# Module 2.5

# Clinical Overview

Redacted under Section 40, Section 41 and Section 43 of the Freedom of Information Act.

## TABLE OF CONTENTS

PAGE

# 1. PRODUCT DEVELOPMENT RATIONALE

This document presents data to support the addition of anaphylaxis as part of the description of systemic allergic reactions to the Adverse Reactions section of the Global Data Sheet (GDS) for all three mupirocin formulations (ointment, cream and nasal ointment).

# 2. OVERVIEW OF BIOPHARMACEUTICS

Not Applicable

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

Not Applicable

# 4. OVERVIEW OF EFFICACY

Not Applicable

# 5. OVERVIEW OF SAFETY

## Global Clinical Safety and Pharmacovigilance

## Safety Evaluation and Risk Management

### Mupirocin: Anaphylaxis

| | |
|---|---|
| **Date of review** | May 2014 |
| **Drug terms included** | Mupirocin [redacted] |
| **Adverse events (AEs) (MedDRA*preferred terms) included** | Anaphylactic reactions - Standard SMQ (Narrow). |

*See Appendix 1Appendix 1 for full list of abbreviations

## 5.1. EXECUTIVE SUMMARY

In May 2014, the Food and Drug Administration (FDA) proposed the following modification with respect to GSK Prior Approval Supplement (PAS) submitted on 22 November 2013: 'Systemic allergic reactions, including anaphylaxis, urticaria, angioedema and generalized rash have been reported in patients treated with Bactroban formulations'

In response to the FDA proposal, GCSP initiated this cumulative review of worldwide reports for severe systemic allergic reactions, specifically, anaphylaxis, associated with mupirocin (all formulations) use in order to include all cases and to determine if a causal relationship between mupirocin and anaphylactic reactions exists and if changes to the mupirocin GDS (all formulations) were warranted.

The current global data sheet (GDS version 14, date 23 August 2013) for mupirocin states that 'systemic allergic reactions such as generalized rash, urticaria, and angioedema' are expected for all three mupirocin formulations (ointment, cream, and nasal ointment).

A search of the published medical literature did not yield any reports of anaphylaxis associated with mupirocin use.

As of 19 May 2014, 32 reports of anaphylactic reactions associated with all formulations of mupirocin have been received. Of these 32 reports, 22 were considered unassessable. The 10 remaining cases described a reasonable temporal relationship between the event and the use of drug; however, four of these reports described a cutaneous hypersensitivity type reaction. The remaining six reports contained sufficient information to allow for assessment and were reviewed. These six reports described anaphylactic/anaphylactoid reactions with a rapid onset of action causing systemic responses which required immediate medical intervention.

Based on the review of data of these six cases from OCEANS including rapid time to onset and clear signs and symptoms of anaphylaxis, it was determined that there is reasonable evidence of a causal association between the use of mupirocin (all formulations) and the development of anaphylaxis.

Considering the number of years of postmarketing experience and the estimated exposure of over 472 million patients, the reporting rate for anaphylaxis with mupirocin would be considered very rare. Therefore, the current review indicates that anaphylaxis may very rarely occur with mupirocin regardless of formulation.

Based on the available information, it is determined that an amendment to the mupirocin GDS to include anaphylaxis as part of the description of systemic allergic reactions for all mupirocin formulations, is warranted.

## 5.2. Background

### 5.2.1. Issue

In May 2014, the FDAs proposed the following modifications with respect to GSK Prior Approval Supplement (PAS) submitted on 22 November: 'Systemic allergic reactions, including anaphylaxis, urticaria, angioedema and generalized rash have been reported in patients treated with Bactroban formulations' (ointment, cream, nasal ointment).

Following this FDA proposal, GSK re-evaluated all of the reported severe systemic allergic reactions associated with mupirocin use, specifically anaphylaxis, in order to be inclusive of all cases. A new safety evaluation was deemed necessary to determine if a causal relationship between mupirocin and anaphylaxis exists and if anaphylaxis should be added as part of the description of systemic allergic reactions for all mupirocin formulations. Anaphylaxis is not currently labelled in the GDS.

A safety evaluation for anaphylaxis with mupirocin was performed in March 2012 (Report Number: 2012N153421). This evaluation concluded that evidence of a causal relationship between anaphylaxis and mupirocin was not robust enough to warrant adding anaphylaxis to the GDS.

In May 2013, an evaluation of systemic allergic reactions (Report Number: 2013N167424) was performed for all formulations of mupirocin. Based on the review of the data from OCEANS, including rapid time to onset and positive dechallenge and/or positive rechallenge for these events, it was determined that there was a possible causal association between mupirocin cream and nasal ointment and events of systemic allergic reactions. Therefore, "systemic allergic reactions such as generalized rash, urticaria, and angioedema' were added to the mupirocin cream and nasal ointment. Systemic allergic reactions are already listed in the GDS for the ointment formulation.

### 5.2.2. Background Information

Mupirocin is a topical antibiotic produced through fermentation of *Pseudomonas flurescens*. Mupirocin inhibits isoleucyl transfer-RNA synthetase, thereby arresting bacterial protein synthesis. Due to this mode of action and its unique chemical structure, mupirocin does not show any cross-resistance with other clinically available antibiotics. Mupirocin ointment is indicated for the topical treatment of primary and secondary bacterial skin infections. Mupirocin cream is indicated for the topical treatment of secondarily infected traumatic lesions such as small lacerations, sutured wounds or abrasions. Mupirocin nasal ointment is indicated for the elimination of nasal carriage of staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA), and can be used prophylactically to reduce *S. aureus* infections in patients receiving hemodialysis or continuous ambulatory peritoneal dialysis treatment.

A systemic allergic reaction occurs when inflammation spreads from a limited area of one organ (such as the skin) to other organ systems in the body. Etiologies may include toxins, allergies or infections. A systemic allergic reaction may involve symptoms such as pruritus, urticaria, angioedema and dyspnea and can progress into life-threatening

anaphylaxis which is an extreme and severe allergic response. The life-threatening anaphylactic response of a sensitized patient typically appears within minutes but sometimes hours after systemic exposure to a specific antigen and is manifested by respiratory distress due to laryngeal edema and/or intense bronchospasm, often followed by vascular collapse, or by shock without antecedent respiratory difficulty. [Fauci, 2012]. The terms 'anaphylaxis' and 'anaphylactoid' are both used to describe this severe allergic reaction. Anaphylaxis is used to describe reactions that are initiated by IgE and anaphylactoid is used in reference to reactions that are not caused by IgE. The effects of the reactions are the same, however, and are generally treated in the same manner. Often, they cannot be distinguished initially. Nonetheless, both conditions are commonly treated with epinephrine to constrict blood vessels, relax smooth muscles in the lungs to improve breathing, stimulate the heartbeat and treat angioedema. Other standard treatment of anaphylaxis should also include antihistamines and corticosteroids.

### 5.2.3. Current labelling

In the current Global Datasheet (GDS v.14, 23 August 2013) systemic allergic reactions such as angioedema, urticaria, and generalized rash are noted as adverse reactions for all three mupirocin formulations (nasal ointment, ointment, cream); however, the GDS does not include terms for anaphylaxis.

## 5.3. Exposure to Drug

Cumulatively, the total exposure to mupirocin (all formulations) from launch through March 2014 is estimated to be approximately over 472 million patients.

## 5.4. Safety data reviewed

This evaluation presents relevant information on reports of anaphylaxis from GSK OCEANS global safety database and published literature. Additionally, the following evaluation for mupirocin was reviewed:

- Mupirocin and Anaphylaxis – March 2012 (Report Number: 2012N153421)

### 5.4.1. Published literature

The published medical literature was queried using Embase and Searchlight for all publications of anaphylaxis associated with mupirocin (all formulations) up to 28 May 2014. Terms searched included "mupirocin" + "anaphylaxis. Results did not reveal reports of anaphylaxis in association with mupirocin.

## 5.4.2. Reports from the GSK Worldwide Clinical Safety Database (OCEANS)

### 5.4.2.1. Database Search Strategy

The GSK worldwide clinical safety database was searched on 19 May 2014 using the following criteria:

- **Data lock point(s):** cumulative through 19 May 2014
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports (attributable and non-attributable). Mupirocin was reported as a suspect drug.
- **MedDRA preferred term(s):** Anaphylactic/anaphyloid shock sub SMQ (narrow) scope) and Anaphylactic reactions SMQ (narrow scope) were both utilized. Hitlists were combined to provide final output.

### 5.4.2.2. Summary of Overall Dataset

A total of 32 reports were retrieved from the GSK worldwide safety database. Of these reports:

- Thirty (30) cases had a healthcare professional (HCP) as a report source and two were received from regulatory authority.
- The reports were received from 9 countries including [redacted]
- Twenty-seven cases met the criteria for a serious adverse event report, although seriousness may have been the result of an event other than anaphylaxis; the remaining five cases were non-serious.
- Seventeen cases were received from spontaneous source (HCP=13, Consumer =2, Regulatory authority =2), 12 from Clinical trials, and 7 from Postmarketing surveillance studies.
- Patient profile included 12 females, 19 males, and gender was unspecified in 1 case.
- Age range between 1 day and 87 years (median 39 years). Cases where ages were specified: 5 (0-9); 13 (20-59); 7 (60-87). ); exact age was not reported for 7 patients.

### 5.4.2.3. Case Evaluation

It is GSK practice to evaluate all reports of an adverse event retrieved from the GSK worldwide clinical safety database. However, due to the nature of spontaneous reporting there will always be some cases that contain insufficient information for assessment, despite adequate follow-up measures. Also, there will be other cases for which it

becomes evident on clinical review of the information provided, that the reported event is not consistent with the diagnostic criteria for that term; this category does not include reports for which there is no accompanying description of the event. Table 1 below summarises the unassessable cases of anaphylactic reactions associated with mupirocin therapy and also those that are considered inconsistent with the diagnostic criteria/definition.

**Table 1 Cases containing insufficient information for assessment and cases inconsistent with the reported term (N=18)**

| Reason | Number of Reports |
|---|---|
| Very poorly-documented cases providing no details about the event (i.e., no time to onset, duration, or outcome) AND no details about the patient other than age or gender AND no dechallenge or rechallenge information *or* otherwise clinically unevaluable cases due to inadequate documentation | 1 [redacted] |
| Description of the event is inconsistent with diagnostic criteria/definition | 17 |

The following cases were excluded:

[redacted] involved adverse events (diffuse urticaria or dermatitis with angioedema) which are indicative of systemic allergic reactions that are considered expected for mupirocin. Additionally, this case was poorly documented (no time to onset, medical history, concurrent medications or outcome) making case assessment difficult.

The remaining **17** cases were from clinical trial or postmarketing surveillance studies that evaluate the efficacy of mupirocin in eliminating the nasal carriage of methicillin-resistant *Staphyloccus aureus*. None of these 17 cases described a true anaphylactic reaction. A review of the cases is as follows:

| | | **Related to Mupirocin** | | |
|---|---|---|---|---|
| **Type of Events reported** | **# of cases** | **yes** | **No** | **Not reported** |
| Death associated with underlying disease (renal failure; hepatic disease, respiratory disease, cardiac disease, pancreatitis, polyvisceral failure, multiorgan failure) | 10 | 0 | 10 | 0 |
| Death due to pre-existing condition (premature, low birth weight, cardiovascular collapse, neurological state) | 5 | 0 | 5 | 0 |

| | | | | |
|---|---|---|---|---|
| Death due to unknown condition but not anaphylaxis | 1 | 0 | 0 | 1 |
| Septic shock due to pre-existing condition | 1 | 0 | 1 | 0 |
| Totals | **17** | 0 | **16** | **1** |

Similarly, there are four cases which document other **very much more likely** causes of the adverse event (e.g., concurrent medical conditions or other treatments), when time to onset or other clinical observations are taken into account. These are summarised in Table 2.

**Table 2 Cases with other very much more likely causes than treatment with mupirocin (n=4)**

| Reason* | Number of Reports |
|---|---|
| Time to onset is inconsistent with a possible effect of mupirocin | 0 |
| Alternative diagnosis or concurrent disease is *very much more likely* to have caused the event, based on reported time to onset or other clinical observations | 3 [redacted] |
| Concurrent drug is *very much more likely* to have caused the event, based on reported time to onset or other clinical observations | 1 [redacted] |

* Although theoretically some reports could have been assigned to more than one category, only one was allocated to each case and this was the first appropriate reason as listed above.

Case [redacted] was received by a consumer who reported the occurrence of a "systemic allergic reaction" in a [redacted] year-old male at an unknown time after starting mupirocin ointment for folliculitis on scalp. Treatment with mupirocin was discontinued and the outcome was resolved with sequelae. Treatment for the adverse event was not provided. The patient's concurrent medical history included chronic allergy.

Case [redacted] described toxic shock syndrome caused by staphylococcus aureus infection in a [redacted] year-old male four days after using mupirocin topically (unknown formulation).

Case [redacted] involved an [redacted] year old male who experienced exfoliative dermatitis two days after starting mupirocin ointment, but the case did not describe an anaphylactic reaction. Co-suspect medication included allopurinol.

Case [redacted] described an adult female who experienced an anaphylactic reaction after using chlorhexidine gluconate oral solution following dental procedure. Mupirocin

nasal ointment was implicated as the cause of some concurrent events that are expected per the GDS (irritation, burning, and itching) but it was not implicated in the anaphylactic reaction.

Of the 32 cases in the overall dataset, 22 fulfilled the criteria for inclusion in Table 1 or Table 2.

From the remaining 10 assessable reports of anaphylactic/anaphylactoid reactions, four were further excluded for the reasons shown below:

- Four ([redacted] described 'anaphylactoid reaction' with the use of mupirocin ointment and involved mainly cutaneous hypersensitivity events such as rash, erythema, pruritus which were considered listed for mupirocin. The events resolved after mupirocin was discontinued and information about treatment or intervention was not provided. Therefore, these cases were excluded from further analysis.

The remaining six of the 10 cases are considered 'Best' cases which provided the best evidence of a possible relationship between the event and the use of mupirocin. These cases reported "anaphylactic/anaphylactoid reactions" and described one or more of the adverse events which were considered indicative of a systemic allergic reaction (e.g., dyspnoea, pharyngeal oedema, swelling face, dizziness, blurred vision, nausea, loss of consciousness, urticaria). These cases are further described below and characteristics of these cases are presented in Table 3.

**Table 3 Characteristics of Remaining Cases (N = 6)**

| | | | |
|---|---|---|---|
| Patient Age | Range | years | 25 - 39 years |
| | Median | years | 28 |
| Patient Gender | Male | n (%) | 3 (50%) |
| | Female | n (%) | 3 (50%) |
| Report Type | Spontaneous Reports | n (%) | 6 (100%) |
| Report Source | Health Care Professional (HCP) | n (%) | 4 (66%) |
| | Regulatory authority (RA) | n (%) | 2 (34%) |
| Time to Onset of Event | Range | *units* | Same day |
| Outcome | Fatal (due to event) | n (%) | 0 (0%) |
| | Resolved with intervention | n (%) | 6 (100%) |

Case [redacted] involved an adult male who applied mupirocin ointment to a staphylococcus aureus infection on his face and shortly thereafter experienced shortness of breath and swelling in the throat and face. He was treated in the Emergency Room and the events resolved. Treatment with mupirocin ointment was discontinued. In the opinion of the pharmacist who reported the case, the anaphylactic reaction was probably related to the use of mupirocin.

Case [redacted] described a [redacted]-year old female who applied mupirocin (unknown formulation) to an open wound post-foot surgery and shortly thereafter, the patient experienced mild laryngeal oedema, dry mouth, and tachycardia. She was diagnosed as having anaphylactoid reaction. Treatment with mupirocin was discontinued. A tourniquet was applied to her leg, she was treated with epinephrine and diphenhydramine IM and her condition improved.

Case [redacted] involved a male patient who applied mupirocin ointment under a bandage to a cut on his heel. Shortly thereafter, the patient became short of breath and developed a rash. He was treated with epinephrine and promethazine and the events resolved. There were no concurrent medications, no concurrent illnesses, and the patient had no known allergies.

Case [redacted] described a [redacted] year old female who took one dose of amoxicillin/clavulanate and then applied mupirocin nasal ointment. Within one hour, the patient experienced redness, pruritus in her face which spread to the whole body. She reported experiencing swollen lips and tongue, dyspnoea and nausea. The next morning in the Emergency Room, her blood pressure was 115/60 mmHg and her heart rate was 96 bpm. Treatment with amoxicillin/clavulanate and mupirocin was discontinued. In the reporter's opinion, the anaphylactic reaction was possibly related to the mupirocin and amoxicillin/clavulanate.

Case [redacted] described a [redacted]-year-old female patient who received mupirocin cream for knee injury and infection. The patient's medical history was not provided. The patient washed the wound with hydrogen peroxide and normal saline and then applied mupirocin to the wound. Shortly after, the patient experienced "anaphylactoid reaction", dizziness, and blurred vision. The patient collapsed to the floor, sweating profusely, 'black and blue on the face was seen' and developed cyanosis. Treatment with mupirocin was discontinued immediately and mupirocin was flushed with normal saline and 10% glucose was given. The symptoms were relieved slightly after 3 minutes. The patient also developed erythematous papules and pruritus and received "muscular injection of calcium colloidal et vit D 2+DX5" and oral loratidine. At the time of reporting, the events were resolved. In the reporter's opinion, the events were possibly related to treatment with mupirocin.

Case [redacted] involved allergic shock in a [redacted] year-old male 20 minutes after receiving mupirocin ointment for joint skin wound. The patient experienced loss of consciousness, allergic reaction, chest distress, dyspnea, and dizziness. The patient also experienced administration site pain and generalized pruritic rash. The patient was treated with colloidal calcium + vit D, dexamethasone, and loratidine. At the time of reporting, the events of loss of consciousness and rash were resolved, the other events were improved.

Relevant information on cases that provide the best evidence of a causal relationship is displayed in **Appendix 2** (Tabulation of "Best" cases).

The current review indicates that anaphylaxis may very rarely occur with mupirocin regardless of formulation based on cases reports received. The allergic reactions in these six cases have a rapid onset of symptoms that are typical features of anaphylaxis affecting

many body systems and required immediate medical intervention. Therefore it was determined that there was sufficient and compelling evidence of a causal relationship between mupirocin and anaphylactic reactions to warrant adding anaphylaxis to the label.

## 5.5. Conclusion

The current GDS for mupirocin states that systemic allergic reactions including urticaria, angioedema and generalized rash are expected mupirocin (all formulations).

Thirty-two reports of anaphylactic reactions have been received. Of these 32 reports, 22 were considered unassessable. A further 10 remaining cases described a reasonable temporal relationship between the event and the use of drug; however, four of these reports described a cutaneous hypersensitivity type of reactions. Overall, where sufficient data was available to allow assessment, the remaining six "Best" reports of anaphylaxis after mupirocin use were identified and reviewed. From these six reports, the anaphylactic/anaphylactoid reactions occurred very rapidly and caused systemic symptoms which required immediate medical intervention.

In summary, based on the review of data of the six "Best" cases from OCEANS worldwide safety database including rapid time to onset and clear signs and symptoms of anaphylaxis, it was determined that there is reasonable evidence of a causal association between the use of mupirocin (all formulations) and the development of anaphylaxis.

Considering the number of years of postmarketing experience and the estimated exposure of over 472 million patients, the reporting rate for anaphylaxis with mupirocin would be considered very rare. Therefore, the current review supports that anaphylaxis may very rarely occur with mupirocin regardless of formulation.

Based on the available information, it is determined that an amendment to the mupirocin GDS to include anaphylaxis as part of the description of systemic allergic reactions for all mupirocin formulations, is warranted.

## 5.6. Recommendation

GSK recommends including "anaphylaxis' as part of the description of systemic allergic reactions to the adverse reactions section of the mupirocin GDS for the ointment, cream and nasal ointment formulations.

Based on the post-marketing adverse events reported to the MAH, the reporting rate of 'anaphylaxis' is very rare.

The proposed wording, relating to the addition of anaphylaxis event, for the mupirocin GDS is presented below and should be appropriately reflected in local labelling. Deleted text is presented as ~~**bold strikethrough**~~. Additional text is presented as ***red, bold italics***. Core safety information is presented as grey shaded text and is considered mandatory for inclusion in all local prescribing information.

### Adverse Reactions

**Ointment:**

**Immune system disorders:**

Systemic allergic reactions ~~**such as**~~ ***including anaphylaxis***, generalised rash, urticaria and angioedema have been reported with mupirocin ointment.

**Cream:**

**Immune system disorders:**

| | |
|---|---|
| Very rare: | Systemic allergic reactions ~~**such as**~~ ***including anaphylaxis***, generalised rash, urticaria and angioedema. |

**Nasal ointment:**

**Immune system disorders:**

| | |
|---|---|
| Very rare: | Cutaneous hypersensitivity reactions. Systemic allergic reactions ~~**such as**~~ ***including anaphylaxis***, generalised rash, urticaria and angioedema |

## 5.7. Benefits and Risks Conclusions

GSK considers that the addition of anaphylaxis to the label does not affect the benefit risk assessment of mupirocin topical ointment, cream, and nasal ointment.

## 5.8. References

Fauci AS, Kasper DL, Jameson JL, Longo DL, Hauser SL. Austen KF. Chapter 317. Allergies, Anaphylaxis, and Systemic Mastocytosis. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accesspharmacy.com/content.aspx?aID=9136197. Accessed July 15, 2013.

# APPENDIX 1 LIST OF ABBREVIATIONS

| Abbreviations | |
|---|---|
| AE | Adverse event |
| BPM | Beats Per Minute |
| FDA | (US) Food and Drug Administration |
| GCSP | Global Clinical Safety Pharmacovigilance |
| GDS | Global Data Sheet |
| GLC | Global Labelling Committee |
| GSK | GlaxoSmithKline |
| HCP | Healthcare Professional |
| IgE | Immunoglobulin E |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mmHg | Millimeters of Mercury |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| OCEANS | GSK's worldwide clinical safety database |
| PAS | Prior Approval Supplement |
| PT | Preferred term |
| RA | Regulatory Authority |
| RNA | Ribonucleic acid |
| SMQ | Standard MedDRA Query |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| BACTOBAN |
| BACTODERM |
| BACTROBAN |
| BETRION |
| EISMYCIN |
| FLUTIBACT |
| MUPIDAR |
| MUPISKIN |
| SELADERM |
| SPECTRODERM |
| STIBACT |
| T-BACT |

# APPENDIX 2 TABULATION OF BEST CASES

## SPONTANEOUS REPORTS OF ANAPHYLAXIS WITH MUPIROCIN OINTMENT, CREAM, AND NASAL OINTMENT TO 19 May 2014

## BEST CASES (n = 6)

| Case Id Country Age/Sex Report Source | Events | Route/formulation | Suspect Drugs | Time To Onset | Concurrent Drugs (Duration) | Relevant History | Laboratory Data | Treatment/ outcome |
|---|---|---|---|---|---|---|---|---|
| [redacted] Adult/Male HCP | Anaphylactic reaction, Dyspnoea, Pharyngeal oedema, Swelling face | Topical /Ointment | Mupirocin | same day | Not reported | Allergic to Penicillin | None | Treated at Emergency room/<br><br>Resolved |
| [redacted] Female HCP | Anaphylactoid reaction | Topical /Ointment | Mupirocin | same day | Not reported | Not reported | None | Adrenaline and diphenhydramine IM/<br><br>Resolved |

| Case Id Country Age/Sex Report Source | Events | Route/formulation | Suspect Drugs | Time To Onset | Concurrent Drugs (Duration) | Relevant History | Laboratory Data | Treatment/ outcome |
|---|---|---|---|---|---|---|---|---|
| [redacted] Unknown/Male HCP | Anaphylactic reaction, Rash, Dyspnoea | Topical /Ointment | Mupirocin | same day | No concurrent medications | No concurrent illnesses | None | IV adrenaline and promethazine/<br><br>Resolved |
| [redacted] Female Regulatory authority | Anaphylactic reaction, Lip swelling, Pruritus, Dyspnoea, Nausea | Topical /Ointment | Mupirocin | 1 hour | Amoxicillin trihydrate + potassium clavulanate | Not reported | None | Treated at Emergency room, /<br><br>Resolved |

| Case Id Country Age/Sex Report Source | Events | Route/formulation | Suspect Drugs | Time To Onset | Concurrent Drugs (Duration) | Relevant History | Laboratory Data | Treatment/ outcome |
|---|---|---|---|---|---|---|---|---|
| [redacted] Female Regulatory Authority | Anaphylactoid reaction, dizziness, vision blurred, hyperhidrosis, cyanosis, papulem pruritus | Topical/ Cream | Mupirocin | same day | Not reported | Not reported | None | Normal saline and 10% glucose. "IM injection of calcium colloidal et vit D 2+DX5" and oral loratidine. Resolved |
| [redacted] Male Physician | Anaphylactic shock, Loss of consciousness, Hypersensitivity, Chest discomfort, Dyspnoea, Dizziness, Administration site pain, Rash pruritic | Topical /Ointment | | 20 minutes | Not reported | Not reported | None | Colloidal calcium + Vitamin D, dexamethasone and loratidine /<br><br>Resolved |

# Module 2.5

# Clinical Overview

## TABLE OF CONTENTS

**PAGE**

# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AERF | Adverse Event Report Form |
| CSI | Core Safety Information |
| GCSP | Global Clinical Safety and Pharmacovigilance |
| GDS | Global Data Sheet |
| GLC | Global Labeling Committee |
| OCEANS | GSK Safety Database |

# 1. PRODUCT DEVELOPMENT RATIONALE

This document presents data to support the addition of wording in the Overdosage section of the GDS following requests from two Health Authorities (the Vietnam Health Authority and the Dominican Republic Ministry of Health) to supplement the "Overdosage" section: symptoms and treatment of overdose.

# 2. OVERVIEW OF BIOPHARMACEUTICS

Not Applicable

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

Not Applicable

# 4. OVERVIEW OF EFFICACY

Not Applicable

# 5. OVERVIEW OF SAFETY

In the current cumulative search of the OCEANS database as of 29 June 2014, a total of 20 reports of "Overdose" with mupirocin were retrieved and reviewed.

Of these 20 reports, nineteen (19) cases described mupirocin overuse or misuse (use in larger amounts, more often or for longer than the time period recommended in the label) and the remaining case described a 1-year old female who accidentally ingested ¾ tube of Bactroban topical ointment. No adverse events (AEs) were reported. The Drug Information Centre had been contacted and recommended that the child be hospitalised for close monitoring; however, the mother apparently decided to keep the child at home as she was not experiencing any effects at the time. An adverse event report form (AERF) was sent to the Drug Information Centre for completion, no further details were reported.

In summary, there were a total of 20 cases of overdose with mupirocin reported since launch. Of those 20 cases:

- Eleven (11) did not result in an adverse event (asymptomatic overdose).
- Five (5) reported Overdose with other AES such as lack of effect/product quality issue/off label use and/or AEs that are not related to Overdose.
- Four (4) reported Overdose that resulted in AE(s). Three of the 4 cases were confounded by a concurrent/underlying condition or concomitant treatment, and the remaining case described a listed AE (burning sensation).

Based on the available information, the experience with overdosage in mupirocin has rather been limited considering the number of years of postmarketing experience (over 29

years) and the extent of patient exposure (over 472 million units of mupirocin have been sold worldwide as of March 2014).

In addition, as there is no specific treatment for an overdose of mupirocin, a general precautionary statements explaining appropriate action in the event of an overdose is essential to convey information to patient.

In summary, the following amendments have been proposed for inclusion in the Overdosage section of the GDS:

- The following statements are considered as non-core safety information as they do not provide sufficient information to be classed as CSI: '***There is currently limited experience with overdosage of mupirocin***' and '***There is no specific treatment for an overdose of mupirocin. In the event of overdose, the patient should be treated supportively with appropriate monitoring as necessary'.***
- The following statement should be highlighted as core safety information in the GDS, as specified by the GLC Handbook guidelines '***Further management should be as clinically indicated or as recommended by the national poisons centre, where available.***'

Therefore, the proposed wording relating to the Overdose for the mupirocin GDS is presented below and should be appropriately reflected in local labelling.

Additional text is presented as ***red, bold italics***. Core safety information is presented as grey shaded text and is considered mandatory for inclusion in all local prescribing information

## Overdosage

### Symptoms and signs

***There is currently limited experience with overdosage of mupirocin.***

### Treatment

***There is no specific treatment for an overdose of mupirocin. In the event of overdose, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.***

# 6. BENEFITS AND RISKS CONCLUSIONS

GSK considers that the addition of the text in Overdosage section to the label does not affect the benefit risk assessment of mupirocin.

# 7. REFERENCES

None

# Module 2.5

# Clinical Overview

# TABLE OF CONTENTS

**PAGE**

# ABBREVIATIONS

| | |
|---|---|
| CI | Contraindication |
| CSI | Core Safety Information |
| CCSI | Company Core Safety Information |
| CLD | Country Labeling Difference |
| EU SmPC | European Union Summary of Product Characteristics |
| GCSP | Global Clinical Safety and Pharmacovigilance |
| GLC | Global Labeling Committee |
| GDS | Global Data Sheet |
| GSK | GlaxoSmithKline |
| LOC | Local Operating Company |
| MRSA | Methicillin-resistant Staphylococcus aureus |
| PEG | Polyethylene Glycol |
| PI | Prescribing Information |
| PSUR | Periodic Safety Update Report |
| PK | Pharmacokinetics |

# 1. PRODUCT DEVELOPMENT RATIONALE

This document presents rationales to support the amendments to the Warnings and Precautions section as well as the Special patient populations of the GDS for mupirocin.

# 2. OVERVIEW OF BIOPHARMACEUTICS

Not Applicable

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

Not Applicable

# 4. OVERVIEW OF EFFICACY

Not Applicable

# 5. OVERVIEW OF SAFETY

## 5.1. Warnings and Precautions

It is stated in the Warnings and Precautions section of the GDS that mupirocin topical ointment is not suitable for intranasal use in neonates or infants.

There have been requests from health authorities seeking clarification as it implies that the ointment can be used intranasally in patient populations other than neonates/infants. Two CLDs have been approved for this text deletion in country PIs. In addition we have received queries from LOCs requiring clarification on this issue.

For clarification purpose and to avoid further confusion, GSK is proposing that the wording pertaining to "neonates or infants" be removed from the warnings and precautions section of the GDS based on the following rationale:

- Per the label indication, mupirocin ointment is intended for topical treatment of primary and secondary bacterial skin infections, therefore it should not be used intranasally by patients of all ages and not just restricted to young children.

- Mupirocin ointment is not formulated for use on mucosal surfaces as it contains a polyethylene glycol (PEG) base, an excipient that could act as an irritant to the nasal passages, and therefore should not be used intranasally in all patient populations.

- To date, the ointment product was never studied for intranasal use in any age groups. Mupirocin nasal formulation is available for intranasal application. It contains 2% calcium mupirocin in a white soft paraffin based ointment and is indicated for the eradication of nasal colonization with MRSA.

In summary, we recommend that the wording "***in neonates or infants***" be deleted from the warnings and precautions section of the GDS based on the lack of clinical trial data to support the intranasal use of topical mupirocin. In addition, it is not deemed appropriate to apply the topical ointment to the nasal cavity when a separate nasal formulation is available.

GSK also recommends the removal of the following sentence " ***For intranasal use, a separate presentation, mupirocin nasal ointment, is available'*** from the information for both the ointment and cream formulations. A Global Data Sheet would not typically contain this type of statement, as it could be viewed as promotional in nature and does not convey important core product information. The indications section of the CI for the ointment and intranasal formulation make it clear as to which formulation is to be used in a given clinical situation.

In addition, GSK proposes the addition of the following statements to harmonise information in the Warnings and Precautions section for the three mupirocin formulations:

- To the Warnings and Precautions section for the nasal ointment formulation to align with the wording seen for the ointment formulation: '***If contaminated, the eyes should be thoroughly irrigated with water until the ointment residues have been removed'***. To the Warnings and Precautions section for the cream formulation to align with the wording seen for the ointment formulation: '***If contaminated, the eyes should be thoroughly irrigated with water until the cream residues have been removed'***. This statement is already included in the EU SmPCs for all three mupirocin formulations as a result of a request from a PSUR Worksharing procedure.

- To the Warnings & Precautions section for the cream formulation: "***This mupirocin cream formulation is not suitable for ophthalmic use and intranasal use***" and to the Warnings and Precautions section for the nasal ointment formulation: " ***This mupirocin nasal ointment formulation is not suitable for ophthalmic use***" for consistency with the text for the ointment formulation

Further, the Warnings and Precautions section has been re-structured to keep the renal impairment issues together. The reposition of the warning statements is amended as follows:

- The text relating to PEG absorption has been moved directly below the "Renal impairment" title.

- The statement regarding elderly patients has been removed from the Warnings and Precautions section and placed in the 'Special Patient Populations' category within the Pharmacokinetics section. This text is made non-core safety information in the GDS as specified by GLC Handbook guidelines.

# 6. CONCLUSION

In summary, based on the rationales provided above, GSK therefore proposes the following amendments for all three formulations of the mupirocin GDS. Deleted text is presented as ~~**bold strikethrough**~~. Additional text is presented as ***red, bold italics***. Core safety information is presented as grey shaded text and is considered mandatory for inclusion in all local prescribing information.

## Warnings and Precautions

***Ointment:***

**Renal impairment**

***Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol based ointments, mupirocin ointment should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment***

~~**Elderly patients: No restrictions unless the condition being treated could lead to absorption of polyethylene glycol and there is evidence of moderate or severe renal impairment.**~~

This mupirocin ointment formulation is not suitable for ophthalmic use, intranasal use ~~**(in neonates or infants),**~~ use in conjunction with cannulae and at the site of central venous cannulation.

~~**For intranasal use, a separate presentation, mupirocin nasal ointment, is available.**~~

Avoid contact with the eyes. If contaminated, the eyes should be thoroughly irrigated with water until the ointment residues have been removed.

~~**Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol based ointments, mupirocin ointment should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment**~~

***Cream:***

~~**For intranasal use, a separate presentation, mupirocin nasal ointment, is available.**~~

***This mupirocin cream formulation is not suitable for ophthalmic use and intranasal use.***

Avoid contact with the eyes. ***If contaminated, the eyes should be thoroughly irrigated with water until the cream residues have been removed.***

***Nasal Ointment:***

***This mupirocin nasal ointment formulation is not suitable for ophthalmic use.***

Avoid contact with the eyes. ***If contaminated, the eyes should be thoroughly irrigated with water until the ointment residues have been removed.***

### Special Patient Populations

~~**No Text.**~~

***Elderly patients: No restrictions unless there is evidence of moderate or severe renal impairment (see* Warnings and Precautions).**

## 7. BENEFITS AND RISKS CONCLUSIONS

GSK considers that the addition/deletion of the above CSI text from the warnings and precautions section of the label does not affect the benefit risk assessment of mupirocin topical ointment, cream, and nasal ointment.

# 8. REFERENCES

None