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Our reference
2021045083

Date 20 April 2022
Subject GVS assessment of ivermectin (Stromectol®) in scabies

Dear Dr Kuipers,

In a letter dated 29 November 2021 (reference CIBG-21-02903), the (outgoing) State Secretary of Health, Welfare and Sport asked the National Health Care Institute to conduct a substantive assessment concerning inclusion of the medicinal product ivermectin (Stromectol®) in the Medicine Reimbursement System (GVS) for use in scabies. Ivermectin (Stromectol®) is available as a tablet for oral administration. Each tablet contains 3 mg of ivermectin.[1]

Ivermectin (Stromectol®)
Ivermectin belongs to a group of medicinal products known as anthelmintics (medicinal products against parasitic worms). This medicinal product selectively binds to chloride ion channels in these invertebrates' nerve cells and muscle cells. That increases cell membrane permeability, paralysing and killing the parasite.[2]

Ivermectin (Stromectol®) has been available on the Dutch market since 2003. It is indicated for the treatment of scabies, caused by *Sarcoptes scabiei*. The treatment of scabies is only indicated if the diagnosis has been established clinically and/or by parasitological examination.[1]

Other indications are:
- Intestinal strongyloidiasis (by Strongyloides stercoralis);
- Microfilaraemia in patients with lymphatic filariasis due to Wuchereria bancrofti;
- Off label: Onchocerciasis (river blindness).[1]

Application for reimbursement
Ivermectin (Stromectol®) is not currently included in the GVS. The application for reimbursement concerns the use of ivermectin (Stromectol®) to treat scabies in individuals ranging from 2 to 80 years of age. It claims that oral ivermectin (Stromectol®) has an equivalent therapeutic value to permethrin cream. The marketing authorisation holder, therefore, requests that ivermectin (Stromectol®) for the treatment of scabies be placed on List 1B of the Healthcare Insurance Regulations with a List 2 condition.

National Health Care Institute
Care
Medicinal Products

Date
20 April 2022

Our reference
2021045083

GVS assessment

Assessment of interchangeability
In the Netherlands, two other medicinal products with an indication for scabies are currently available. These are permethrin 5% cream (Loxazol®)[3] and benzyl benzoate liniment 25% FNA (Formulary of Dutch Pharmacists).[4] Permethrin 5% cream (Loxazol®) is included in the GVS on List 1B;[5] benzyl benzoate liniment 25% FNA is a pharmacy preparation [6]. Both medicinal products are administered locally, while ivermectin has an oral route of administration. Therefore, ivermectin (Stromectol®) is not interchangeable with another medicinal product included in the GVS. Therefore, ivermectin (Stromectol®) is eligible for inclusion on List 1B.

The recommended dosage is a one-off oral dose to achieve an ivermectin concentration of 200µg/kg body weight. The Dutch guidelines [2,10] recommend two treatments.

Therapeutic value
The National Health Care Institute concludes that oral ivermectin (Stromectol®) has an equivalent therapeutic value to permethrin cream in the treatment of scabies in patients ranging from 2 to 80 years of age. As a result, ivermectin (Stromectol®) complies with established medical science and medical practice.

The assessment of established medical science and medical practice is contained in **Annex 1** to this letter.

Budget impact analysis
In 2014, Dutch general practices recorded an incidence of 'scabies and disorders caused by other mites' of approximately 1 per 1000 person-years. The Netherlands Center for Occupational Diseases (NCvB) reported an increase in the number of notifications of scabies infections in the period from 2012 to 2016. However, according to the National Institute for Public Health and the Environment (RIVM), this does not accurately reflect the actual number of cases. The NCvB's figures probably involve some underreporting.[2] Figures released by the Netherlands Institute for Health Services Research (NIVEL) show that the incidence continues to rise.[11]

According to the relevant treatment guidelines, for some patient groups ivermectin for oral administration is a supplement or equivalent alternative to permethrin 5% cream.[2] Thus, the calculated budget impact is based on a substitution or market penetration of 50%. According to the Genees- en hulpmiddelen Informatie Project (GIP; Medicines and medical devices information project) database, 34,295 individuals were using permethrin cream in 2020.[7] Allowing for a market penetration of 50%, 17,148 patients are expected to use ivermectin in the third year after inclusion. It should be noted that permethrin is also available without a prescription, and that not all patients consult their general practitioner before starting treatment. It is assumed that only those patients who currently obtain permethrin on prescription will start taking ivermectin.

It is assumed that patient compliance will be 100% and that there will be two treatments per person, since the Dutch guidelines[2,3] recommend that the treatment should be administered twice. The pharmacy purchase price of ivermectin (Stromectol®) is €42.13 per 10 tablets. The recommended dosage for the treatment of scabies is two separate oral doses, to achieve an ivermectin

National Health Care Institute
Care
Medicinal Products

Date
20 April 2022

Our reference
2021045083

concentration of 200 µg/kg body weight. Assuming an average weight of about 75 kg[8], 15 mg of ivermectin – which corresponds to 5 tablets of ivermectin – will be administered. The price of ivermectin per patient is €21.07/day. The price of the total (two-stage) treatment would then be €42.14. The pharmacy purchase price of permethrin cream (Loxazol®) is €9.72 per 30 grams. The recommended dosage in adults is a maximum of 30 grams, which is equivalent to a whole tube. For children, the maximum dosage is 15 grams, but it will still be necessary to dispense a whole tube for this purpose. The price of permethrin would then be €9.72/day. Here, too, people are advised to use permethrin as a two-stage treatment. This means that the price of the total (two-stage) treatment would be €19.44. The difference is €22.70 per treatment.

Based on the above assumptions, the additional costs to the pharmaceutical budget if ivermectin (Stromectol®) were to be included in the basic health care package would amount to €389,260 in the third year after inclusion. There is considerable uncertainty with regard to prevalence, as the prevalence of scabies may be increasing. In addition, it has been assumed that there is 50% market penetration. In the event of 75% market penetration, the budget impact would amount to a maximum of €583,890.

Advice on inclusion in the GVS
The National Health Care Institute recommends that ivermectin (Stromectol®) be included in List 1B and List 2 of the Healthcare Insurance Regulations, and that it be subject to the conditions stated below. Inclusion in List 1B will lead to limited additional costs.

Condition
only for administration to an insured person for:
- *scabies*

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

Annex 1

National Health Care Institute
Care
Medicinal Products

Date
20 April 2022

Our reference
2021045083

Assessment of established medical science and medical practice

Background

Scabies
Scabies in humans is caused by the scabies mite *Sarcoptes scabiei var hominis*, which has an oval, white body with flat top and bottom surfaces, and 8 legs. This scabies mite has brushes and spines that it uses to dig tunnels in the human epidermis. The main symptoms are skin damage caused by the mite's tunnels, itching, and an inflammatory reaction in the skin. As time passes, the itching gets worse. [2]

Treatment guidelines for scabies
The treatment for scabies is specified in the *Scabies* guidelines issued by the Dutch College of General Practitioners[10] and by the National Coordination Centre for Communicable Disease Control (LCI), which is part of the RIVM. The LCI's guideline has recently been updated.[2]

Medical management consists of concomitant treatment of the patient and the treatment group with a scabicidal agent. The treatment group consists of individuals who require treatment at the same time as the patient. The purpose of concomitant treatment is to prevent individuals from becoming reinfected immediately after treatment. The guideline states that scabicidal agents are the only medicinal products that are effective in reducing itching. Antihistamines, menthol powder, and oily creams can also provide some relief from the itching.

Three scabicidal agents are currently available in the Netherlands:
- permethrin 5% cream (local);
- ivermectin tablets 3 mg (oral);
- benzyl benzoate liniment 25% FNA (local).

Table 1 below indicates which medicinal product is recommended for specific patient groups.

National Health Care Institute
Care
Medicinal Products

Date
20 April 2022

Our reference
2021045083

Table 1 Recommended medicinal product by patient group.[2]

Patient group	Recommended medicinal product
Infant <4kg	Two local treatments with benzyl benzoate 25%, with an interval of 7 days between them.
Infant / children >4 kg <15 kg and/or 5 years of age	Two treatments with local permethrin 5%, with an interval of 7 days between them. or Ivermectin 200 µg/kg p.o. Two treatments with an interval of 7 days between them.
Children >15kg / adults	Two treatments with local permethrin 5%, with an interval of 7 days between them. or Ivermectin 200 µg/kg p.o. Two treatments with an interval of 7 days between them.
Mentally/physically disabled adults and vulnerable elderly people/psychogeriatrics	Two treatments with local permethrin 5%, with an interval of 7 days between them. or Ivermectin 200 µg/kg p.o. Two treatments with an interval of 7 days between them.
Pregnant women	Two treatments with local permethrin 5%, with an interval of 7 days between them. Second option: 2 treatments with benzyl benzoate 25%, with an interval of 7 days between them.
Breastfeeding women	Two treatments with local permethrin 5%, with an interval of 7 days between them. Second option: 2 treatments with benzyl benzoate 25%, with an interval of 7 days between them. (3rd option: 2 treatments with ivermectin 200 µg/kg p.o. , with an interval of 7 days between them.)
Patient with scabies crustosa	Combination treatment by dermatologist Two to three treatments with ivermectin 200 µg/kg p.o., with an interval of 7 days between them and Two to three treatments with local permethrin 5%, with an interval of 7 days between them. Can be used together on the same day. Treat more often if necessary
Immunoincompetent patient	Two treatments with ivermectin 200 µg/kg p.o., with an interval of 7 days between them and Two treatments with local permethrin 5%, with an interval of 7 days between them. Can be used together on the same day.
Patients with extensive skin erosions or eczematous skin	Two treatments with ivermectin 200 µg/kg p.o., with an interval of 7 days between them.
Outbreaks in institutions: Affected patients (clinical scabies) and individuals from the treatment group with symptoms of scabies	Two treatments with ivermectin 200 µg/kg p.o., with an interval of 7 days between them or Two treatments with local permethrin 5%, with an interval of 7 days between them

Outbreaks in institutions: Individuals from the treatment group with no symptoms of scabies	Local permethrin 5%, one-off or Ivermectin 200 µg/kg p.o., one-off
Healthy adults/contacts from the treatment group with no symptoms of scabies	Local permethrin 5%, one-off or Ivermectin 200 µg/kg p.o., one-off

Place in the treatment
Several factors are involved when choosing between the two options – permethrin cream and oral ivermectin:

- Compliance by patients and their housemates with regard to the application of permethrin cream.[2, 10] Language barriers can make it more difficult for people to understand instructions for use, perhaps causing them to opt for oral treatment. Similar considerations apply to individuals with an intellectual disability, who may find it more difficult to follow instructions. Those who live alone may have difficulty applying permethrin to their back, so ivermectin is likely to be more effective in such cases.
- Age, contraindications, pregnancy, and breastfeeding
- Previous failures with permethrin[2, 10] or ivermectin[2]
- Group treatment in institutions, because topical administration is complicated in these settings[2,10]
- Patients' immune systems (combination therapy indicated)[2]
- The patient's wishes and/or those of their contacts[2]
- In the event of proven persistent/reinfection after 4 weeks, consult the Community Health Services (GGD) to identify the reason for this persistent/reinfection and to decide on extended or combination therapy[2].

Desirable and undesirable effects

Description of the literature
A literature review using the search terms "ivermectin", "permethrin", and "scabies" yielded a single Cochrane meta-analysis that directly compared the effectiveness and safety of permethrin cream, ivermectin cream, and oral ivermectin.This 2018 study by Rosumeck et al. included 15 controlled studies with a total of 1896 scabies patients ranging from 2 to 80 years of age. The studies were mainly conducted in southern Asia and North Africa. The primary endpoint was complete recovery from scabies 7, 14, and 30 days after the start of treatment. The secondary outcomes were the number of re-treated participants, the occurrence of adverse effects, and the number of drop-outs due to adverse effects. In the meta-analysis, Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of evidence.[9]

Desirable effects
In the pooled analysis, after one week significantly more individuals in the permethrin treatment group had completely recovered than those in the ivermectin treatment group. The figures were 43% versus 65% (RR 0.65; 95% CI 0.54-0.78), low-quality evidence. After two weeks, the difference in effect was no longer significant (RR 0.91; 95% CI 0.76-1.08), low-quality evidence. After four weeks, the absolute effect on complete recovery was comparable and was around

90% (RR 1.00; 95% CI 0.86-1.16), high-quality evidence based on a single study. Two analyses investigating the effect of multiple doses also showed no significant difference in terms of complete recovery after four weeks. **Table 2** lists the results on the primary endpoint, complete recovery after 7, 14, and 30 days.

Table 2 Results in terms of complete recovery after 7, 14, and 30 days in Rosumeck et al. 2018

Outcome parameter	Absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants	GRADE according to Rosumeck et al.
	Risk with permethrin cream	Risk with oral ivermectin			
Complete recovery week 1	654 per 1000	425 per 1000 (353 to 510)	RR 0.65 (0.54 to 0.78)	613 (6 RCTs)	Low
Complete recovery week 2	744 per 1000	677 per 1000 (565 to 804)	RR 0.91 (0.76 to 1.08)	459 (5 RCTs)	Low
Complete recovery week 4 (one administration for both medicinal products)	900 per 1000	900 per 1000 (774 to 1000)	RR 1.00 (0.86 to 1.16)	80 (1 RCT)	High
Complete recovery week 4 (1 to 3 doses for both medicinal products)	932 per 1000	857 per 1000 (764 to 959)	RR 0.92 (0.82 to 1.03)	581 (5 RCTs)	Low
Complete recovery week 4 (2 doses of IVER vs. 1 dose of PERM)	900 per 1000	873 per 1000 (747 to 1000)	RR 0.97 (0.83 to 1.14)	80 (1 RCT)	High
*The risk in the intervention group (and the 95% CI) is based on the assumed risk in the control group and the relative effect of the intervention (and the 95% CI). CI: confidence interval. IVER: ivermectin.PERM: permethrin. RCT: randomized controlled trial.					

The above results indicate that oral ivermectin and local permethrin are comparable in terms of the desirable effect of complete recovery.

Undesirable effects
Rosumeck et al. indicated that the included studies were suboptimal in terms of the reporting of adverse effects. **Table 3** below lists the results.

Table 3 Results of adverse effects and drop-outs due to adverse effects in Rosumeck et al. 2018

Outcome parameter	Absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants	GRADE according to Rosumeck et al.
	Risk with permethrin cream	Risk with oral ivermectin			
Number of	0 per 1000	0 per 1000	No estimate	55 (1 RCT)	Moderate

participants with ≥1 AE – week 2					
Number of participants with ≥1 AE – week 4	39 per 1000	51 per 1000 (14 to 190)	RR 1.30 (0.35 to 4.83)	502 (4 RCTs)	Low
Termination of participation in the study due to AE – week 4	0	0	-	305 (3 RCTs)	Moderate
*The risk in the intervention group (and the 95% CI) is based on the assumed risk in the control group and the relative effect of the intervention (and the 95% CI). AE: adverse events (adverse effects). CI: confidence interval. RCT: randomized controlled trial.					

The adverse effects listed in the Summaries of Product Characteristics (SmPC) of ivermectin (Stromectol®) and permethrin (Loxazol®) are presented in **Table 4**.

Table 4 Adverse effects of oral ivermectin (in scabies)/permethrin cream according to their SmPCs.[1, 3]

Frequency	Oral ivermectin	Permethrin cream
	A transient increase in itching may occur at the start of scabies treatment.	
Frequent (1-10 %)		itching, (erythematous) rash, dry skin, paraesthesia, burning sensation in the skin.
Rarely (0.01-0.1%)		Headache.
Very rarely (<0.01%)	Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS).	Dyspnoea, skin scratching, folliculitis and skin hypopigmentation.
Unknown	Transient hypereosinophilia, liver function disorder including acute hepatitis, elevation of liver enzymes, hyperbilirubinaemia and haematuria.	Contact eczema, urticaria. Nausea.

There is a slight difference between the adverse effects reported for oral ivermectin and those reported for permethrin cream. Based on the above results, oral ivermectin does not appear to pose a greater risk of undesirable effects than permethrin cream.

Conclusion

Based on the above results, the National Health Care Institute concludes that oral ivermectin (Stromectol®) has an equivalent therapeutic value to permethrin cream in the treatment of scabies in patients ranging from 2 to 80 years of age. As a result, ivermectin (Stromectol®) complies with established medical science and medical practice.

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