with topical therapy as part of its justification for its revised proposed indications. This is addressed further as part of the benefit-risk assessment.

⁵¹Grossin M. Searching for Sarcoptes. *Ann Dermatol Venereo*/2001 ; 128:69-70. PMID 11226908

Table 8. Summary of RCTs in Typical Scabies

Table 1: Summary of RCTs in typical scabies	Study design	Microscopic diagnosis	Scabietides in prior 4/52	N; % lost to follow up	Efficacy endpoint (cure)	Treatment	Dose	Cure rate		
								Wk 1	Wk 2	Wk 4
Bachewar 2009	R, C, OL	N	Y ⁶	103; 22%	No new skin lesions (papules, vesicles and classical burrows)	IV n=34 BB2 n=35 PER n=34	200µg/kg single dose ¹ Two topical applicat ² overnight ¹ Single topical applicat ² overnight ¹	56% 76% 82% p=NR	100% 92% 96% p=NR	
Choulea 1999	R, C, DB, DD	N ⁴	N	53; 19%	Absence of both pruritus and clinical lesions or a reduction of signs/symptoms to a score of 1 (mild pruritus and lesions)	IV n=26 LIN n=27	150-200µg/kg single dose ² Single topical applicat ² overnight ²		74% 54% p=0.22	95% 96% p>0.99
Ly 2009	R, C, OL	N ⁴	N	181; 12%	Disappearance of skin lesions and itching	IV n=65 BB1 n=68 BB2 n=48	150-200µg/kg single dose ² Single topical applicat ² for 24hrs ² Two topical applicat ² for 24hrs ²		25% 54% 69% p<10 ⁻⁴	43% 77% 96% p<10 ⁻⁴
Madan 2001	R, C, SB	Y	NR	200; 25%	No signs or symptoms of scabies	IV n=100 LIN n=100	200µg/kg single dose Single topical applicat ² overnight		36% 22%	83% 44% p=NR
Mustaq 2010	R, C, OL	N ⁶	N	100; 14%	Complete disappearance of itching, skin lesions and mites on light microscopy	IV n=44 ⁷ PER n=42 ⁷	200µg/kg single dose ² Single topical applicat ² overnight ²		54% 48% p=0.5	80% 88% p=0.157
Nnoruka 2001	R, C, OL	Y	N	58; NR	Complete disappearance of initial skin lesions and pruritus ⁴	IV n=29 BB1 n=29	200µg/kg single dose ² Single topical applicat ² for 72hrs ²	31% 10%	66% 35%	93% 48% p=NR
Usha 2000	R, C, OL	Y	N	85; 0	Complete clearance of pruritus, skin lesions, mites & products on microscopy	IV n=40 PER n=45	200µg/kg single dose ² Single topical applicat ² overnight ²		70% 98% p=0.003	95% 100% p=0.22
Macotela - Ruiz '93 (Summary)	R, C, DB ⁷	N ⁷	NR	55; NR	Absence of itching and no dermatologically active lesions ⁷	IV n=29 Plac n=26	200µg/kg single dose Single dose	74% 16% p<0.5 ⁷		

R randomised
IV ivermectin
C controlled
PER 5% permethrin
DB double blinded
BB1 25% benzyl benzoate one application
DD double dummy
BB2 25% benzyl benzoate two applications
OL open label
NR not reported
SB single blind (outcomes assessor)
LIN 1% lindane

¹ repeated after 1 week in cases of treatment failure. ² repeated after 2 weeks in cases of treatment failure. ³ repeated after 1 and then 2 weeks in cases of treatment failure. ⁴ parasitological microscopy was performed at study entry, but negative microscopy results (61% in Ly 2009 and not reported by Choulea 1999) did not result in exclusion. ⁵ performed only in "cases of doubt". ⁶ skin scrapings were also examined weekly for 4 weeks but results were not presented other than a rather ambiguous statement that the examination of skin scrapings after treatment did not show any eggs, larva or adult parasites. ⁷ According to Strong 2010 (and presumably based on full translation and/or contact with the authors). The IV vs. placebo treatment failure risk ratio was calculated to be 0.24 (95%CI: 0.12 – 0.51). ⁸ but not in prior 1/52. ⁹ number of patients not lost to follow up. Numbers of patients treated in each group was not reported in the paper.

Safety

Ivermectin is an old drug which has not been the subject of a formal clinical development program. Consequently there is no consolidated safety database for this drug and its safety data for the treatment of scabies is bibliographic in nature. Notwithstanding the limitations posed by the quality of reporting of safety information in the published papers, the adverse event profile for ivermectin use in treatment of scabies appears to be similar to that observed for its other indications. Headache, abdominal pain, mild diarrhoea and rash were the main adverse events reported in published clinical trials.

The main report of note was one of fatal complications in elderly patients in a long-term care facility following treatment for scabies.⁵⁸ The deaths were preceded by changes in the behaviour of the patients with anorexia, listlessness and lethargy. When these results were first published the TGA reviewed the findings in the context of a then ongoing clinical trial and found the apparent causes of death and the elapsed times between ingestion of ivermectin and death were quite diverse. At the time it was concluded that, although a statistical association was shown in the article, the totality of evidence did not support a causal role of ivermectin in the deaths. The patients had multiple intercurrent medical conditions and had also been treated repeatedly with lindane, a known neurotoxic agent. The sponsor also noted that the FDA had criticised the methodology employed by the authors and questioned whether deaths in this report had any real relationship to ivermectin.

Overall, there were insufficient numbers of elderly subjects aged 65 years and over to characterise the safety in this population. Consequently, the sponsor has proposed to include the following advice in the PI: "Clinical studies of Stromectol did not include sufficient numbers of elderly subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, treatment of elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy". This is appropriate.

The clinical evaluator did not specifically comment on safety in children. Published paediatric safety data for ivermectin are quite limited, with only summary data having been presented in many of the articles. Given the public health need outlined above, potentially significant numbers of children could be exposed to ivermectin and the absence of high quality data in this population is of some concern. The sponsor's *Clinical Overview* acknowledged there are theoretical concerns in young children (<5 years) based on observations of depression, tremors, ataxia, coma and breathing difficulties in animal studies. The sponsor pointed to the following general safety data for ivermectin in children:

- no side effects were reported in two large series of children aged 1 to 14 years treated with ivermectin for head lice (Jairi 1997; Jairi 1998); neither of these papers were included in the submission and thus the sponsor's statement could not be corroborated;
- millions of doses of ivermectin have been administered to children aged 5 to 15 years for the treatment of onchocerciasis, without reports of significant systemic complications^{52, 53};
- no adverse effects were reported from a program of mass treatment of children with scabies with 160-250 µg/kg ivermectin in the Solomon Islands; and

⁵² Meinking T L, et al. *The treatment of scabies with Ivermectin*. New England Journal of Medicine, 1995; **333**(1): 26-30.

⁵³ Gladstone H B, et al. *Crusted scabies in an immunocompetent child: Treatment with Ivermectin*. Pediatric Dermatology, 2000; **17**(2): 144-148.

- an 8 mg/kg accidental overdose (4000 times the recommended dose) in a child caused acute emesis, mydriasis and sedation which rapidly reversed.⁵⁴

The sponsor noted there was almost no data available for children aged <5 years (<15kg) treated with ivermectin. Data were available from the following papers:

- Roberts et al 2005⁵⁵; the sponsor stated that 2 children aged <5 years received up to 5-7 doses of 150-200 µg/kg ivermectin in this study without side effects. (However, this paper did not specifically mention side effects or adverse reactions or whether safety data were collected and an absence of evidence has been misconstrued as evidence of absence);
- Patel 1999; a child aged 2 years who was unresponsive to other treatments received a single dose of 200 µg/kg ivermectin. Apart from a slight increase in erythema and itch during the first 24 hours after treatment, there were no side-effects from the medication;
- Larralde 1999⁵⁶; a 4 year old child was treated with 2 doses of 200 µg/kg ivermectin administered weekly without side effects; and
- Marliere 1999⁵⁷; a child aged 2 years who was unresponsive to other multiple treatments received a single dose of 200 µg/kg ivermectin, which was “well tolerated”.

In view of the limited paediatric data, the sponsor has proposed to include precautionary advice in the PI that ivermectin should not be used in children weighing <15 kg and aged <5 years as safety in these groups has not been established. This was considered to be appropriate.

Benefit-risk assessment

The CER provides a good summary of the benefits and risks of ivermectin in relation to its proposed use in scabies.

The published data are not optima, but notwithstanding the limitations, ivermectin appears to have an acceptable level of efficacy in the treatment of *typical scabies* as a second line agent and is well tolerated with mostly mild adverse reactions in the form of headache, abdominal pain, diarrhoea and rash. The Delegate agreed that this indicates a net benefit in this setting.

The sponsor has proposed that patients with typical scabies be treated with ivermectin on 2 occasions 1-2 weeks apart. This is supported by the data obtained from the RCTs and is consistent with current clinical practice guidelines. It is also consistent with the lifecycle of the scabies mite. Given that the eggs hatch every 8 to 10 days and the serum half-life of ivermectin is 16 hours, a second dose of ivermectin should ensure eradication of any newly hatched scabietic nymphs.

With regard to crusted scabies, the qualitatively and quantitatively lower efficacy and safety data needs to be weighed against the fact that crusted scabies represents a much greater clinical challenge, with greater risks from ineffective treatment. In particular:

- crusted scabies is associated with increased morbidity and mortality;

⁵⁴Lankas G.R., Minsker D.H. and Robertson R.T. Effects of ivermectin on reproduction and neonatal toxicity in rats. *Food and Chemical Toxicology* 1989 27:8 (523-529)

⁵⁵Roberts, et al. Crusted scabies: clinical; and immunological findings in seventy-eight patients and a review of the literature. *Journal of Infection* 2005; **50**: 375-381.

⁵⁶Larralde M, et al. *Ivermectin – Responsive Crusted Scabies in Four Patients*. *Pediatric Dermatology*, 1999; **16**(1): 69-70.

⁵⁷Marliere V, et al. *Crusted (Norwegian) scabies induced by use of topical corticosteroids and treated successfully with Ivermectin*. *Journal of Pediatrics*, 1999; **135**(1): 122-124.

- there is a high failure rate when treating crusted scabies with permethrin or other single agent anti-parasitic agents and treatment is often more protracted and often requires hospitalisation; and
- septicaemia is common and frequently polymicrobial and thus an effective treatment regimen is needed in order to reduce the potential for secondary bacterial complications with *Staphylococcus aureus* and *Streptococcus pyogenes*. 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.

Although there is some conjecture as to the overall cure rate reported by the sponsor, it appears that the majority of patients with crusted scabies were adequately managed with one to two oral doses of ivermectin in combination with topical antiscabidicidal therapy. Based on the above considerations, the first round evaluator's final position was that there was enough evidence to indicate the benefit-risk balance would be favourable for the first line treatment of in crusted scabies when used in combination with topical keratinolytic and antiscabetic agents. The Delegate agreed with that position.

The dosage regimen proposed for the treatment of crusted scabies incorporates repeated dosing according to the severity of the infection. This seems reasonable given that the condition is characterised by hyperinfestation where patients may have millions of mites within heavily crusted lesions affecting the palms and soles, and within thickened and dystrophic nails. However, the sponsor's proposed regimen only includes concomitant therapy with topical scabicides. The Delegate considered that the dosage regimen within the PI should include a reference to the use of topical keratinolytics on days when scabicides are not applied to assist with the reduction of scaling that harbours the mite. Also, some concerns have been raised that a two weekly dosing interval with ivermectin can be inadequate in more severe cases, suggesting that more frequent dosing is required. This is reflected in the eTGs where it is recommended that 3 single 200 µg/kg doses of ivermectin be used on Days 1, 2 and 8 for moderate cases, and five single 200 µg/kg doses of ivermectin may be used on Days 1, 2, 8, 9 and 15, with 2 further doses on Days 22 and 29 for extremely severe cases. This regimen is consistent with that used by Roberts 2005⁵⁵ for the treatment of crusted scabies in Indigenous Australians in the largest published case series. Although the study lacked any definite efficacy endpoints such as cure rates in terms of clearing of lesions and symptoms of crusted scabies, Roberts attributed a significant decrease in mortality in the study population over the study period to the more intensive ivermectin use together with a protocol for early use of antibiotics in suspected secondary bacterial sepsis.

Request for Advisory Committee on Prescription Medicines (ACPM) advice

The Delegate requested that the ACPM discuss and provide advice on the following issues:

- whether the submitted data have adequately demonstrated the benefits and risks of the use of ivermectin as a second line agent for the treatment of typical scabies;
- whether the submitted data and benefit-risk balance are sufficient to support use the use of ivermectin in combination with topical antiscabetics as first line treatment for crusted scabies, taking into account the particular clinical challenges posed by this condition; and
- whether the recommended regimens for moderate and severe crusted scabies should be more explicit within the PI.

The Committee was also asked to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Merck Sharp & Dohme (Australia) Pty Limited (MSDA) concurred with the clinical evaluators' recommendations and the Delegate's proposed recommendations to approve the extension of the indication of ivermectin to include the treatment of scabies as follows:

Stromectol (ivermectin) is indicated for the treatment of:

- onchocerciasis and intestinal strongyloidiasis (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.

MSDA had originally proposed that the extension of indication for ivermectin be simply for the treatment of human sarcoptic scabies. However, when responding to the TGA's consolidated questions at the end of the first round evaluation, MSDA proposed to change the indication to that as stated above. The first round clinical evaluator's final position was that there is enough evidence to indicate a favourable benefit-risk balance for the first line treatment of crusted scabies when used in combination with topical keratolytic and antiscabetic agents. The Delegate agreed with the clinical evaluator's position.

Introduction

There is an unmet public health need for effective treatments for scabies in Australia. MSDA was approached by National Aboriginal Community Controlled Health Organisation (NACCHO) to make oral ivermectin available for use in scabies to address an urgent clinical need for a more suitable treatment in the Indigenous population. However, due to the lack of clinical trials conducted by MSD with ivermectin use in scabies (typical or crusted), the approach to submit a literature based application was taken to support the registration of this extended indication for Stromectol. The data supporting efficacy is therefore not robust. However, the benefits of an oral antiscabetic treatment, such as ivermectin, outweigh the risks, as elaborated in the following pages. MSDA therefore considers that, even with the limitations of the available data, there are sufficient reasons and evidence to support the approval of this proposed extended indication. The likely benefits of patient access to this oral treatment for scabies in Australia far outweigh the limitations of the data.

Adequacy of submitted data

This submission contained a draft RMP and clinical data comprising 1 pharmacokinetic (PK) study (066) and a literature based review of efficacy and safety of ivermectin in the treatment of typical and crusted scabies. The literature search used was agreed with the TGA.

Adequacy of submitted data demonstrating benefit-risk balance of the use of ivermectin as a second line agent for the treatment of typical scabies

The evidence submitted in support of the efficacy of ivermectin in typical scabies comprised 9 published randomised controlled clinical trials (RCTs) in which ivermectin was compared mainly to topical therapies; a Cochrane review which assessed almost all of the aforementioned RCTs and many observational studies, altogether comprising several thousand patients.

Across the RCTs, cure rates amongst patients receiving ivermectin ranged from 43% to 95%. The many observational studies demonstrated efficacy of ivermectin in treatment of typical scabies, especially following failure of topical therapy or in mass treatment community treatment programs.

Adequacy of submitted data demonstrating benefit-risk balance of the use of ivermectin in combination with topical antiscabietics as first line treatment of crusted scabies

The evidence submitted in support of the efficacy of ivermectin in crusted scabies consisted of published case series and reports involving 260 cases, the majority of which were managed in a clinic setting following confirmation of high mite count. The overall cure rate was reported by MSDA to be 87%. Although the evaluator questioned how this overall cure rate was derived, it was noted that the majority of patients were adequately managed with one or two oral doses of ivermectin.

Benefit-risk assessment

The standard treatment of human scabies in Australia is the topical application of permethrin 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. However, this treatment does not always prove to be efficacious. The control of scabies is critical to controlling streptococcal skin infection and its sequelae. This is particularly pertinent in an Australian setting in which there are such high rates of acute rheumatic fever and acute post-Streptococcus glomerulonephritis among the Indigenous community in central Australia. This further confirms the unmet public health need for effective treatments for scabies in Australia.

The benefits of an oral antiscabietic treatment such as ivermectin over a topical one are:

- the ease and convenience of use particularly in hot humid climates resulting in increased patient compliance,
- 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,
- in difficult-to-treat patients, for example, immunocompromised patients in whom crusted scabies is more common and where prior topical therapy has failed,
- more accepted and therefore more effective mass community treatment due to it being an efficacious and a well-tolerated oral treatment,
- suitable to reduce the burden in endemic settings,
- has a recognised safety profile from its extensive use to date.

As stated by the clinical evaluator, ivermectin seems to have little or no risks.

The most comprehensively reported safety data came from the PK study wherein healthy volunteers were administered oral ivermectin in multiple doses of up to 60 mg given 3 times a week or in single doses of up to 120 mg (which is approximately 10 times the proposed dose of 200 µg/kg for treatment of scabies). These doses were generally well-tolerated with no evidence of mydriatic effect or other neurological toxicity. The most commonly reported clinical adverse event (AE) was headache which occurred in equal proportions of ivermectin- and placebo-treated subjects. Other AEs reported were nausea, dizziness and rash. No serious AEs were reported in the study.

The clinical evaluator found that there were no significant safety concerns reported with the use of ivermectin in any of the published scabies studies, except for one report of fatal complications in an elderly patient from a long-term care facility.⁵⁸ However, Barkwell's findings were not confirmed in subsequent studies, some of which used even higher doses of ivermectin. In addition, when these results were first published, the TGA reviewed the findings in the context of a then ongoing clinical trial and found the apparent causes of death and the elapsed times between ingestion of ivermectin and death were quite

⁵⁸ Barkwell R, et al. *Deaths associated with Ivermectin treatment of scabies*. The Lancet, 1997; **349**: 1144.

diverse. At the time it was concluded that, although a statistical association was shown in the article, the totality of evidence did not support a causal role of ivermectin in the death.

Overall, the adverse event AE profile for ivermectin use in the treatment of scabies appeared to be similar to that observed for other indications for which it is approved. In the published randomised clinical trials, the main AEs were headache, abdominal pain, mild diarrhoea and rash.

Special patient populations

Elderly: There were insufficient numbers of elderly subjects aged 65 years and over to characterise the safety in this population and wording to this effect has been included under the 'Precautions' section in the PI, which the Delegate found appropriate.

Paediatrics: In view of the limited paediatric data, MSDA has proposed to include precautionary advice in the PI that ivermectin should not be used in children under 15 kg and under 5 years of age as safety in these groups has not been established. The Delegate found this appropriate.

PSUR: A PSUR was submitted covering the period April 2010-April 2011 with an estimated 1,423,010 patient treatment courses that were administered for all indications. *An updated PSUR was included with this response covering the period April 2011-April 2012.*

RMP: A Risk Management Plan (RMP) was originally submitted. The RMP evaluator raised questions and requested that a revised RMP, addressing the outstanding issues in the RMP evaluation report, be submitted. *MSDA confirms that a revised RMP incorporating the RMP evaluator's recommendations was submitted to the TGA on the 7 May 2013. All changes that were required to be made to the PI, as a result of this evaluation, have been made.*

MSDA noted the Delegate's comments to negotiate and finalise the RMP with OPR and that the implementation of the final agreed version of the RMP will be imposed as a condition of registration in the event of product approval.

Dosage regimen for moderate to severe crusted scabies in the PI

The Delegate also requested the ACPM to discuss and provide advice on the following issue:

- Should the recommended regimens for moderate and severe crusted scabies be more explicit within the PI?

The currently proposed dosage in the PI for crusted scabies is as follows:

Crusted scabies (ivermectin in combination with a topical scabicide administered as):

- Mild cases: 2 doses (1 dose on Day 1 and another dose between Day 8 and 15)
- Moderate to severe cases: More than 3 doses may be required for effective treatment.

MSDA proposed a dose for the moderate to severe forms of crusted scabies based on available clinical data. The Delegate mentioned that some concerns have been raised that a two weekly dosing interval with ivermectin can be inadequate in more severe cases, suggesting that a more frequent dosing is required. The electronic Therapeutic Guidelines (eTGs) recommend that 3 single 200 µg/kg doses of ivermectin may be used on Days 1, 2 and 8 for moderate cases and 5 single 200 µg/kg doses of ivermectin may be used on Days 1, 2, 8, 9 and 15, with 2 further doses on Days 22 and 29 for extremely severe cases. This treatment is consistent with that used by Roberts 2005⁵⁹ for the treatment of crusted scabies in Indigenous Australians in the largest published case series. Although the study lacked any definite efficacy endpoints such as cure rates in terms of clearing of lesions and

⁵⁹ Roberts L J, et al. *Crusted scabies: Clinical and immunological findings in seventy-eight patients and a review of the literature.* Journal of Infection, 2005; **50**(5): 375-381.

symptoms of crusted scabies, Roberts attributed a significant decrease in mortality in the study population over the study period to the more intensive ivermectin use together with a protocol for early use of antibiotics in suspected secondary bacterial sepsis.

MSDA had no objection to amending the dosage regimen for the moderate to severe cases of crusted scabies, in line with the Australian treatment guidelines and the Delegate's proposal.

Summary

Efficacy

The bulk of the evidence submitted for typical scabies was obtained from observational studies comprising several thousands of patients. These publications, in which the majority of the evaluated patients were treated with ivermectin following failure of topical scabies treatment, provide supportive evidence of efficacy. The Delegate agreed with the clinical evaluator that notwithstanding the conclusions of Strong 2010 (Cochrane Review)⁶⁰ that ivermectin appeared to be an effective oral treatment as a second line therapy in patients with typical scabies. However, ivermectin would provide a potentially useful therapeutic alternative for patients in whom standard topical therapies have been ineffective or are contraindicated due to skin irritation/eczematisation. This proposed usage is consistent with the current accepted clinical practice in Australia as reflected in the eTGs. The revised proposed indication reflects this position.

MSDA considered that treatment with ivermectin in crusted scabies should be first line in combination with topical therapy for all the reasons as stated above.

Safety

Ivermectin is an old medicine and has been available on the Australian market since 1997 as a 6 mg tablet. The 3 mg tablets were registered in 1999 to replace the 6 mg strength. Notwithstanding the limitations posed by the quality of reporting of safety information in the published papers, the adverse event profile for ivermectin use in treatment of scabies appears to be similar to that observed for its other indications. Headache, abdominal pain, mild diarrhoea and rash were the main adverse events reported in the published clinical trials.

Conclusions

Based on an unmet public health need for effective treatments for scabies in Australia and the benefits of an oral antiscabetic treatment, MSDA considered that the evidence submitted with this application supports the approval of this revised proposed extended indication.

MSDA proposed the use of Stromectol as a first line treatment in crusted scabies in conjunction with topical therapy and as a second line treatment in human sarcoptic scabies when prior topical treatment has failed or is contraindicated.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered this product to have an overall positive benefit-risk profile for the indication as proposed;

Stromectol (ivermectin) is indicated for treatment of:

Onchocerciasis and intestinal strongyloidiasis (anguillulosis)

Crusted Scabies in conjunction with topical therapy

⁶⁰ Strong M, Johnstone P. Interventions for treating scabies (Review). The Cochrane Collaboration. 2010

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 ACPM agreed with the Delegate that dosage regimen proposed for typical scabies is supported by the evidence submitted. However, there is limited evidence to recommend more explicit regimens for moderate and severe crusted scabies. The absence of such evidence should be countered by information in the PI about the lifecycle of the scabies mite to assist prescribers with the timing of repeat doses.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory negotiation of the Risk Management Plan.
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Information in the *Dosage and Administration* section of the PI and relevant sections of the CMI on the parasite's life cycle to support dosing regimens.
- a statement in the *Precaution* section of the PI and relevant sections of the CMI advising caution in children under 5 years or under 15 kg.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Stromectol (ivermectin 3 mg) tablets for oral administration, indicated for:

Stromectol (ivermectin) is indicated for the treatment of:

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

Specific conditions applying to these therapeutic goods

The Ivermectin (Stromectol) Risk Management Plan (RMP), version 2.0, dated 7 May 2013, included with submission PM-2012-01113-3-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety

Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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