Module 2.5

Clinical Overview

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ABBREVIATIONS

HLR	High Level Resistance
MIC	Minimum Inhibitory Concentration
MIC_{50}	Minimum Inhibitory Concentration required to inhibit the growth of 50% of organisms
MIC_{90}	Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms
MRCNS	Methicillin-resistant coagulase negative *Staphylococcus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
MSCNS	Methicillin-susceptible coagulase negative *Staphylococcus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
MSSE	Methicillin-susceptible *Staphylococcus epidermidis*
R	Resistant
RNA	Ribonucleic acid
tRNA	Transfer-ribonucleic acid

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1. PRODUCT DEVELOPMENT RATIONALE

Not applicable to this Type II Variation.

2. OVERVIEW OF BIOPHARMACEUTICS

Not applicable to this Type II Variation.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

3.1. Introduction

This application for a variation is submitted following a request from the MHRA (in their role as P-RMS for the recent PSUR worksharing procedure) to amend section 5.1 of the SmPCs for mupirocin. GSK has been asked to revise the format of section 5.1 to align with guidance note CPMP/EWP/558/95, Rev 1 ("Note for Guidance on the evaluation of medicinal products indicated for treatment of bacterial infections") and submit the appropriate data to support this revision of the labelling.

3.2. Pharmacokinetics

3.3. Pharmacodynamics

3.3.1. Microbiological Profile

Mupirocin is a non-systemic antibiotic originally isolated from certain strains of *Pseudomonas fluorescens* (British Pharmacopeia 2011) under submerged fermentation (Gisby and Bryant, 2000). Mupirocin shares no structural relationships with other antibiotics currently available. It consists of a short fatty acid side-chain ester linked to monic acid, the tail end of which side-chain appears to mimic the carbon skeleton of the amino acid isoleucine. (Hughes et al, 1980; Casewell and Hill, 1987)

The name "pseudomonic acid" was ascribed originally to the major metabolite [pseudomonic acid A], which accounted for most of the observed antibiotic activity (Sutherland et al., 1985). The term "mupirocin" has now been accepted as the approved generic name for pseudomonic acid A (Casewell and Hill, 1985). Mupirocin, as well as the other pseudomonic acids, has been synthesised (Bryskier, 2005). The drug was introduced first into clinical practice for the treatment of skin infections in the UK in 1985 and is now available in more than 90 countries (Kresken et al, 2004).

Mode of Action

Mupirocin has a novel mechanism of action (inhibition of isoleucyl tRNA synthesis) which differs from that of other available antibiotics (Gisby and Bryant, 2000).

The effect of mupirocin has been studied on the major metabolic processes in *Staphylococcus aureus* where mupirocin has been shown to strongly inhibit both protein synthesis and RNA synthesis. DNA and cell wall formation (through peptidoglycan synthesis) are inhibited to a lesser extent and interference with these processes is considered to be a secondary effect. The primary effect of low concentrations of the antibiotic is the inhibition of protein synthesis, leading to bacteriostasis. (Hughes and Mellows, 1978[b])

Mode of action studies as to mupirocin were continued using *Escherichia coli.* These studies have demonstrated that the primary target of mupirocin in the bacterial cell wall is isoleucyl [Ile]-tRNA synthestase, the enzyme which charges the appropriate tRNA with isoleucine – an essential component of protein synthesis (Farmer et al 1992; Hughes et al, 1980). It has been postulated that, as an analogue of isoleucine, mupirocin is a powerful competitive inhibitor of Ile-tRNA synthetase. The antibiotic competes for the active site of the enzyme. It binds specifically but reversibly to the enzyme, thus preventing incorporation of isoleucine into growing protein chains and thereby inhibiting bacterial protein synthesis. It has been suggested that the inhibition of RNA synthesis is a consequence of a protective mechanism imposed in response to the pseudomonic acid-induced lack of the amino acid isoleucine. (Hughes and Mellows, 1978[a]).

Bacteriostatic and Bacteriocidal Activities

The mode of action of mupirocin suggested that its antibacterial action was bacteriostatic and MIC and MBC studies have since confirmed that the activity of mupirocin is indeed largely bacteriostatic (Casewell and Hill, 1985).

However, studies of killing kinetics have also shown that the molecule is stable and that prolonged exposure to mupirocin results in sustained, albeit slow, bacteriocidal action. (Casewell and Hill, 1987; Casewell and Hill, 1985) The results of viable count studies to measure the bactericidal effects produced by mupirocin against staphylococci showed that the antibiotic caused an inhibition of growth during the initial period of the test, followed by a period of bactericidal activity which resulted in a marked reduction in the number of bacteria at 24h (Sutherland, 1985). Wuite et al (1985) found that the antibiotic was bactericidal in action at the high concentrations (20,000 mg/liter) present in the 2% formulation used in the studies conducted by his group; local therapy is said to offer an advantage in the treatment of superficial skin infections in that relatively high concentrations of an antibacterial agent can be placed directly at the site of infection (constrained only by the development of local hypersensitivity reactions). Bryskier (2005) notes as well that the reduction in bacterial cell numbers from initial levels is dependent upon the concentration of the antibiotic.

The activity of mupirocin is significantly enhanced in an acidic medium and the notion has been advanced that this feature may well be advantageous in relation to the acid pH associated with the skin and its environment (Sutherland et al 1985). The pH of normal skin is about pH 5.5 and this acidity might be expected to contribute to the anti-staphylococcal activity of mupirocin *in vivo* (Casewell and Hill, 1985). Cookson (1998) has also noted that the bactericidal properties of mupirocin appear to be enhanced at a lower (more acidic) pH approximating that of many parts of the skin.

Mechanism of Resistance

Mupirocin sensitive strains are defined as having minimal inhibitory concentration [MIC] values in the range of 0.12 to 4.0 µgrams/ml (Farmer et al, 1992).

The widespread use of mupirocin has resulted in the emergence of mutant strains expressing mupirocin resistance – a matter of clinical significance as this phenomenon raises concerns as to the continued efficacy of the antibiotic (Simor et al, 2007; Jones et el, 2006; Bryskier, 2005; Hurdle et al, 2004). Two types of resistance to mupirocin have been described in *S. aureus*: low-level and high-level, and these are thought to result from different mechanisms.

High-level resistance [MICs $\geq$ 512 µgrams/ml] (Gilbart et al, 1993) has been described in strains of *S. aureus* isolated from patients on a dermatology ward in summer 1987, i.e. not long after the agent's initial use in clinical practice (Cookson 1990; Rahman et al, 1987). High-level resistance is mediated by the acquisition of an unusual plasmid containing a new gene (*mupA*) that encodes a second, and novel, Ise-tRNA synthetase enzyme whose function is not inhibited by mupirocin (Hodgson et al, 1994).

Low-level resistance in *S. aureus* is more common and is thought to result from point mutations within the usual staphylococcal chromosomal gene (ileS) for the target iso-leucyl tRNA synthetase enzyme (Antonio et al, 2002). Acquired low-level resistance results in elevated MICs into the range of 8 to 256 µg/ml; low-level mupirocin resistance could be trained *in vitro* and low-level resistance was observed in an early *in-vivo* study (Cookson, 1998).

The clinical significance of low-level mupirocin resistance is still a matter of debate (Hurdle et al, 2004), whereas it is now generally agreed that strains with high-level mupirocin resistance cannot be eradicated with mupirocin (Kresken et al, 2004).

Intrinsic resistance of such gram-negative organisms as the *Enterobacteriaceae* to mupirocin could be due to the poor ability of the compound to permeate through the bacterial outer wall and interact with the isoleucy-tRNA synthetase of such bacteria [i.e., failure to penetrate the cell envelope and reach its target site] (Wilson et al, 1995; Capobianco et al, 1989).

Cross Resistance

Due to its unique chemical structure and to its particular mode of action, mupirocin does not show any cross-resistance with other clinically available antibiotics (Sutherland et al, 1985).

Microbiological Susceptibility

Mupirocin has potent antibacterial activity (Wilson, 1995). The antimicrobial spectrum of mupirocin against representative strains of aerobic and anaerobic gram-positive bacteria is set forth in the listing below [adapted from Sutherland et al, 1985].

Mupirocin is active primarily against gram-positive cocci (coagulase-positive and coagulase- negative *staphylococci*; *streptococci*), with the exception of *Enterococcus* spp which are distinctly less susceptible (Bryskier, 2005; Wilson et al, 1995; Sutherland et al, 1985).

Mupirocin is active against *S aureus* [a coagulase-positive *staphylococcus*], whether the strains are susceptible or resistant to penicillin G, tetracyclines, erythromycin A, fusidic acid, lincomycin, chloramphenicol or meticillin [the latter now discontinued in the UK] (Bryskier, 2005). Activity has also been observed against coagulase-negative *staphylococci* (Cookson 1990).

Mupirocin possesses good activity against beta-hemolytic *streptococci* of the Lancefield A, C, and G groups, with Group B *streptococci* being slightly less susceptible. Variable susceptibility is observed amongst the viridians group *streptococci*, depending on species. (Bryskier, 2005).

Mupirocin possesses moderate activity against some gram-positive bacilli such as *Erysipelothrix rhusiopathiae* and *Listeria monocytogenes*; other aerobic gram-positive bacteria, including *Corynebacterium* spp. and *Micrococcus luteus* are less susceptible, as are anaerobic gram-positive bacteria such as: *Peptostreptococci* spp., *Clostridium* spp. and *Propionibacterium acnes* (Sutherland et al, 1985).

Gram-positive aerobic enterococcal species such as *E. faecalis* and *E. faecium* are inherently resistant. (Bryskier, 2005)

Mupirocin is inactive against anaerobes. Although inactive against anaerobic cocci, mupirocin is as active against *Staphylococcus aureus* under anaerobic conditions as it is under aerobic conditions. (Sutherland et al, 1985)

Antibacterial spectrum in part is impacted by innate target affinity and access, and unknown bases (Hughes et al., 1980; Capobianco et al., 1989).

Taking into account the above discussion and the approved indication of the product, the following additional information is considered appropriate for the SmPC:

Commonly susceptible species
*Staphylococcus aureus**
*Streptococcus pyogenes**
Streptococcus spp. (β-haemolytic, other than *S. pyogenes*)
Species for which acquired resistance may be a problem

Staphylococcus spp., coagulase negative
Inherently resistant organisms
Corynebacterium spp.
Micrococcus spp.

4. OVERVIEW OF EFFICACY

Not applicable to this Type II Variation.

5. OVERVIEW OF SAFETY

Not applicable to this Type II Variation.

6. BENEFITS AND RISKS CONCLUSIONS

A proposed amendment to the SmPC, based on the data provided above is detailed in m1.3.1. GSK believes this revision will update and enhance the prescribing information available to physicians.

7. REFERENCES

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