PUBLIC SUMMARY DOCUMENT

Product: IVERMECTIN, 3 mg tablet, Stromectol®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The major submission sought Authority Required (STREAMLINED) listing for the treatment of scabies when prior topical treatment has failed or is contra-indicated and for crusted scabies in conjunction with topical therapy.

2. Background

The PBAC noted that ivermectin is currently PBS subsidised for the treatment of onchocerciasis and stronglyloidiasis. The PBAC had not previously considered a submission for ivermectin for the treatment of scabies.

The PBAC noted that the Department had approached the sponsor to invite a submission for ivermectin for scabies. The PBAC also noted the support of the National Aboriginal Community Controlled Health Organisation (NACCHO) for the availability of ivermectin for this indication.

3. Registration Status

Ivermectin is currently TGA registered for the treatment of:
a) onchocerciasis and intestinal strongyloidiasis (anguillulosis)
b) crusted scabies in conjunction with topical therapy
c) human sarcoptic scabies when prior topical treatment has failed or is contraindicated.

4. Listing Requested and PBAC's View

The submission sought the following listing:

Authority required (STREAMLINED)
Treatment of scabies when prior topical treatment has failed or is contra-indicated
Treatment of crusted scabies in conjunction with topical therapy

Note: 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 PBAC noted that the sponsor proposed additional NOTES for the restriction in the Pre-Sub-Committee Response:
NOTE: The treating physician should ensure that treatment failure with topical therapy is not due to incorrect application.
NOTE: Ivermectin is NOT REIMBURSED for first line treatment of typical scabies

Listing was sought on the basis of clinical need and cost consequence of not treating typical scabies after failure of topical treatment or crusted scabies.

The PBAC noted the significant prevalence of scabies in remote communities among both children and adults. The PBAC agreed with the ESC that scabies is a disease that is a significant problem for the indigenous population, but considered that it was appropriate that ivermectin should be available to the broader population. Scabies afflicts, for example, residents of nursing homes, prison inmates, the homeless and immunocompromised individuals.

The PBAC considered, given the difference in the proposed treatment guidelines, that separate restrictions should be created for the indications of crusted scabies and typical scabies.

The PBAC noted that, in regard to typical scabies, the sponsor presented the opinion of three clinical experts who considered that ivermectin is currently used after failure of permethrin and benzyl benzoate. The PBAC agreed with the ESC and considered that it was reasonable to expect that both permethrin and benzyl benzoate would be used before treatment with ivermectin, but leakage into first line treatment of typical scabies may occur.

The PBAC considered that the restriction should state that children aged less than 5 years and/or weighing less than 15kg should be precluded from receiving ivermectin given the precaution listed in the approved Product Information and the limited safety data[1] in this group.

The PBAC considered that true resistance to topical treatments was rare and that the continued presence of mites was more commonly due to re-infection or misapplication of (or non-compliance with) topical therapy rather than in vitro resistance. The PBAC therefore considered that the restriction should require that patients attempt treatment with both topical treatments available in Australia before using ivermectin.

The PBAC noted that the sponsor proposed an Authority Required (STREAMLINED) listing, which is consistent with the other listings for ivermectin. The PBAC considered this to be appropriate.

The proposed restriction did not detail the circumstances in which it could be determined that topical treatment has failed. According to the Therapeutic Guidelines (Dermatology) the itching of scabies may take up to 3 weeks to resolve post treatment and part of this itching may be irritation from the antiscabetic agent itself. Further use of antiscabetic agents is not recommended during this time. If oral therapy is available on the PBS it may reduce persistence with topical therapy. The PBAC considered that the restriction should specify an amount of time, guided by clinical practice, that must elapse between topical and oral therapy.

The PBAC noted that ivermectin is not ovicidal, and considered that this underlined the importance of using both doses of ivermectin to ensure complete eradication. The PBAC considered such practice could increase the efficacy of the treatment and mitigate against the development of mite-resistance to ivermectin.

[1] Bécourt et al, Treatment of scabies with oral ivermectin in 15 infants: a retrospective study on tolerance and efficacy. Br J Dermatol. 2013;169(4):931-3

5. Clinical Place for the Proposed Therapy

Scabies is a parasitic infestation of the skin caused by the mite *Sarcoptes scabiei, var hominis*, a human pathogen, which is spread by close physical contact between infected persons. Whilst the majority of patients suffer from typical scabies, some patients develop crusted scabies, a severe form of scabies characterised by crusted lesions affecting the palms and soles, and thickened and dystrophic nails. Scabies infestation can lead to pyoderma, (skin sores infested with bacteria, especially group A *streptococcus* or *Staphylococcus aureus*). These bacterial infections can cause significant morbidity and is associated with post-streptococcal glomerulonephritis (APSGN) and possibly acute rheumatic fever (ARF)/ rheumatic heart disease (RHD).

For crusted scabies, ivermectin plus topical treatment (including PBS listed permethrin) is proposed as first line treatment of crusted scabies.

For typical scabies, topical treatments permethrin cream and benzyl benzoate lotion are used first-line in Australia. Ivermectin is proposed for the treatment of patients who have failed topical therapy. The submission highlighted that ivermectin could be used in one of two ways:

- After the failure of both permethrin and benzyl benzoate; or
- After the failure of permethrin only (ivermectin replaces benzyl benzoate).

The submission claimed that 80-90% of ivermectin use for the treatment for scabies would be for patients with crusted scabies, based on the opinion of a small sample of clinical experts.

The PBAC considered that ivermectin in conjunction with topical treatment is currently the only effective treatment for crusted scabies, while the appropriate clinical place of ivermectin for the treatment of typical scabies in practice was after the failure of permethrin and benzyl benzoate.

6. Comparator

The submission proposed placebo as the main comparator.

The PBAC considered this the appropriate comparator for the treatment of crusted scabies.

The PBAC noted that benzyl benzoate is the most appropriate comparator for patients with typical scabies who have failed one round of permethrin treatment. Given the expected appropriate clinical place for ivermectin, the PBAC considered that placebo was the appropriate comparator for the treatment of typical scabies after the failure of both permethrin and benzyl benzoate.

7. Clinical Trials

The PBAC noted that no randomised control trials (RCT) have been carried out in patients with typical scabies after failure of topical treatment or in patients with crusted scabies. The submission presented one placebo-controlled trial (n=55, Macotela–Ruiz, 1993).

The PBAC noted the following issues with the applicability of the trial population to the proposed PBS population:

- This study was undertaken in patients with typical scabies, not crusted scabies.
- Patients have not failed topical therapy first or are contraindicated to topical therapy
- The age range of patients with typical and crusted scabies in the Australia are broader than in the trial population, for example, residents of nursing homes are affected by scabies outbreaks.
- Patients are treated with a single dose of ivermectin, whilst in clinical practice, at least two doses are recommended, as ivermectin is not ovicidal.

Additional studies were presented in the evaluation of the submission to analyse the comparative clinical effectiveness:

- Clinical reports (non-randomised) of ivermectin for the treatment of crusted scabies. (from Section C of the submission).
- Analysis of 5 direct trials comparing ivermectin and benzyl benzoate for the treatment of typical scabies (from the Cochrane Review, Strong and Johnstone, Interventions for treating scabies).

A table summarising the published trials presented in the submission and evaluation is shown below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
Macotela – Ruiz	The treatment of scabies with oral ivermectin.	Gac Med Mex, 1993, 129 (2) 201-205
Non-randomised studies		
Huffam	Ivermectin for Sarcoptes scabiei hyperinfestation.	International Journal of Infectious Diseases, 1998; 2(3): 152-154.
Leppard	The use of Ivermectin in controlling an outbreak of scabies in a prison.	British Journal of Dermatology, 2000; 143(3): 520-523.
Nofal	Variable response of crusted scabies to oral Ivermectin: report on eight Egyptian patients.	JEADV 2009; 23: 793-797.
Obasanjo	An outbreak of scabies in a teaching hospital: Lessons learned.	Infection Control and Hospital Epidemiology, 2001; 22(1): 13-18.
Passach	Management of endemic outbreaks of scabies with allethrin, permethrin, and Ivermectin.	International Journal of Dermatology, 2000; 39(6): 463-470.
Alberici	Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies.	British Journal of Dermatology, 2000; 142(5): 969-972.
Dia	Crusted scabies in Dakar apropos of 11 cases seen in a year.	Dakar medical, 1999; 44(2): 243-245.
Ndiaye	Crusted (Norwegian) scabies in Dakar (Senegal).	Sante (Montrouge, France), 1999; 9(4):243-248.
del Mar	Treatment of 18 children with scabies or cutaneous larva migrans using Ivermectin.	Clinical and Experimental Dermatology, 2002; 27(4): 264-267.
Klein	Ivermectin: A first-line treatment for HIV-related crusted (Norwegian) scabies.	J. Infect, 1996; 32(1): 78-79.

Larralde	Ivermectin Responsive Crusted Scabies in Four Patients.	Pediatric Dermatology, 1999; 16(1): 69-70.
Nandwani	Crusted Norwegian scabies in a specialist HIV unit.	Genitourin Med, 1996; 72: 453-454.
Pellizer	Ivermectin treatment of AIDS-related, crusted scabies.	European Journal of Dermatology,1996; 6(5): 396.
Sullivan	Successful use of ivermectin in the treatment of endemic scabies in a nursing home.	Australasian Journal of Dermatology, 1997; 38: 137-140.

The PBAC noted that no consumer comments were received for this item.

8. Results of Trials

The comparative effectiveness of ivermectin is summarised in the table below:

Results of cure/failure rate across clinical evidence

Trial ID	Ivermectin n with event/N (%)	Main comparator n with event/N (%)	Absolute difference RD± NNT (95% CI)	Relative difference RR (95% CI)
		Placebo		
Macotela–Ruiz	23/29 (79.3%)	4/26 (15.4%)	0.64 [0.44,0.84]	5.16[2.05,12.94]
Crusted scabies				
Total ivermectin use	162/182(86.8%)	N/A	N/A	N/A
Ivermectin with any topical treatment	82/102 (80.4%)	N/A	N/A	N/A
Ivermectin with permethrin	37/52 (71.2%)	N/A	N/A	N/A
ivermectin vs benzyl benzoate (failure rate)				
		benzyl benzoate		
Pooled (5 trials)	80/176 (45.5%)	88/220 (40.0%)		1.13 [0.9,1.42]

The PBAC considered that, on balance, the available clinical evidence was sufficient to inform an assessment of the comparative effectiveness of ivermectin for crusted scabies and typical scabies after failure of topical therapy. Noting the comparisons in the Cochrane Review (Strong and Johnstone), the PBAC considered that effectiveness of ivermectin was not superior to correctly applied permethrin or benzyl benzoate for the treatment of typical scabies.

The PBAC considered that clinical evidence may underestimate the treatment effect of ivermectin because one dose rather than two doses of ivermectin was used in clinical trials of typical scabies. As ivermectin is not ovicidal, the PBAC considered that a second dose separated by one to two weeks would increase the clinical cure rate.

With regard to comparative harms, the PBAC noted that in the main trial (Macotela–Ruiz), no adverse effects were observed in patients treated with either ivermectin or placebo. The Cochrane Review (Strong and Johnstone) analysed adverse events in 9 RCTs where ivermectin was used in a treatment arm (vs placebo, vs. permethrin, vs. benzyl benzoate, vs. lindane). Overall, mild and transient adverse events were observed in 4.94% of 385 trial participants receiving ivermectin, including aggravation of symptoms (0.78%), headache (0.52%), hypotension (0.26%), abdominal pain (1.56%), vomiting (0.26%) pustular rash (0.78%), cellulitis (0.26%), mild diarrhoea (0.52%).

A summary of the comparative benefits and harms for ivermectin versus placebo and versus benzyl benzoate is presented in the table below.

Benefit/harm summary: vs placebo

Outcome	N (1)	RR (95%CI)	Event rate/100 patients/treatment		Increment
			ivermectin	placebo	
Benefits[a]					
Clinical Cure, Day 7	55	5.16 (2.05,12.94)	79.3	15.4	63.9 (44,84)
Harms[b]					
Abdominal pain/ vomiting/mild diarrhoea	385		2.3	Assume 0.0	2.3

Benefit/harm summary: vs benzyl benzoate

Outcome	N (5)	RR (95%CI)[c]	Event rate/100 patients/treatment		Increment
			ivermectin	benzyl benzoate	
Benefits[b]					
Treatment failure	396	1.13 (0.91,1.42)	45.5	40.0	5.5
Harms[b]					
Abdominal pain/ vomiting/mild diarrhoea	208		10.8	0.0	10.8
Dermatitis/pruritus and irritation/burning or stinging	208		0.0	26.6	26.6

The PBAC noted that based on these trials, for every 100 patients treated for typical scabies with single dose ivermectin compared to comparator:

- 54 - 63 patients would be cured, while 60 patients would be cured of typical scabies following treatment with benzyl benzoate.
- 2-10 patients would experience abdominal adverse effects, while 27 patients would experience dermal adverse effects following treatment with benzyl benzoate.

Based on the pooled data on the treatment of crusted scabies, for every 100 patients treated with ivermectin compared to comparator, 71-87 patients would be cured.

9. Clinical Claim

The submission described ivermectin as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo. The PBAC considered that, based on the available data, this claim is likely supported for:

- Treatment of crusted scabies.
- Treatment of typical scabies when prior treatment with permethrin and benzyl benzoate has failed or is contra-indicated.

For the treatment of typical scabies when prior treatment with permethrin has failed or is contra-indicated, the PBAC considered that ivermectin is likely to be superior in terms of comparative safety over benzyl benzoate. The PBAC agreed with ESC that the claim of non-inferiority over benzyl benzoate is only weakly supported by trial data because of significant heterogeneity across trials. In all trials only a single dose of ivermectin was used, therefore treatment efficacy may have been underestimated.

10. Economic Analysis

The submission presented a cost-consequence analysis, comparing the cost of treating scabies with the cost consequence of not treating scabies. The PBAC considered that the approach was appropriate and consistent with the clinical data. The submission presented the cost per cure, based on treatment with combinations of ivermectin, permethrin and benzyl benzoate. As permethrin is already PBS listed and benzyl benzoate is not PBS listed, the incremental cost to the PBS of treating scabies is the ivermectin component of the treatment.

The PBAC considered that the data on the consequences of not treating scabies was very limited and that the submission had not quantified some potential benefits of treatment, including:

- Immediate health benefits of treating a mite infestation
- Cost avoided by a reduction in bacterial infections associated with scabies (sepsis, pyoderma, acute post-streptococcal glomerulonephritis (APSGN), and possibly acute rheumatic fever (ARF)/rheumatic heart disease(RHD))
- Infestations avoided by the treatment of 'core transmitters' (patients with crusted scabies).

The PBAC agreed with the ESC that the proposed price of ivermectin was reasonable in the context of crusted scabies. The PBAC noted that the link between scabies and APSGN is plausible based on epidemiology studies and associations identified in clinical trials[2] but the link with ARF and RHD has not been fully demonstrated. The PBAC agreed with the ESC that with the available evidence, it was appropriate to take a conservative approach in accepting the direct health benefits of treating scabies. The PBAC noted that accepting the link between scabies and ARF/RHD would be likely to have a large impact on the cost-effectiveness of ivermectin and other treatment options for scabies.

[2] *During a 3-year study, both the proportion of children with haematuria and its mean level fell while the prevalence of scabies dropped from 25% to less than 1%.*
Lawrence G et al, Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. Bull World Health Organ. 2005;83(1):34-42.

Summary of cost per cure of scabies (based on 70 kg adult patient)

Treatment	Cost per cure	Incremental cost to the PBS per cure (ivermectin)
Crusted Scabies		
ivermectin and permethrin	less than $500	less than $500
Typical scabies after failure of topical treatment		
Permethrin, then ivermectin	less than $500	less than $500
Permethrin, then benzyl benzoate, then ivermectin	less than $500	
Study		**Cost of not treating scabies**
Whitehall et al, 2013	Cost of transportation from remote areas, hospital stay (4-5 days on average)	Minimum cost per admission for treating scabies is between $5,000 and $10,000.
Skull et al, 1999	Presentation of Staph. aureus with skin sores/scabies had an average hospital stay of 59.6 days and required an average of 31.5 antibiotic treatment days	The average cost per admission with scabies/skin sores was greater than $25,000$31,088

11. Estimated PBS Usage and Financial Implications

This submission was not considered by DUSC.

In the submission, the estimated amount of ivermectin that will be used for the treatment of scabies was based on the historical supply of packs rather than on patient estimates. The number of packs estimated to be used for the treatment of scabies was calculated by subtracting the estimated total use of ivermectin in Australia (from an IMS data report of sales data from wholesalers and manufacturers direct sales and reports the sales into Retail Pharmacies and hospitals) from the use of ivermectin for the treatment of PBS listed indications (onchocerciasis and strongyloidiasis) from Medicare Australia published section 85 prescriptions) and the use of ivermectin in the Section 85 'Closing the Gap' (CTG) and Section 100 Remote Area Aboriginal Health Services (RAAHS) programmes, derived from data which was not available to the sponsor.

The likely number of packs per year was estimated in the submission to be between 10,000 – 50,000 per year in Year 5, at an estimated net cost per year to the Government of less than $10 million in Year 5.

The PBAC considered that the submission's estimate of the cost to the PBS may be overestimated for the following reasons:

- The submission assumed that the Commonwealth will fund 100% ivermectin use in Australia.
- No cost offsets were applied.
- The co-payment was assumed to be $0.

The PBAC noted that the submission, likely due to a paucity of data, was not able to estimate the proposed patient population, namely patients with crusted scabies, patients with scabies who have failed topical treatment or are contra-indicated to topical treatment. The PBAC considered that it was reasonable to accept that the majority of future use of ivermectin would be for the treatment of scabies. The PBAC considered that there is a high risk of leakage to

first-line treatment in patients with typical scabies and household contacts, given the inconvenience and poor adherence to topical treatment, the convenience of taking a tablet, and the possibility of other untreated patients with infestations or household contacts sharing unused tablets remaining in a pack.

The PBAC noted that in vivo resistance to ivermectin has been described in nematodes, mediated by the transfer of resistance genes between worms. Currie (2004)[3] reported 'evidence of ivermectin resistance in 2 patients with multiple recurrences of crusted scabies who had previously received 30 and 58 doses of ivermectin over 4 and 4.5 years, respectively', but the mechanism of resistance is unknown.

12. PBAC Outcome

The PBAC recommended the Section 85 listing of ivermectin, as an Authority Required (STREAMLINED) benefit for treatment of patients with crusted scabies in conjunction with topical therapy and for treatment of patients with typical scabies when prior topical treatment with both permethrin and benzoyl benzoate has failed or is contra-indicated. The PBAC noted that, with this listing, ivermectin for the treatment for scabies would continue to be available in the Section 100 RAASH Programme.

The PBAC was satisfied that ivermectin provides, for some patients, a significant improvement in efficacy over placebo.

The PBAC made its recommendation based on the high clinical need, modest overall financial impact to the PBS and the positive consequence of avoided health costs following treatment with scabies.

The PBAC considered that ivermectin in conjunction with topical therapy was currently the only effective treatment available for crusted scabies.

For the indication of typical scabies, the PBAC considered that there were a number of Quality Use of Medicines issues raised by the availability of ivermectin on the PBS, which may be addressed in the restriction and by prescriber and patient education.

- Maintaining proper topical treatments as first-line treatment;
- Minimising the risk of leakage of ivermectin into first-line treatment;
- Minimising the risk of mite-resistance to ivermectin;
- Minimising deviation of ivermectin to inappropriate treatment groups (first-line treatment or household contacts).

The PBAC advised that prescriber and patient education could be based on the experience of community-based education programmes associated with organisations, such as the National Aboriginal Community Controlled Health Organisation (NACCHO), the Northern Territory Department of Health - Healthy Skin Programme and the 'one disease at a time' organisation.

[3] Currie et al, First documentation of in vivo and in vitro ivermectin resistance in Sarcoptes scabiei. Clin Infect Dis. 2004 ;39(1):e8-12

The PBAC advised the Minister that under Section 101 3BA of the National Health Act, ivermectin should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

The PBAC advised that ivermectin for typical and crusted scabies is appropriate for prescribing by nurse practitioners.

The PBAC advised that the Safety Net 20 Day Rule should not apply.

Recommendation:
Add new indications:

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
IVERMECTIN tablet, 3mg, 4	2	2	Stromectol	MSD

Condition:	Crusted (Norwegian) scabies
Restriction:	Authority Required (STREAMLINED)
Treatment criteria:	Patient must be undergoing topical therapy for this condition. OR Patient must have a contra-indication to topical treatment
Clinical criteria:	The condition must be established by clinical and/or parasitological examination
Population criteria	Patient must weigh 15 kg or over; AND Patient must be 5 years of age or older.

Condition:	Human sarcoptic scabies
Restriction:	Authority Required (STREAMLINED)
Clinical criteria:	The condition must be established by clinical and/or parasitological examination. AND Patient must have completed and failed sequential treatment with topical permethrin and benzyl benzoate and finished the most recent course of topical therapy at least 4 weeks prior to initiating oral therapy. OR Patient must have a contra-indication to topical treatment
Population criteria	Patient must weigh 15 kg or over; AND Patient must be 5 years of age or older
Administrative Advice	This drug is not PBS-subsidised for first line treatment of typical scabies

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Whilst MSD welcomes the PBAC's decision to approve this much-needed product, the sponsor believes that listing in typical scabies after failure of topical therapy is overly restrictive and may prevent access to this product for some rural and remote patients.