Module 2.5

Clinical Overview

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ABBREVIATIONS

ECOFF	Epidemiological Cut-Off
EUCAST	The European Committee on Antimicrobial Susceptibility Testing
GDS	Global Data Sheet
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
MIC	Minimum Inhibitory Concentration
R	Resistant
S	Susceptible
WT	Wild Type

1. PRODUCT DEVELOPMENT RATIONALE

This document presents data to support the modification of the breaking point to the pharmacodynamic effects 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

5.1. Background

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.

5.2. Proposed change

GSK propose to modify the following breakpoints for all the formulations of mupirocin in the current GDS.

Current breakpoint section in mupirocin GDS:

Mupirocin breakpoints:

Ointment:

S less than or equal to 4 micrograms/ml; R greater than or equal to 8 micrograms/ml.

Cream:

No Text.

Nasal Ointment:

S less than or equal to 256 micrograms/ml; R greater than or equal to 512 micrograms/ml.

Proposed modified breakpoint section in mupirocin GDS:

Mupirocin breakpoints for *Staphylococcus* spp.

Ointment, Cream and Nasal Ointment:

Susceptible: less than or equal to 1 microgram/ml;

Intermediate: 2 to 256 micrograms/ml

Resistant: greater than 256 micrograms/ml

The actual concentration of a topical agent at the site of infection will be much greater than an in vitro based MIC based breakpoint. In the case of mupirocin, the GDS susceptible breakpoint of ≤4 µg/mL for the ointment was based on MIC distributions published in the Finlay et al, 1997 publication (Finlay 1997) and the GDS susceptible breakpoint of ≤256 µg/mL for the nasal ointment was based on determination of high level resistant strains at >256 µg /mL. The EUCAST susceptible breakpoint was set at 1 µg/mL. In absence of any clinical data, for the susceptible breakpoint, EUCAST used the epidemiological cutoff value (highest MIC observed in the normal distribution of wild type organisms), which they decided was at 1 µg/mL. In Figure 1, the graph shows the actual MIC distributions for *S. aureus*, MSSA and MRSA. Although bars are not visible at MICs of 1, 2 and 4, there were low numbers detected at these concentrations as shown in Table 1 (from the EUCAST rationale document). Therefore, because of inherent MIC variations, some strains with MICs of 2 and 4 could potentially be low level resistant strains and therefore were not considered when setting the susceptible breakpoint at 1 µg/mL (EUCAST rationale document). Because low level resistant strains have been found to have MIC values between 8 and 256, an intermediate breakpoint of 2-256 would include those strains that are expressing these low level resistance mechanisms. The EUCAST

resistant breakpoint of >256 µg/mL coincides with the detection of the high level resistance mechanism as shown in Figure 1.

6. BENEFITS AND RISKS CONCLUSIONS

In conclusion, for consistency with the EUCAST breakpoints, GSK propose to align the GDS breakpoints for the 3 mupirocin formulations (cream, ointment and nasal ointment) to: ≤1 µg/mL susceptible, 2-256 intermediate and >256 resistant.

Based on this conclusion and the available supporting data summarized in section 1.1 GSK considers that the modification of the breaking point does not affect the benefit risk assessment of mupirocin.

Figure 1. Mupirocin MIC distributions for *S. aureus* from EUCAST

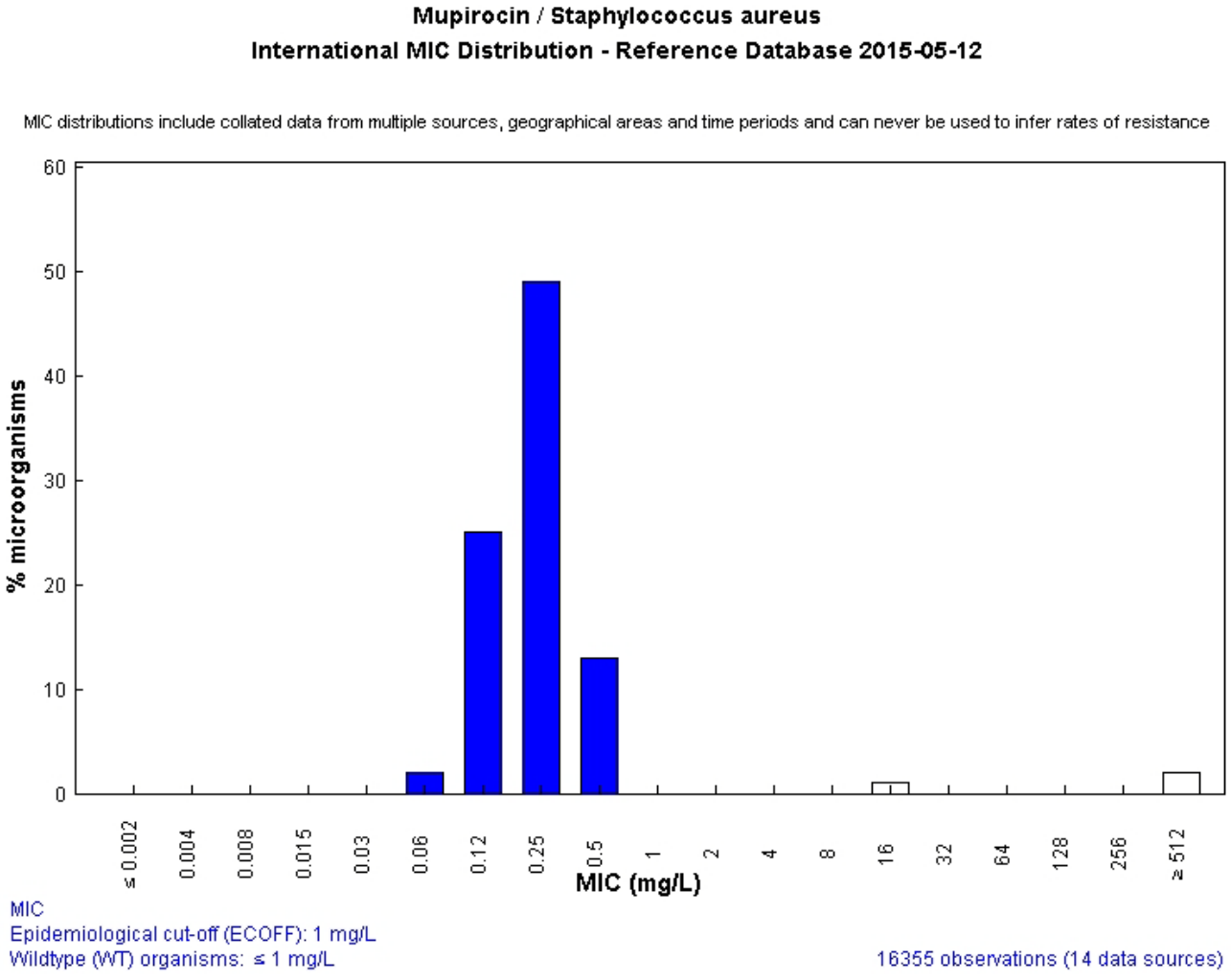

Table 1. Mupirocin MIC distributions and epidemiological cut-off (ECOFF) values from EUCAST

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Staphylococcus aureus	0	0	0	4	14	478	4248	8141	2272	129	52	95	94	194	86	35	56	24	433	1.0
Staphylococcus aureus MRSA	0	0	0	0	1	10	123	1452	733	30	7	22	15	19	11	0	0	0	34	1.0
Staphylococcus aureus MSSA	0	0	0	0	0	5	117	881	162	5	0	1	0	0	0	0	0	0	2	1.0

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms.

7. REFERENCES

1. “European Committee on Antimicrobial Susceptibility Testing. Mupirocin: Rationale for the clinical breakpoints, version 1.0,
2010. http://www.eucast.org.

2. Finlay JE, Miller LA, Poupard JA. Interpretive criteria for testing susceptibility of staphylococci to mupirocin. Antimicrob Agents Chemother. 1997May;41(5):1137-9.