

16 October 2017

Miconazole (Daktarin) 20 mg/g oral gel: co-administration with warfarin now contraindicated except when Daktarin oral gel is specifically prescribed and used under medical supervision with close monitoring of INR

Dear Healthcare Professional,

Johnson & Johnson in agreement with the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- A contraindication has been introduced for concomitant use of miconazole oral gel (Daktarin) with warfarin, except when miconazole oral gel is specifically prescribed and used under medical supervision with close monitoring of INR.
- Miconazole is systemically absorbed and is known to inhibit CYP2C9 and CYP3A4, which can lead to prolonged effects of warfarin.
- Bleeding events, some with fatal outcomes have been reported with concurrent use of miconazole oral gel and warfarin.
- Patients should be advised to stop treatment with miconazole oral gel and seek medical advice if they experience unexpected bleeding or bruising.

Background on the safety concern

Miconazole oral gel is indicated in the management of fungal infections of the oral cavity and gastrointestinal tract in adults and paediatric patients 4 months or older. Miconazole is effective against some Gram positive bacteria in adults and paediatric patients 4 months and older, including *Streptococcus pyogenes*, *Staphylococcus aureus* and *Erysipelothrix*.

Miconazole is systemically absorbed and is known to inhibit both CYP2C9 and CYP3A4. Warfarin is a racemic mixture of S- and R-enantiomers. The more active S-warfarin enantiomer is primarily metabolised by CYP2C9. Decreased clearance of S-warfarin by inhibiting its hepatic metabolism leads to potentiation of the anticoagulant effect.

Increases in INR and bleeding events such as epistaxis, contusion, haematuria, melaena, haematemesis, haematoma and haemorrhages have been reported in patients treated with oral anticoagulants such as warfarin in association with miconazole oral gel. Some events had fatal outcomes.

Despite the current risk minimisation measures outlined in the product information, cases of suspected drug interaction between miconazole oral gel and warfarin continue to be reported. Cumulatively to August 2016, the overall reporting rate in Ireland for spontaneous cases reporting

bleeding with miconazole oral gel and concomitant use of warfarin was 5.11 (per 100,000 treatment course). Consequently, a contraindication has been introduced for concomitant use of miconazole oral gel with warfarin, except when miconazole oral gel is specifically prescribed and used under medical supervision with close monitoring of INR.

Patients should be advised to stop treatment with miconazole oral gel and seek medical advice if they experience unexpected bleeding or bruising, nosebleeds, coughing up blood, blood in the urine, black tarry stools or coffee ground vomit.

The product information for miconazole oral gel will be updated accordingly.

Please distribute this communication to all relevant staff.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Adverse events can also be reported to Johnson & Johnson at 1800 22 00 44

Annexes

Sections of the Summary of Product Characteristics (SmPC) have been updated. The additional updated texts have been provided below:

Section 4.3 Contraindications

Co-administration with warfarin is contraindicated except when oral miconazole gel is specifically prescribed and used under medical supervision with close monitoring of INR

Section 4.4 Special Warnings and Precautions for Use

Miconazole is systemically absorbed and is known to inhibit CYP2C9 and CYP3A4 (see Section 5.2 Pharmacokinetic Properties) which can lead to prolonged effects of warfarin. Bleeding events, some with fatal outcomes have been reported with concurrent use of miconazole oral gel and warfarin

The label (outer carton and tube) will state: WARNING: Do not use if you are taking warfarin unless Daktarin is prescribed by your doctor.

Patients should be advised that if they experience unexpected bleeding or bruising, nosebleeds, coughing up blood, blood in the urine, black tarry stools or coffee ground vomit, to stop treatment with miconazole and seek medical advice.

Section 4.5 Interactions with other Medicinal Products and other forms of interaction

Co-administration with warfarin is contraindicated except when oral miconazole gel is specifically prescribed and used under medical supervision with close monitoring of INR

Section 4.8 Undesirable Effects

Increases in INR and bleeding events such as epistaxis, contusion, haematuria, melaena, haematemesis, haematoma and haemorrhages have been reported in patients treated with oral



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anticoagulants such as warfarin in association with miconazole oral gel. Some events had fatal outcomes.

The full prescribing information is available from www.medicines.ie or www.hpra.ie

Yours sincerely,

Dr Gill Nelson
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