



Miconazole Label Statements

Consultation on need for a warning regarding interaction with warfarin and harmonisation with Australian required statements

Medsafe

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About Medsafe

- ☞ Medsafe is the New Zealand Medicines and Medical Devices Safety Authority and is responsible for the regulation of therapeutic products in New Zealand through administration of the Medicines Act 1981.
- ☞ Medsafe is a business unit of the New Zealand Ministry of Health.
- ☞ Medsafe's Mission is: 'To enhance the health of New Zealanders by regulating medicines and medical devices to maximise safety and benefit.'
- ☞ In working to achieve the stated mission Medsafe:
 - applies accepted international practice to the regulation of therapeutic products
 - prepares and maintains regulatory guidelines reflecting sound science and promoting evidence based decisions
 - applies processes that are consistent, transparent and minimise the costs of regulatory action
 - provides timely and unbiased information to health professionals and consumers about the safe use of therapeutic products.

Background

The Medicines Adverse Reactions Committee (MARC) at their 167th meeting recommended that Medsafe updates the Label Statements Database to include a compulsory warning statement for all miconazole-containing products available without prescription, regarding an interaction with warfarin.

Topical miconazole containing medicines are available without a prescription. The classification of miconazole-containing medicines is outlined in Table 1.

The Label Statements Database lists the warning and advisory statements that are required on medicine and related product labels under regulations 12(1)(i) and 14(1)(f) of the Medicines Regulations 1984 for medicines.

Table 1: Classification of miconazole containing medicines

Ingredient	Conditions (if any)	Classification
Miconazole	for the treatment of oral candidiasis; for vaginal use	Restricted
Miconazole	except when specified elsewhere in this schedule; except in medicines for tinea pedis only or when sold in practice by a podiatrist registered with the Podiatrists Board	Prescription
Miconazole	for external use except in medicines for tinea pedis only or when sold in practice by a podiatrist registered with the Podiatrists Board	Pharmacy Only
Miconazole	for external use in medicines for tinea pedis only or when sold in practice by a podiatrist registered with the Podiatrists Board	General Sale

The Label Statements Database is the mechanism through which consumers are informed of the warnings and precautions that are necessary for the safe use of medicines available without prescription. Consumers can also be informed of the necessary warnings and precautions in medicine data sheets and consumer medicine information (CMI). However, in New Zealand, CMI are voluntary for all medicines and data sheets are voluntary for pharmacy only and general sales medicines.

Introduction

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.

Topical miconazole containing medicines include:

- ☞ those for oral mucosal application such as oral gel
- ☞ topical cream
- ☞ those for intravaginal use – cream and pessaries.

Cases of interactions occurring in patients taking warfarin and using these products have been reported around the world including New Zealand.

Regulatory authorities have provided warnings regarding this interaction due to the potentially life threatening effects of the increased anticoagulant effect of warfarin.

- ☞ MHRA Drug Safety Update vol 9 issue 11, June 2016.
- ☞ Health Canada – Canadian Adverse Drug Reaction Newsletter 2001.
- ☞ FDA safety warning 2001.
- ☞ Medsafe in 2003, 2005 and 2013 through *Prescriber Update*.

The purpose of this document is to provide information on this potential interaction and Medsafe's proposal to include warning statements in the Label Statement Database for miconazole containing medicines.

Interaction between warfarin and topical miconazole-containing medicines

Case reports

A selection of the more recent published case reports are outlined below. The intent of highlighting these cases is to provide evidence that this interaction can occur and in what circumstances.

Murakami et al [1]

The authors report the results of a retrospective study. All patients were taking warfarin and miconazole oral gel. The message of the case series was that international normalised ratios (INR) may remain elevated for some time after warfarin is discontinued.

86/M. INR increased from 1.07 to 4.47 and remained high for 13 days until miconazole discontinued. INR remained at 3.84 for the next 35 days.

63/M. INR decreased from 1.6 to 1.09 and remained for 2 days. Miconazole was stopped and INR increased to 2.33 and remained high for 12 days.

65/M. INR increased from 2.55 to 4.55 and remained high for 5 days. Miconazole was stopped and INR remained at 3.8 for 20 days.

85/F. INR increased from 1.62 to 1.65 for 5 days. Miconazole was stopped and warfarin decreased but INR remained at 2.48 for next 6 days.

85/M. INR increased from 1.56 to 3.16 for 8 days. Miconazole was stopped and warfarin decreased, INR remained at 4.32 for 13 days.

74/F. INR increased from 1.75 to 8.07 for 7 days. Miconazole was discontinued and warfarin decreased. INR remained at 4.96 for the next 6 days.

Hook et al [2]

68/M treated with warfarin, miconazole (route not stated but indication was oral lichen planus) and metronidazole developed a large bruise on his right torso. He stopped taking warfarin after reading the patient information leaflet. Urgent INR was reported as 5.9.

De Pauw et al [3]

49/F on warfarin started using miconazole oral gel. She presented with an INR of 12.7.

89/F on warfarin presented with spontaneous bleeding of the gums and lips, ecchymoses on both arms, haematuria and rectal bleeding. INR was 17. She had been using miconazole oral gel for a week.

70/F on warfarin, one week after starting miconazole oral gel experienced epistaxis and haematuria. INR was 18.6.

74/F taking warfarin started having variable INR values up to 6. It was discovered she had been using miconazole oral gel. INR stabilised after stopping miconazole.

Ufondu et al [4]

Two men and two women aged 63-78 years developed elevated INR after starting topical miconazole. After 3-7 days of combined warfarin and miconazole INR increased from 2.0-3.3 to 6.1-16. One patient experienced minor bleeding.

McAvinchey et al [5]

86/M took miconazole gel for ulcerated tongue while also taking warfarin. INR increased to >10. Warfarin was stopped and replaced with clopidogrel and aspirin. INR reduced and the tongue lesions resolved.

Thomas et al [6]

50/F taking warfarin for prevention of DVT. Two days after routine check with INR 2 she started using miconazole vaginal cream. At next visit INR was 4.4 and she had used 1,000 mg miconazole in 5 consecutive doses. Miconazole was discontinued and following week INR was 2.3.

Morgan et al [7]

75/F stable on warfarin (INR 2.3-2.5) was prescribed miconazole oral gel by her dentist. 18 days later INR had increased to 14.1 and she had large bruises on arms and legs. After 4 days off warfarin INR was 6.2.

Devaraj et al [8]

80/M had been taking warfarin long term for atrial fibrillation, and his mean dose over the preceding 12 months was 6 mg daily. This dose had kept his INR between 2.2 and 3.1, but at a routine appointment it was found to be 21.4, although there had been no evidence of bruising or bleeding. He denied any change to his normal warfarin dose and had continued with his other usual once daily drugs (atenolol 50 mg, isosorbide mononitrate 20 mg, and diltiazem 400 mg). However, he had been applying topical miconazole cream for a fungal infection over the right groin area during the previous two weeks. He was admitted to hospital, where his warfarin and miconazole were withdrawn and he was given fresh frozen plasma. His INR returned to 3.2 and his warfarin was reinstated five days later at a daily dose of 6 mg. Since he was discharged he has remained on warfarin 6 mg and his INR has been stable.

Thirion et al [9]

53/F treated with warfarin developed ecchymosis after she started intravaginal miconazole. INR had been stable at 1.77-4.65 for 18 months. On third day of miconazole INR was 9.77. Warfarin was stopped for 2 days and then resumed. She required a further 7 day treatment with miconazole, her warfarin dose was decreased by 28% and 6 days later INR was 3.27. One year later she required another course of miconazole, warfarin dose was decreased by 19%, five days later INR was 7.13.

Shenfield et al [10]

43/F taking warfarin for 7 years due to recurrent DVT was prescribed miconazole oral gel for oral thrush. 10 days after starting she noticed a bruise and stopped miconazole. Central back pain and haematuria occurred over the next three days. She stopped warfarin and presented with marked haematuria, INR was elevated.

Clinical studies

One study was identified. Hellfritzsich et al [11] performed a cohort cross-over study to evaluate the potential drug-drug interaction between warfarin and miconazole oral gel. The authors used a clinical database called Thrombobase which includes information on vitamin K antagonist treated patients. Between 1998 and 2012 there were around 7,400 warfarin users. Potential interactions were assessed by comparing INR values before and after initiation of miconazole.

Miconazole oral gel was initiated in 53 warfarin users in the database. There were 17 warfarin users exposed to miconazole oral gel who met the study inclusion criteria. The mean INR increased from 2.5 (95% CI: 2.1-2.8) to 3.8 (2.8-4.8); mean INR increase 1.4.

Cases reported to the Centre for Adverse Reactions Monitoring

The Centre for Adverse Reactions Monitoring (CARM) receive and investigate reports of suspected adverse reactions to medicines. Cases of note are presented to the MARC for further review and recommendations for action.

A summary of reports detailing a potential interaction between warfarin and topical miconazole-containing medicines is provided in Table 2.

Table 2: Summary of cases reporting a potential interaction between warfarin and topical miconazole containing medicines reported to CARM

ID	Date	Age/ gender	Medicine details	Comments
017417	Jul 88	57/M	Oral gel	Bleed reported
024835	Sep 93	82/F	Oral gel, enalapril, thyroxine, digoxin	Bleed reported
028349	Apr 95	68/F	Oral gel, nifedepine, theophylline, prednisone	Bleed reported
028584	Jun 95	46/F	Oral gel, frusemide, spironolactone, ranitidine	Bleed reported
030004	Feb 96	70/F	Oral gel, medroxyprogesterone	No bleed reported
031049	May 96	79/F	Oral gel, budesonide, salbutamol, amphotericin B	Bleed reported
032712	Nov 96	67/F	Oral gel	Bleed reported
039263	Sep 98	83/M	Oral gel, frusemide, famotidine, terazosin	Bleed reported
056475	Jun 03	71/F	Oral gel, sotalol, amiodarone, hydroxyurea	No bleed reported
063181	Nov 04	73/F	Oral gel, diclofenac, paroxetine, simvastatin	Bleed reported
063752	Jan 05	81/F	Oral gel, metoprolol, simvastatin, cilazapril / hydrochlorothiazide	Bleed reported
074678	Mar 07	68/F	Oral gel, olanzapine, metformin, eformoterol	No bleed reported
079124	Jun 08	75/F	Oral gel	Bleed reported
091305	Aug 10	87/F	Oral gel, doxycycline, frusemide, digoxin	Bleed reported
105395	Jan 13	81/F	Oral gel, allopurinol, cefaclor, diltiazem	Bleed reported INR >20

106817	May 13	77/M	Oral gel, verapamil, fluticasone/salmeterol, omeprazole, digoxin cilazapril	Bleed reported INR >10
109356	Jan 14	79/F	Oral gel	Bleed reported INR elevated from 2.4 to 6.9
119413	Jan 16	88/M	Oral gel	No bleed reported. Used Decozol for 2 weeks INR >10
120848	May 16	67/M	Oral gel	No bleed reported. INR reported as very high returned to normal after stopping miconazole
120847	May 16	85/M	Cream, omega 3, garlic	No bleed reported. Used cream 3-4 times, INR 6.6, no other changes to medicines

Information published by other Regulators

MHRA

Up to 13 April 2016, the MHRA had received 146 Yellow Cards that report possible drug interactions between miconazole and warfarin. Most reports (128, 88%) concerned the oral gel form of miconazole.

The most frequently reported events were: increased international normalised ratio (INR, 111 reports); contusion (21); haematuria (17); and epistaxis (8). Approximately half of the 146 cases reported an INR increase above 10—ie, the patient was at significantly increased risk of bleeding events (noting that the target INR range for a patient on long-term warfarin therapy is usually between 2 and 3). In 3 cases, a fatal outcome was reported as a result of a haemorrhagic event.

Health Canada

In 2001 the agency reported 2 relevant case reports.

52/F presented with right sided renal haemorrhage 12 days after starting vaginal miconazole.

80/M had a CVA while using topical miconazole and warfarin, however the concurrent medicines and conditions made it impossible to establish causality.

Sponsors of miconazole-containing vaginal products were asked to update labelling, monograph and prescribing information.

FDA

In 2001 the FDA had received 2 reports of an interaction between warfarin and intravaginal miconazole resulting in abnormal blood clotting tests in both cases and bruising, bleeding gums and nose bleed in one case.

Harmonisation with Australian required statements

The required advisory statements for medicine labels (RASML) is the Australian equivalent to the Label Statements Database. The following statements for miconazole preparations for vaginal use are required.

- ☞ See a doctor if you are pregnant or diabetic.
- ☞ Seek medical advice before first course of treatment.
- ☞ See a doctor if problem returns.
- ☞ See a doctor if no better after [*Insert number of days as per approved Product Information*] days.

No mandatory label warning for warfarin interactions is required. However, the Australian regulatory guidelines for over the counter (OTC) medicines (ARGOM) Appendix 5 sets clear expectations for informing consumers of warfarin interactions for products for topical oral mucosal application containing miconazole:

Some azole antifungal agents (miconazole and fluconazole, in particular) may increase international normalised ratio (INR, a measure of blood clotting) levels in patients who are taking warfarin or other anticoagulants [due to inhibition of Cytochrome P450 2C9 (CYP2C9), which metabolises (S)-warfarin)].

The product information for OTC topical products for oral mucosal application containing miconazole should state that miconazole has been shown to increase INR levels in patients taking warfarin, as inhibition of CYP2C9 by miconazole reduces the metabolism of warfarin. Therefore, these patients may be at risk of increased bleeding or bruising. Consistent information should be included in the CMI for these products.

The labels or package inserts of OTC topical products for oral mucosal application containing miconazole should include a statement advising people who are taking warfarin or other anticoagulants to ask their doctor or pharmacist before using the product, because bleeding or bruising may occur.

Products Affected

Table 3: Miconazole-containing medicines available without prescription

Brand name	Dose form and strength	Sponsor	Classification	Data sheet / CMI published
Daktarin	Lotion 2%	Johnson & Johnson (New Zealand) Limited	Pharmacy only	No / No
Daktarin	Oral gel 2%		Restricted	Yes / No
Daktarin	Topical cream 2%		Pharmacy only	No / No
Daktarin	Topical powder 2%, powder spray 2%		Pharmacy only	No / No
Daktarin	Tincture topical solution 2%		Pharmacy only	No / No
Daktozin	Topical ointment (0.25%, zinc oxide 15%)		Pharmacy only	No / No
Decozol	Oral gel 2%	AFT Pharmaceuticals Ltd	Restricted	Yes / No
Miconazole	Topical cream 2%	Multichem NZ Limited	Pharmacy only	No / No
Micreme	Topical cream 2%	Mylan New Zealand Ltd	Pharmacy only	No / No
Micreme	Vaginal cream 2%		Restricted	Yes / Yes
Micreme H	Topical cream 2% (hydrocortisone)		Restricted	Yes / Yes
Resolve Jock Itch	Topical cream 2%	Douglas Pharmaceuticals Ltd	Pharmacy only	No / No
Resolve Nappy rash	Topical ointment (0.25%, zinc oxide 15%)		Pharmacy only	No / No
Resolve Plus	0.5% Topical cream		Pharmacy only	Yes / No
Resolve Plus	1.0% Topical cream		Restricted	Yes / No
Resolve	Topical solution 2%		Pharmacy only	No / No
Resolve Thrush	Vaginal cream 2%		Restricted	Yes / No
Resolve Tinea	Topical cream 2%		Pharmacy	No / No
Resolve Tinea	Topical powder 2%		Pharmacy	No / No

Discussion and conclusions

The majority of cases in the literature and reported to regulators describe an interaction between warfarin and the oral gel formulation of miconazole. This is probably because most of an oral gel dose will be swallowed, leading to greater exposure to miconazole.

Some of the literature cases describe a positive dechallenge (where the patient recovered after stopping miconazole use). In addition there are some cases describing a positive rechallenge (where the events recurred on reusing miconazole). Some very high INRs were reported as well as bleeding. While the number of reports appears to be low the outcome of the interaction may be life threatening.

Miconazole oral gel is classified as a restricted medicine and therefore a data sheet must be provided and a pharmacist must be involved in the sale. Nevertheless, cases of potentially serious interactions involving miconazole oral gel continue to be reported to CARM.

Reports of interactions occurring between warfarin and other topical miconazole products have also been reported, although less frequently. In these cases the interaction may have occurred as the product was applied to broken or inflamed skin, potentially increasing the absorption of miconazole.

It is likely that this interaction is under reported. The cases reported to CARM mainly involve patients who experienced bleeds. It is likely that there are also cases where the interaction did not result in a bleed.

Although label statements are not required in Australia the information must be provided in the patient leaflet if it is not on the package for the oral gel.

In New Zealand package label statements can be mandated, but package inserts are voluntary. A statement on the label can also act as a reminder to the pharmacist and pharmacy staff to question customers about warfarin use. Medsafe considers it important for patients to know about this interaction before purchasing the product as they may wish to use an alternative antifungal product.

Therefore, Medsafe is proposing that the Label Statements Database is updated to include warning statements for all miconazole-containing medicines that are available without prescription.

Proposed Label Statements

Medsafe proposes that a warning regarding the potential for interaction with warfarin is included on the labels of all topical miconazole-containing products (ie, topical cream, intravaginal preparations and oral mucosal presentations). The proposed statement is

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*].

Medsafe proposes that the Label Statements Database is also updated to include the following statements for intravaginal miconazole-containing products:

- ☞ See a doctor if you are pregnant or diabetic
- ☞ Seek medical advice before first course of treatment
- ☞ See a doctor if problem returns
- ☞ See a doctor if no better after [Insert number of days as per approved Product Information] days.

Medsafe is seeking comments on:

- ☞ whether a warning statement about the warfarin interaction is required for all topical miconazole products
- ☞ which of the proposed statements is preferred and why
- ☞ whether the Australian required advisory statements for intravaginal miconazole products should be mandated in New Zealand
- ☞ a suitable target date for implementation.

References

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