Medicines Adverse Reactions Committee

Meeting date	10/06/2021	Agenda item	3.1.1
Title	**Consideration of bufexamac medicines under section 36 of the Medicines Act 1981**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Bufexamac	**Product name**	**Sponsor**	
PHARMAC funding	Not applicable		
Previous MARC meetings	144th Meeting - 2 December 2011 Consideration of bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives (s36) Other indications were not considered at this meeting.		
International action	The Australian Therapeutic Goods Administration (TGA) removed bufexamac-containing products from the Australian Register of Therapeutic Goods (ARTG) on 18 September 2020 due to an unacceptable risk of serious skin reactions and inadequate evidence that bufexamac is effective.		
Prescriber Update	None		
Classification	General sale medicine for topical products containing bufexamac ≤ 5% (Topical products containing bufexamac > 5% are classified as Prescription)		
Usage data	N/A		

Advice sought	**The Committee is asked to advise:**
	• Whether the Minister should
	  ○ Prohibit the sale or supply of bufexamac medicines or
	  ○ impose conditions on the sale or supply of the medicine
	• Whether additional actions are required such as reclassification.
	• Any further communication (in addition to MARC's Remarks and the previously published Safety Communication) is needed.		

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1 PURPOSE

Medsafe is referring bufexamac to the MARC to complete a process initiated under section 36 of the Medicines Act 1981. The section 36 notice was sent to the sponsor of an approved bufexamac-containing medicine after the Therapeutic Goods Administration (TGA) removed all bufexamac-containing medicines from the Australian Register of Therapeutic Goods (ARTG).

2 BACKGROUND

2.1 Bufexamac

Bufexamac is a non-steroidal anti-inflammatory medicine for topical application.

Bufexamac is an active ingredient in Antiseptic Soothing Cream (bufexamac 50 mg/g, chlorhexidine gluconate 1 mg/g, and lidocaine hydrochloride 10 mg/g), which is a General Sale medicine indicated for the treatment of insect bites, stings and itches, and minor burns and sunburn. Antiseptic Soothing Cream (Multichem NZ Ltd) was the only product containing bufexamac with approved status when the section 36 notice was issued in December 2020. The product had not been supplied since 2018 and the sponsor lapsed the approval in April 2021.

2.2 Serious skin reactions associated with bufexamac

Serious skin reactions have been reported overseas following the use of topical bufexamac-containing products. The TGA determined that the benefit-risk balance of bufexamac-containing products is unacceptable and removed bufexamac-containing products from the ARTG on 18 September 2020 [1].

On 20 October 2020, the New Zealand sponsor for Antiseptic Soothing Cream, Multichem NZ Ltd, informed Medsafe of the action taken by the TGA. The sponsor noted that Antiseptic Soothing Cream had been out of stock in New Zealand since 2018 but an order had been placed with the manufacturer to resupply the product to the market. The sponsor asked whether Medsafe intended to follow the TGA and revoke the approval in New Zealand.

On 10 December 2020 Medsafe issued a notice under section 36(1) of the Medicines Act 1981, requesting the sponsor to provide evidence of the safety and efficacy of Antiseptic Soothing Cream within 60 days[1]. The information requested included:

1. A summary of the efficacy of bufexamac in the approved indication, including absolute numbers of the patients expected benefits where available and data on the efficacy of comparators.
2. A review of all spontaneous reports of suspected adverse reactions to bufexamac and a review of the literature on safety of bufexamac.
3. Information on the number of patients using Antiseptic Soothing Cream in New Zealand.
4. Any analyses of clinical trial data that may have been performed.
5. Any other relevant information you may have.
6. Proposals for risk minimisation plans for New Zealand.

[1] Medsafe initially sent the notice to the sponsor on 27 October 2020, but the email was not received as the sponsor had not notified Medsafe of a change in the pharmacovigilance contact person. The letter was resent on 10 December 2020 and the 60 days are counted from this date.

Medsafe comment

A section 36 notice is a request by Medsafe (on behalf of the Director General) for the sponsor to provide evidence that a medicine is safe and effective for the therapeutic purpose for which it is sold. If the sponsor is unable to satisfy Medsafe that the benefit-risk balance for the medicine remains favourable. Medsafe may refer the matter to the Medicines Adverse Reactions Committee (MARC) under section 36(2) of the Act.

The MARC may advise the Minister to:

- Prohibit the sponsor from selling or supplying the medicine (ie, revoke the consent for distribution) or
- Impose conditions on the sale or supply of the medicine.

Medsafe also issued a Safety Communication on 10 December 2020: Antiseptic Soothing Cream: review of the benefits and risks requested under section 36 of the Medicines Act 1981.

The sponsor responded on 17 December 2020. The response did not include evidence of the product's safety or efficacy. Instead, the company confirmed that the product was not currently supplied in New Zealand, and sought feedback on two possible future actions to address the potential safety concerns:

- [redacted]
- [redacted]

Medsafe considered that the sponsor's proposal [redacted] would not satisfy the section 36 requirements. [redacted]

As the sponsor did not provide evidence of safety and efficacy in response to the section 36 notice, Medsafe decided to refer the matter to the MARC under section 36(2) of the Act. Medsafe notified the sponsor of this intended action on 23 April 2021.

On 27 April 2021, the sponsor requested Medsafe to change the registration status for Antiseptic Soothing Cream to 'approval lapsed'.

2.3 Previous action taken in New Zealand

Medsafe previously reviewed the benefit-risk balance for bufexamac in 2011, after products containing bufexamac were withdrawn from the European market due to concerns of allergic contact dermatitis (**Annex 1**). The European Medicine Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) had concluded that the benefits of bufexamac do not outweigh its risks and recommended that the marketing authorisations for medicines containing bufexamac be revoked throughout the European Union [2].

At the time, two products containing bufexamac had consent for distribution in New Zealand:

- Paraderm (bufexamac) – indicated for *relief of dermatitis, rash and hives*

- Paraderm Plus (bufexamac, lidocaine, chlorhexidine) – indicated for *cuts, abrasions, insect bites, stings, itches, sunburn and minor burns*

Medsafe issued a section 36 notice to the sponsor (Pfizer New Zealand Limited) requesting safety and efficacy data to support the continued consent for distribution of their medicines in New Zealand.

Medsafe considered that the information provided by the sponsor for the single ingredient product Paraderm did not support a favourable benefit-risk balance. The matter was therefore referred to the MARC under section 36(2) of the Medicines Act 1981.

Medsafe referred the issue to the MARC in 2011, asking the Committee to consider the benefit-risk balance of bufexamac-containing medicines indicted for the relief of dermatitis, rash and hives (**Annex 2**). The MARC discussed the issue at the 145th meeting on 10 March 2011 (Minutes - 145th MARC meeting: 3.1.1 Consideration of bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives under section 36 of the Medicines Act 1981). The Committee concluded that the benefit-risk profile of bufexamac-containing medicines was unfavourable for the indication *relief of dermatitis, rash and hives*. The Committee recommended that the consents to distribute bufexamac-containing medicines indicated for *the relief of dermatitis, rash and hives* should be revoked.

The combination product, Paraderm Plus, was not included in the MARC's recommendation. The product could continue to be marketed, but with conditions imposed by Medsafe under section 36(3)b of the Act. The conditions included removal of *cuts and abrasions* from the indication and addition of a label warning about the risk of skin reactions. The approval for Paraderm Plus lapsed on 30 October 2013.

Antiseptic Soothing Cream, which contains the same ingredients as Paraderm Plus, was approved on 10 July 2014. It is indicated for *insect bites, stings and itches, and minor burns and sunburn* and carries the same label warnings that were required for Paraderm Plus.

2.4 CHMP Assessment of bufexamac-containing medicines

On 12 January 2010, the German Federal Institute for Drugs and Medical Devices (BfArM) notified the EMA of its intention to revoke the marketing authorisations for bufexamac-containing medicines due to an increased risk of serious allergic contact dermatitis and risk factors for contact sensitisation to bufexamac. Consequently, the EMA referred the matter to the Committee for Medicinal Products for Human Use (CHMP) for review. [3]

The CHMP reviewed the benefit-risk balance of bufexamac-containing medicinal products, noting that contact allergic dermatitis is difficult to differentiate from the underlying condition for which bufexamac is used.

The CHMP considered that:

- The risk of developing a contact allergic reaction to bufexamac is high, and the risk is higher in patients with pre-disposing conditions, such as certain forms of eczema. The allergic reactions can be serious enough to require hospitalisation.
- Bufexamac is a potent and frequent sensitiser, even after short-term use. The risk of allergic reactions increases with repeated exposure due to sensitisation.
- The adverse skin reactions are very similar to the indication, which may lead to delays in diagnosis and treatment. Cases of contact allergic reaction are likely to have been under-reported due to the difficulty in differentiating between treatment failure and an allergic reaction.
- Data presented to the CHMP to support the effectiveness of bufexamac were very limited. Studies dating from the development of bufexamac in the 1970s and 1980s were not of a high enough standard to confirm efficacy. More recent controlled studies provided very limited evidence of efficacy for bufexamac for dermatological and proctological indications.

The CHMP concluded that medicinal products containing bufexamac for topical use are harmful under the normal conditions of use, and the benefit-risk balance for bufexamac is not favourable. The Committee therefore recommended that the marketing authorisation for medicinal products containing bufexamac should be revoked.

2.5 Data sheets

2.5.1 New Zealand

Antiseptic Soothing Cream does not have a data sheet as it is classified as a general sale product, for which data sheets are not required.

2.6 Usage

Antiseptic Soothing Cream has been out of stock in New Zealand since March 2018, and the last batch supplied to the New Zealand market expired in October 2019.

No information is available on the usage of Antiseptic Soothing Cream prior to the stock outage in 2018 as the product is a general sale medicine.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Schnuch et al, 2005

A common and insidious side-effect: allergic contact dermatitis caused by bufexamac used in the treatment of dermatitis. Results from the Information Network of Departments of Dermatology (IVDK) [4]

This paper was published in German in the *Deutsche medizinische Wochenschrift* (German Medicines Weekly).

The study was conducted to estimate the incidence of allergic contact dermatitis (ACD) to bufexamac. During the study period (July 1999 to December 2004) patch tests of bufexamac 5% were conducted on 39,392 unselected patients from 40 German dermatology departments in the IVDK[2]. The tests were read at 72 hours. The dichotomised test results were analysed for possible risk factors from the patients' history and clinical diagnosis using Poisson regression analysis.

Contact allergy to bufexamac was diagnosed in 560 of 39392 patients (1.4%, 95% confidence interval 1.3-1.5), standardised for sex and age. The Poisson regression analysis indicated a significantly increased risk associated with multiple sensitisation, perianal eczema, underlying atopic dermatitis, leg dermatitis, and female gender. Patients from Eastern Germany had a lower risk than for patients in other areas, but this was explained by lower prescriptions rates in that region.

Extrapolation of frequency of the allergic response in the study to the whole German population yielded an incidence rate of approximately 6000 cases per year.

The authors concluded that in view of the high frequency of sensitisation, the pitfalls in diagnosis, the severity of the course of disease and the lack of efficacy of the drug, the risk-benefit ratio was critical.

Medsafe comment

The study was published in German and only the English abstract was accessed for this review.

Limitations such as the generalisability of the study findings were not discussed in the abstract.

[2] *Informationsverbund Dermatologischer Kliniken* (Information Network of Departments of Dermatology)

The study recruited patients from a dermatology clinic. The study population is likely to be at greater risk of an allergic skin reaction to bufexamac skin testing than the population in general due to a higher prevalence of atopic skin conditions in this population. It is also not clear from the available information what proportion of patients had previously been exposed (sensitised) to bufexamac.

In New Zealand, bufexamac (in combination with lidocaine and chlorhexidine) is approved for the treatment of insect bites, stings and itches, and minor burns and sunburn (not dermatitis). The population exposed to bufexamac in New Zealand is therefore likely to differ significantly from the study population, so the results cannot be generalised.

3.1.2 Pan and Nixon, 2012

Allergic contact dermatitis to topical preparations of bufexamac [5]

This Australian study was similar to the earlier study by Schnuch *et al*. The authors retrospectively reviewed the patch test database at the Skin and Cancer Foundation Inc. and identified 19 cases of positive reactions to bufexamac (5% petrolatum) from 451 people patch tested. The bufexamac reaction was considered relevant to the presenting dermatitis in 13 of 19 (68%) patients. The authors noted the severity and the unusually polymorphic eruptions observed in some of the cases.

The authors concluded that bufexamac allergic contact dermatitis is under-reported in the English literature and that clinicians should consider the possibility of allergic contact dermatitis to bufexamac-containing preparations in all patients where there is a history of exposure, even if used for only a short time.

3.2 CARM data

As at 31 May 2021, the Centre for Adverse Reactions Monitoring has received four spontaneous reports of adverse reactions associated with the use of bufexamac.

[redacted]

Table 1. CARM case reports for adverse reactions associated with products containing bufexamac (to 31 March 2021)

Report ID	Date	Age (years)	Sex	Medicine(s)	Reaction
009260	Apr 1980	90	M	Bufexamac	Localised skin reaction
010416	Oct 1981	49	F	Bufexamac	Rash
055343	Mar 2003	52	F	Paraderm Plus	Contact dermatitis
138462	Sep 2020	35	M	Paraderm Plus Budesonide/eformoterol Testosterone	Application site dermatitis

4 DISCUSSION AND CONCLUSIONS

Under section 36(1) of the Medicines Act 1981, Medsafe requested the sponsor of Antiseptic Soothing Cream (containing bufexamac) to provide evidence that the product is safe and effective for the therapeutic purpose for which it is sold.

The sponsor did not provide the evidence requested, but instead proposed [redacted] Medsafe's view was that neither action proposed by the sponsor would satisfy the section 36 requirements [redacted]. Medsafe proceeded to refer the matter to the MARC for its advice under section 36(2).

On notification of the proposed referral to the MARC, the sponsor requested Medsafe to change the status of the medicine to 'approval lapsed'. It is possible that a sponsor may wish to submit an application for a bufexamac-containing product in the future. Medsafe is therefore seeking advice from the MARC on whether, under section 36(3), to:

a) prohibit the importer or manufacturer from selling or supplying the medicine or
b) impose conditions on the sale or supply of the medicine by the importer or manufacturer.

Furthermore, topical medicines containing bufexamac ≤ 5% are classified as 'general sale' so they can easily be imported into New Zealand. Given the risk of dermatological reactions associated with the use of bufexamac, the Committee may wish to recommend referring bufexamac to the Medicines Classification Committee to review its classification.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the Minister should
  - Prohibit the sale or supply of bufexamac medicines or
  - impose conditions on the sale or supply of the medicine
- Whether additional actions are required such as reclassification.
- Any further communication (in addition to MARC's Remarks and the previously published Safety Communication) is needed.

6 ANNEXES

1. Review of the risk-benefit profile for bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives under section 36 of the Medicines Act 1981. (Medsafe, 2011)

2. MARC Report: *Consideration of bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives under section 36 of the Medicines Act 1981*. 145th MARC Meeting (10 March 2011).

7 REFERENCES

1. Therapeutic Goods Administration. 2020. *Bufexamac. Safety advisory - risk of serious skin reactions* 8 September 2020. www.tga.gov.au/alert/bufexamac (26 May 2020).
2. European Medicines Agency. 2010. *Bufexamac* 22 April 2010 (last updated 10 November 2011). www.ema.europa.eu/en/medicines/human/referrals/bufexamac (26 May 2021).
3. European Medicines Agency. 2010. *CHMP Assessment Report for bufexamac containing medicinal products. (EMA/CHMP/232654/2010)* 22 April 2010.
4. Schnuch A, Gefeller O and Uter W. 2005. [A common and insidious side-effect: allergic contact dermatitis caused by bufexamac used in the treatment of dermatitis. Results from the Information Network of Departments of Dermatology (IDVK)]. *Deutsche medizinische Wochenschrift (1946)* 130(50): 2881-2886. 10.1055/s-2005-923320
5. Pan Y and Nixon R. 2012. Allergic contact dermatitis to topical preparations of bufexamac. *Australasian Journal of Dermatology* 53(3): 207-210. https://doi.org/10.1111/j.1440-0960.2012.00876.x