

Summary of data on the benefits and risks for bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives

This is a summary of the risk-benefit review undertaken by Medsafe and provided to the Medicines Adverse Reactions Committee (MARC) to assist in their consideration of bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives.

This review was triggered by the withdrawal of similar medicines in Europe by the European Medicines Agency (EMA) and was referred to the MARC under section 36 of the Medicines Act 1981.

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1.0 BACKGROUND

1.1 *What is bufexamac?*

Bufexamac is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs work by blocking the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins which promote inflammation, pain and fever. By blocking the COX enzymes, NSAIDs reduce prostaglandin levels throughout the body, resulting in a reduction of ongoing inflammation, pain and fever. The mechanism of action and pharmacokinetic properties of bufexamac have not been established.

1.2 *What bufexamac-containing medicines are available in New Zealand?*

Bufexamac was first approved for use in New Zealand in August 1977 under the trade name Parfenac. There are two bufexamac-containing medicines approved in New Zealand – Paraderm and Paraderm Plus.

Paraderm is the only bufexamac-containing medicine in New Zealand indicated for the relief of dermatitis, rash and hive, while the approved indications for Paraderm Plus differ from these. **Therefore Paraderm is the only product which will be included in this section 36 review.**

1.3 *What is Paraderm?*

Paraderm is a topical cream, which contains 5.1% bufexamac as the sole active ingredient. It is a Pharmacy only medicine approved for the *rapid relief from dermatitis, rashes and hives*. Paraderm has not been marketed in New Zealand since 2002. There are a number of alternatives available for the same indications, including topical corticosteroids and antihistamines.

1.4 *Where else is bufexamac available?*

Bufexamac remains available for the treatment of dermatitis in Switzerland. While bufexamac is approved in Australia, it is not approved for dermatitis, rash or hives. All medicines containing bufexamac are in the process of being withdrawn in the European Union (see section 5.1) and have never been available in the United States of America or Canada.

2.0 DETAILS OF THE INDICATIONS

The information contained in the following sections on skin conditions was obtained from DermNet NZ – the website of the New Zealand Dermatological Society (www.dermnetnz.org) on 21 February 2011.

2.1 Dermatitis

Dermatitis is a general term that describes an inflammation of the skin. The New Zealand Dermatological Society states that dermatitis affects about one in every five people at some time in their lives. It results from a variety of causes and has various patterns. The terms 'dermatitis' and 'eczema' are often used interchangeably. Triggers such as psychological stresses can provoke or aggravate dermatitis, presumably by suppressing normal immune mechanisms.

Various types of dermatitis include:

- Atopic dermatitis which is particularly present in children often with a family history of dermatitis or asthma.
- Contact dermatitis which is provoked irritants.
- Allergic contact dermatitis due to skin contact with certain substances usually identifiable with patch testing.
- Seborrhoeic dermatitis, like dandruff, due to irritation from toxic substances produced by yeasts on the scalp and face.
- Infective dermatitis which is usually provoked by a bacterial or fungal infection.
- Gravitational dermatitis, which arises on the lower legs of the elderly due to swelling and poorly functioning leg veins.

Topical steroids are the most commonly used medical treatments for relieving the symptoms of dermatitis, sometimes followed by antibiotics, antihistamines or systemic steroids if topical steroid treatment fails.

2.2 Rash

A rash is a change of the skin which affects its colour, appearance or texture. A rash may be localised or generalised. Rashes may be itchy, warm, bumpy, dry, cracked, blistered and/or swollen and may be painful. The presence of a rash may be a sign or symptom which can aid in the diagnosis of certain conditions. The causes, and therefore treatments for rashes, vary widely. Common rashes can usually be easily treated using steroid topical creams (such as hydrocortisone) or non-steroidal treatments.

2.3 Hives

Hives (urticaria) are raised, often itchy, red patches and weals on the surface of the skin. The release of chemicals such as histamine from mast cells in the skin causes blood vessels to leak and results in tissue swelling. The weals can be a few millimetres or several centimetres in diameter, often surrounded by a red flare and frequently itchy. Hives can result from exposure to an allergen, or from an autoimmune disease. More commonly, there is no evidence for autoantibodies and the patient is said to have idiopathic urticaria.

Treatment for hives depends on the type of urticaria, its severity and how long it has been present. Oral antihistamines control wealing and itching for the majority of patients but do not affect the underlying cause. Other treatments may include oral steroids, tricyclic medications, antileukotriene agents, antimalarials, antibiotics, immunosuppressants, antifibrinolytic agents or ultraviolet radiation treatment.

3.0 EFFICACY OF BUFEXAMAC

Medsafe reviewed the literature provided by the sponsor that evaluated the efficacy of bufexamac in the relief of dermatitis, rash and hives.

3.1 *Dermatitis*

Study reports for almost 20 controlled, double-blinded trials were provided by the sponsor in support of bufexamac in the relief of symptoms of various types of dermatitis and eczema. These studies claim that bufexamac is an equi-effective treatment compared with topical corticosteroids containing fluocinolone, betamethasone and dexamethasone. However, the studies were undertaken in the 1970s, with between 20 and 40 participants in each and were generally of a lower standard than expected with today's good clinical research practice.

In a larger double-blind, controlled, multicentre trial in 193 patients found that triamcinolone and hydrocortisone produced a statistically significant benefit over bufexamac. Furthermore, there was no statistically significant difference in effect between bufexamac and placebo (excipients of the bufexamac cream).¹

The sponsor also provided two uncontrolled studies relating to the general anti-inflammatory effects of bufexamac investigating its efficacy in dermatitis. One of these was provided by the sponsor as a study report which detailed a study undertaken in 1973 which investigated the clinical efficacy of bufexamac in 35 patients with acute inflammatory skin diseases. Treatment lasted approximately seven days with favourable results obtained in 82.9% of the cases. The second study provided by the sponsor employed an open survey design to investigate the efficacy of bufexamac in 50 patients with mild to moderately severe dermatoses. Evaluation and grading of lesions were done at the initial visit and over three follow-up visits scheduled at weekly intervals. Clinical response was given an overall score for each patient which was further delineated by weighting. Overall evaluations of efficacy revealed good responses in 86%. The conditions failing to respond were chiefly neurodermatitis and psoriasis. The authors noted that patients with seborrheic, contact or solar dermatitis tended to respond most favourably to bufexamac with scores above the median.² Although these uncontrolled studies suggest that bufexamac is as useful in the relief of inflammatory skin diseases, they did not include any active comparator or placebo controls.

Medsafe notes that many of the studies provided by the sponsor in support of the efficacy of bufexamac in dermatitis were carried out in the 1970s and early 1980s when clinical trial standards were lower than they are today. Furthermore the studies were underpowered and subject to chance improvement and observer bias. Many of the studies also lacked clear definitions of the indications being treated. One of the largest of the controlled studies identified, found no significant difference between bufexamac and placebo. Therefore, these studies cannot be considered to provide good evidence of efficacy for bufexamac in the relief of dermatitis.

¹ Christiansen J., et al. (1977). Efficacy of bufexamac (NFN) cream in skin diseases. A double-blind multicentre trial. *Dermatologica*. **154**(3): 177-184.

² Solano E. (1980). General dermatologic use of hydroxamic acid. *Clinical Therapeutics*. **3**(4): 229-233.

3.2 Rash

Medsafe noted that no studies were provided by the sponsor which investigated the efficacy of bufexamac in the relief of rash. Therefore it cannot be concluded that bufexamac is efficacious in the treatment of rash.

3.3 Hives

Medsafe noted that no studies were provided by the sponsor which investigated the efficacy of bufexamac in the relief of hives. Therefore it cannot be concluded that bufexamac is efficacious in the treatment of hives.

4.0 SAFETY OF BUFEXAMAC

There is limited information available on the overall established safety profile for bufexamac from reliable sources. In its assessment of the safety profile of bufexamac, Medsafe reviewed the following:

- The French Summary of Product Characteristics for Parfenac.
- Spontaneous data from the sponsor provided to the EMA.
- The PSUR for Parfenac.
- Data from the Centre for Adverse Reactions Monitoring (CARM).
- Published literature and internal reports provided by the sponsor.

Local intolerance to bufexamac causing burning and irritation has been attributed to components of the cream. Urticaria, folliculitis, and pyoderma can occur when occlusive dressings are used. An erythema multiforme-like rash associated with contact dermatitis has also been reported.³

4.1 European Summary of Product Characteristics

As Paraderm is a Pharmacy only medicine, the sponsor is not required to provide a data sheet or CMI for this product in New Zealand. As part of their response to the section 36 notice, the sponsor provided Medsafe with a copy of the French Summary of Product Characteristics (SPC) which is considered to be the Reference Safety Information for Parfenac (a European brand name for a topical medicine containing bufexamac only).

The French SPC states that Parfenac is indicated for the symptomatic treatment of pruritus from inflammatory skin conditions. It contraindicates the use of bufexamac in patients with hypersensitivity to bufexamac (or the excipients of Parfenac), in patients with contact eczema, atopic dermatitis, infected skin or nappy rash. It also contraindicates use in patients with injured skin (wounds, burns, oozing or ulcerated lesions).

³ Meyler's Side Effects of Drugs. *Fifteenth edition*.

The *Warnings* section of the French SPC advises that bufexamac is an allergenic substance and therefore the risks of use should be weighed against the expected benefit and that in the event of allergy, treatment should be discontinued. The *Warnings* section also advises that repeated treatment on large areas, on damaged skin, or under occlusion may cause systemic effects. These effects are particularly worrisome in infants and young children because of the risk presented by the surface/weight ratio and the phenomenon of spontaneous occlusion in skin folders under diapers.

The *Precautions* section of the French SPC states that in the case of bacterial or mycotic secondary infection, use of bufexamac should be preceded by specific treatment.

The *Adverse Effects* section of the French SPC notes the possibility of allergic contact eczema and allergic skin manifestations (sometimes extensive or generalised) particularly on damaged skin. It also advises that although trans-cutaneous absorption of bufexamac is very low, the risk of systemic effects inherent in non-steroidal anti-inflammatory agents cannot be ruled out entirely.

4.2 Review of spontaneous data presented to the EMA

Medsafe provided the MARC with a review of safety data which was provided by the sponsor to the European Medicines Agency (EMA) for their review of the risk-benefit profile for bufexamac-containing medicines.

The data included sales data and a review of the European sponsor's pharmacovigilance database with a focus on adverse event reports of epidermal and dermal conditions.

Almost half of the reports identified the indication for bufexamac, most of which specified the use of bufexamac for eczema and dermatitis. Contact dermatitis and eczema were also the most frequently reported adverse events, raising the possibility that lack of efficacy could be the explanation for some these adverse events.

Eczema and dermatitis were also the most frequently reported terms in serious reports. An analysis of the data by Medsafe identified the three most commonly reported epidermal and dermal adverse events associated with bufexamac resulting in hospitalisation as being eczema (15.9% of total hospitalisations), contact dermatitis (8.9%) and erythematous rash (5.8%). Other commonly reported events which resulted in hospitalisation were condition aggravated (4.9% of total hospitalisations), pyrexia (2.7%) and hypersensitivity (2.1%).

Medsafe noted that the frequency of reports of contact dermatitis and rate of hospitalisations could not be determined because sales data does not allow a reasonable estimate of patient exposure due to different indications, and various dosage regimens.

However, the number of serious reports and the number of dermatological adverse events resulting in hospitalisation is concerning. No data was provided on the reason for hospitalisation in each case e.g., serious adverse skin reactions, severity of the underlying condition, infective complications or perhaps it may be simply that the patient was admitted to hospital for patch-testing. Furthermore, it is also unclear whether the reports of dermatitis could simply reflect lack of efficacy of bufexamac rather than a true adverse event.

4.3 Periodic Safety Update Report

Medsafe provided the MARC with a review of the Periodic Safety Update Report (PSUR) for Parfenac (a bufexamac cream, emulsion, lotion and ointment that was available in Europe). No new safety signals were identified in the PSUR.

4.4 New Zealand experience

During the period between 1965 and 30 June 2010, the Centre for Adverse Reactions Monitoring received three reports associated with bufexamac-containing medicines, the last of which was reported in March 2003. All of the reported adverse events related to a localised skin reaction (dermatitis or rash).

Medsafe notes that the data in the CARM database does not suggest a signal for skin reactions associated with bufexamac in New Zealand. However, as with all over-the-counter medicines, adverse events to bufexamac are likely to be under-reported. This can be due to a lack of recognition of side effects, a lack of awareness of consumers about the ability to report adverse reactions or a lack of understanding that, like prescription medicines, medicines purchased over-the-counter can cause adverse events, including serious reactions.

4.5 Published literature

Medsafe undertook a review of the available literature relating to the safety of bufexamac. The review included literature provided by the sponsor and also information identified from a literature search by Medsafe. Inclusion of literature was limited to full text or abstract available in English language and human species. Almost all of the studies referred to skin-related adverse events, particularly allergic contact dermatitis.

Allergic contact dermatitis is a subset of contact dermatitis that is immune-mediated. Onset generally occurs several hours to a few days after exposure to the allergen. Allergens responsible for allergic contact dermatitis can usually be identified by patch-testing. During patch-testing, the patient is exposed to chambers containing the test substance for 48 hours. The immune response is believed to consist of both a sensitisation phase and an elicitation phase, involving several immune cell types and cytokines. The reaction is generally considered a Type IV immune response, involving cell mediated immunity.

There are a number of published case reports of adverse skin reactions, particularly contact allergic reactions, following the use of bufexamac in the literature. Most of the case reports detailed positive patch-testing for bufexamac. However, these cases detailed reports in referred patients who may have been using bufexamac for eczema and dermatitis – conditions which are common in atopic patients who are predisposed to developing allergic hypersensitivity reactions. Medsafe was unable to identify any studies that reported the incidence or prevalence of contact allergic dermatitis attributable to bufexamac in the general population. Although some studies reported on the prevalence of bufexamac sensitisation of 1-2%, the populations included in the studies would be more likely to have had a positive patch-test because they were already under suspicion for the possibility of contact dermatitis or likely to be atopic. Therefore this data cannot be extrapolated to the general population.

One study used epidemiologic methods to determine a “relative incidence” of contact allergy in the German population from patch-testing data in the German Information Network of Departments of Dermatology (IVDK).⁴ Drug exposure was estimated from sales data. The authors noted that the relative incidence of contact sensitisation to topical corticosteroids ranged from 0.3 for dexamethasone to 23.3 cases per 100,000 defined daily doses per year for amcinonide. The relative incidence for hydrocortisone was calculated at 10.7 cases per 100,000 defined daily doses per year, while that calculated for bufexamac was 75.7. No other topical NSAIDs were tested for comparison with bufexamac.

It is of interest that because of the high number of contact-allergic reactions to bufexamac in patch-tested patients, the substance was included in the German Contact Dermatitis Group (DKG) standard patch series in Germany.

The sponsor provided two unpublished studies which contained safety information. In one of these studies (undertaken in 1977), no safety events occurred in 100 patients with atopic dermatitis who were treated with bufexamac for two weeks. In the second study (undertaken in 1973), one out of 30 patients with a variety of inflammatory skin conditions experienced an exacerbation, however this patient was being treated with bufexamac for acute eczema. The patient showed slight improvement after three days of treatment but discontinued after seven days due to enhanced erythema.

4.6 Medsafe’s summary of the safety of bufexamac in all indications

Medsafe considers that there is evidence from the case reports that bufexamac may cause allergic contact reactions in some patients, particularly atopic individuals. It has been associated with significant rates of sensitisation on the basis of patch-testing, however there is insufficient data available from controlled studies to determine the frequency and/or prevalence of bufexamac sensitisation in the general population.

Many of the cases of contact allergic dermatitis reported in the literature involved patients using bufexamac for the treatment of eczema and dermatitis - conditions which are common in atopic patients who are predisposed to developing allergic hypersensitivity reactions. Furthermore, the incidence of sensitisation to bufexamac was estimated in studies using data from an epidemiologic survey system which holds the results of skin patch-testing in various populations already under suspicion for the possibility of contact dermatitis.

A review of the European sponsor’s pharmacovigilance database revealed that most of the adverse event reports received for bufexamac related to skin reactions, many of which suggest allergy. A reporting rate for such events could not be determined because this is no reasonable estimate of patient exposure to bufexamac, however the distribution of the product by the European sponsor has been extensive. Many of the reports in the database were serious. The rate of hospitalisation in these reports is concerning.

⁴ Menezes de Padua C., et al. (2008). Allergic contact dermatitis to topical drugs – epidemiological risk assessment. *Pharmacoepidemiology and Drug Safety*. 17(8): 813-821.

5.0. OUTCOME OF REVIEWS BY OTHER REGULATORS

5.1 *European Medicines Agency (EMA)*

Based on their evaluation of the available data the European advisory committee (CHMP) concluded that, for all indications approved in Europe, the benefits of bufexamac-containing medicines do not outweigh the risks. Therefore, on 22 April 2010, the CHMP adopted an opinion recommending that the marketing authorisations for medicinal products containing bufexamac be revoked in the European Union.⁵

5.1.1 *Basis for the decision.*

In the European Union, bufexamac was approved for use to relieve the symptoms of inflammation of the skin (such as redness and itching) in conditions such as eczema and dermatitis. It was also approved for use in combination with other substances to control the symptoms of inflammation that can occur around the anus in patients with haemorrhoids or anal fissure.

The primary basis for the CHMP recommendation was that the risk of developing a contact allergic reaction to bufexamac, potentially serious enough to require hospitalisation, is high and even higher in patients with pre-disposing conditions, such as certain forms of eczema, for which bufexamac is frequently prescribed in Europe. Furthermore, because these reactions are very similar to the disease being treated, it can lead to delays in the diagnosis or treatment of the patient's condition. The CHMP also noted that bufexamac is a 'sensitiser' causing reactions to get worse with repeated exposure.

The CHMP considered that cases of contact allergic reactions to bufexamac are likely to be underreported due to the difficulty in differentiating between treatment failure and an allergic reaction.

The CHMP noted that the data in support of the efficacy of bufexamac were very limited. Most of the studies dated from the original development of bufexamac in the 1970s and 1980s, and were of a lower standard than expected today. The few more recent, controlled studies did not demonstrate efficacy of bufexamac.

The CHMP concluded that the high allergenic potential of bufexamac is not justifiable in light of the present-day medical knowledge and questionable evidence of efficacy for bufexamac, for the indications approved in Europe (dermatological and proctological conditions). Furthermore, the CHMP considered that alternative anti-inflammatory treatments were widely available for the indications for which bufexamac is approved.

Medsafe noted that the majority of the CHMP review concerned use of bufexamac in the treatment of skin conditions such as dermatitis, which is consistent with the approved indications for Paraderm in New Zealand.

⁵ EMA Press Release. *European Medicines Agency recommends revocation of marketing authorisations for bufexamac.* 22 April 2010.

5.2 Therapeutic Goods Administration (TGA)

There are a number of products containing bufexamac approved in Australia, however these products contain bufexamac in combination with other active ingredients and are not indicated for the relief of dermatitis, rash or hives. Therefore, the situation in Australia is not considered relevant in the section 36 review of bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives.

5.3 SwissMedic

Switzerland is not part of the European Union, and therefore the recommendations of the EMA do not apply to medicines in Switzerland.

Parfenac is the only bufexamac-containing medicine available in Switzerland. It is available only in pharmacies and is indicated for various forms of eczema, excluding atopic eczema or dermatitis.

The Swiss medicines regulator (SwissMedic) noted the EMA recommendation to revoke the marketing authorisations for medicines containing bufexamac due to the risk of severe contact dermatitis. This resulted in a review of the risk-benefit profile of bufexamac by SwissMedic.

In September 2010, SwissMedic advised that bufexamac-containing medicines would not be deregistered in Switzerland. The agency considered that the use of these medicines had already been restricted in Switzerland, with the removal of the indications for neurodermatitis and radiodermatitis, as well as new contraindications in atopic individuals, patients with anal eczema and patients who have previously experienced hypersensitivity to any component of the preparation. These restrictions were in-line with previous regulatory action in the European Union.⁶

SwissMedic also noted that bufexamac should not to be used under an occlusive dressing and that due to the lack of data regarding use in children and adolescents, bufexamac should not be used in these populations.

SwissMedic also advised that in the case of new skin eruptions or worsening of existing skin rash, bufexamac should be discontinued and advice sought from a healthcare professional.

5.4 Other major regulators

Medsafe is not aware of any products containing bufexamac that are approved in the United States or America or Canada.

⁶ SwissMedic Healthcare Professional Communication. *Parfenac Crème und Salbe, Wirkstoff Bufexamac: Kontaktallergien – Situation in der Schweiz nach Entzug der Zulassung in der EU*. September 2010.

6.0 DISCUSSION AND CONCLUSIONS

Paraderm is approved in New Zealand for the rapid relief from dermatitis, rashes and hives. Although Paraderm is not currently marketed in New Zealand and has not been since 2002, its approved indications for in New Zealand are similar to those in Europe which were reviewed by the CHMP.

The available data is inadequate to conclude efficacy of bufexamac in the relief of dermatitis and no studies could be identified investigating the efficacy of bufexamac in the relief of rash or hives. Furthermore, a number of reports of contact allergic reactions to bufexamac have been noted internationally, some requiring hospitalisation. However comparative data on the risk of contact dermatitis (particularly the rate of hospitalisation) with other topical NSAIDs has not been considered. Although the risk-benefit balances for alternative treatments have not been evaluated in this review, these events have been noted with topical corticosteroids and are listed in relevant data sheets such as Locoid Lipocream (hydrocortisone).

There is no evidence of a safety concern in New Zealand for bufexamac-containing medicines indicated for the relief of dermatitis, rash and hives. However this is not surprising given no such medicines have been marketed for nine years.

Given that contact allergic dermatitis could have similar characteristics to dermatitis, rash and/or hives, a delay in the diagnosis or treatment of the patient's reaction or prolongation of their condition may result. In addition to the risk of allergic contact dermatitis, the use of bufexamac may delay more effective treatment of the underlying condition in these patients. Furthermore, the data suggests that atopic individuals (who may be prone to episodes of dermatitis) have an even higher risk of contact allergic dermatitis.

Therefore, Medsafe concurs with the CHMP assessment of the safety and efficacy data for bufexamac and consider it is directly applicable to Paraderm.

7.0 MEDSAFE RECOMMENDATIONS

The adverse event of allergic contact dermatitis mimics the condition being treated which may result in a delay in the diagnosis or treatment of the patient's reaction or prolongation of their condition. Furthermore, dermatitis (or eczema) can be a serious condition requiring treatment.

Medsafe concludes that there is a concerning rate of contact allergy associated with bufexamac and unproven efficacy for bufexamac in the relief of dermatitis, rash and hives. Furthermore, there does not appear to be a clinical need for bufexamac in the relief of dermatitis, rash and hives in New Zealand, given Paraderm has not been marketed for nine years.

These factors suggest that the balance of benefits and risks is unfavourable for bufexamac-containing medicines in the relief of dermatitis, rash and hives. Therefore, Medsafe recommends the revocation of consent to distribute bufexamac-containing medicines that are indicated for the relief of dermatitis, rash and hives.