Johnson & Johnson Pacific

5 April 2017

Product Regulations
Medsafe
PO Box 5013
Wellington 6140
NEW ZEALAND

Dear Sir/Madam,

Re: Addition of warning statement on labels for topical miconazole containing medicines available without a prescription.

The Medicines Adverse Reactions Committee at their 167th meeting recommended that Medsafe update the Label Statements Database to include a compulsory warning statement for miconazole containing products that are available without prescription regarding an interaction with warfarin. The reason for this is because the Centre for Adverse Reactions Monitoring (CARM) continues to receive reports of potentially life threatening events in patients taking warfarin and using miconazole containing medicines.

Medsafe proposes adding the following statements to the Label Statements Database for **all** topical miconazole products irrespective of whether they are included in leaflets, as leaflets cannot be mandated.

Either*: Do not use [this product] if you are taking warfarin unless a healthcare professional advises you to.*

Or:
Patients taking warfarin - talk to a healthcare professional before using [this product]

The potential for drug interactions between oral miconazole and warfarin is well established. The mechanism is understood to be inhibition by miconazole of one of the main cytochrome P450 isozymes involved in warfarin metabolism: CYP2C9, resulting in reduced warfarin clearance and an enhanced anticoagulant effect.

When considering the cases reported to CARM it is clear that there is evidence to suggest that interaction can occur between warfarin and miconazole oral gel and potentially vaginal products,

however there is no clear evidence for other topical forms of miconazole containing medicines (applied to the skin). This finding also aligns with information published by other regulators including MHRA, Health Canada and FDA.

Johnson & Johnson recently conducted a review of miconazole and the Company Core Data sheet (CCDS) was recently updated for miconazole oral gel only.

The CCDS for miconazole oral gel only was recently updated to contraindicate concomitant use of miconazole oral gel with warfarin, due to the higher risk of patients experiencing a serious drug reaction when using miconazole oral gel in combination with warfarin in a non-monitored clinical setting. However, the same conclusion was not drawn with miconazole/ miconazole nitrate products applied to the skin.

It was found that systemic absorption of miconazole is limited, with a bioavailability of 1 to 2% following intravaginal administration, and less than 1% following topical application. This decreases the likelihood of interactions with warfarin. Although we do not have specific data on miconazole penetration through an open wound, absorption through mucous membranes of the vagina could be a good indicator of the ability of the drug to be absorbed through an open wound. Included with this response are four relevant articles that indicate minimal absorption, based on plasma levels, when miconazole is applied to the vagina.[1,2,3,4]

Based upon the cumulative review of cases reporting concurrent use of miconazole and miconazole nitrate formulations and combinations (excluding miconazole oral gel) and warfarin, and based upon review of the limited literature documenting a pharmacokinetic interaction between miconazole/miconazole nitrate (topical formulations) and warfarin, the Company has concluded that no updates or strengthened warning to the labeling of other dosage forms of miconazole (other than oral gel) are recommended.

Therefore, Johnson & Johnson maintains that a warfarin interaction warning should be required in the Medsafe Label Statements Database for miconazole oral gel, however not for other topical preparations that are applied to the skin given this presents such low risk and there is limited evidence to suggest it is an issue. Furthermore, we also would like to also highlight that this is especially true for topical products indicated for infants with nappy rash such as Daktozin topical ointment. Therefore, if Medsafe maintain that a statement is required for all topical miconazole containing products, products indicated for infants should be excluded from this decision, as infants are unlikely to be taking warfarin concomitantly with topical miconazole products.

Specific questions raised by Medsafe:

Question 1:
Whether a warning statement about the warfarin interaction is required for all topical miconazole products

Answer 1
No. As discussed above, evidence suggests that a statement is required for miconazole used on mucosal membranes (oral gel and potentially vaginally applied products). However not topical products applied to the skin given the risk is so low.

Question 2:
Which of the proposed statements is preferred and why?

Answer 2:
Either statement proposed by Medsafe is acceptable. We believe both are "words to the effect" of each other.

Question 4:
A suitable target date for implementation.

Answer 4:
We recommend that an implementation date of 18 months' minimum should be proposed which aligns with Australian RASML implementation timing. This timing allows enough time for artwork to be updated in time for subsequent production batches. This is especially important for slow moving products.

Yours faithfully,

[redacted]
Regulatory Affairs Senior Manager
Johnson & Johnson Pacific Pty Ltd
[redacted]

References:

1. Abrams L, Weintraub H. Disposition of radioactivity following intravaginal administration of ^{3}H-miconazole nitrate. American Journal of Obstetrics & Gynecology. December 15, 1983. 147(8): 970-971. EDMS-ERI-136774651.

2. Brugmans J, et al. Systemic Antifungal Potential, Safety, Biotransport and Transformation of Miconazole Nitrate. European Journal of Clinical Pharmacology. 1972. 5: 93-99. EDMS-ERI-136774652.

3. Daneshmend T K. Systemic absorption of miconazole from the vagina. Journal of Antimicrobial Chemotherapy. 1986. 18: 507-511. EDMS-ERI-136774653.

4. Vucovich R A, et al. Vaginal absorption of two imidazole antifungal agents, econazole and miconazole. Seventy-Eighth Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Dallas, Texas. March 24-25, 1977. EDMS-ERI-136774654.

Medsafe consultation submission

Addition of warning statements on labels of topical miconazole-containing medicines	
Name and designation	[redacted], Regulatory Affairs Manager
Company/organisation name and address	Johnson & Johnson (New Zealand) Limited
Contact phone number and email address	[redacted]

I would like the comments I have provided to be kept confidential: *(Please give reasons and identify specific sections of response if applicable)* Please remove company name and name of person who has made submission. (Reasons for requesting confidentiality must meet Official Information Act 1982 criteria)	☒ Yes ☐ No
I would like my name to be removed from all documents prior to publication on the Medsafe website.	☒ Yes ☐ No
I would like for my name not to be included within the list of submissions published on the Medsafe website.	☒ Yes ☐ No

It would help in the analysis of stakeholder comments if you provide the information requested below.

I am, or I represent, an organisation that is based in:

☐ New Zealand ☒ Australia ☐ Other (*please specify*):

I am, or I represent, a: *(tick all that apply)*

☐ Importer	☐ Manufacturer	☐ Supplier	☒ Sponsor
☐ Government	☐ Researcher	☐ Professional body	☐ Industry organisation
☐ Consumer organisation	☐ Member of the public	☐ Institution (e.g. university, hospital)	
☐ Regulatory affairs consultant	☐ Laboratory professional		

☐ Health professional – *please indicate type of practice*:

☐ Other - *please specify*:

Please return this form to:

Email: medsafeapplications@moh.govt.nz including 'Miconazole warning statements' in the subject line

Or Post: Product Regulation
Medsafe
PO Box 5013
Wellington 6145

Medsafe is seeking comments on:

Whether a warning statement about the interaction between warfarin and miconazole is required for all topical miconazole containing medicines available without prescription.

- If a warning is not required for all products please provide your reasoning

No we don't believe it should apply to all topical formats. We believe it should only be required for miconazole oral gel. Details of the reasons why is included in the attached letter.

Which of the proposed warning statements about the interaction between warfarin and miconazole is preferred?

- Please provide your reasoning, this will help Medsafe when considering future warning statements

Either statement proposed by Medsafe are acceptable, we believe both are "words to the effect" of each other.

Please include additional pages if necessary.

Whether the statements required in Australia for intravaginal miconazole products should be included in the Label Statements Database.

- Please provide your reasoning

- Are the statements acceptable or should they be reworded?

What is a suitable target date for implementation:

- Please provide justification

We recommend that an implementation date of 18 months' minimum should be proposed which aligns with Australian RASML implementation timing. This timing allows enough time for artwork to be updated in time for subsequent production batches. This is especially important for slow moving products.

Please include additional pages if necessary.