

## Can miconazole oral gel be used by patients taking a statin?

Prepared by UK Medicines Information ([UKMi](#)) pharmacists for NHS healthcare professionals  
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### Background

Miconazole is an azole antifungal used for treating oral and intestinal fungal infections (1,2). It is available as an oral gel which can be applied topically to lesions or ingested for intestinal infections (1,3). The Summary of Product Characteristics (SmPC) for miconazole oral gel (*Daktarin*) contraindicates co-administration of miconazole with drugs that are metabolised by the cytochrome P450 (CYP450) isoenzyme CYP3A4 including some HMG-CoA reductase inhibitors (statins) (1).

This Medicines Q&A explores the evidence for the interaction between miconazole oral gel and statins.

### Answer

When miconazole oral gel is applied locally, a sufficient quantity to cause systemic effects may be swallowed or absorbed systemically (2). Miconazole can inhibit the metabolism of drugs metabolised by CYP3A4 and CYP2C9 isoenzymes (3). Miconazole oral gel has been reported to increase INR in patients taking warfarin, indicating that it is absorbed systemically in sufficient amounts to result in clinically significant drug interactions (4,5).

The ability of azole antifungals to inhibit CYP450 isoenzymes is variable. Itraconazole and ketoconazole are potent inhibitors of CYP3A4 (but not potent inhibitors of CYP2C9); miconazole and fluconazole inhibit CYP3A4 and CYP2C9 (1,6-8). Fluconazole is a moderate CYP3A4 inhibitor (8). The potency by which miconazole inhibits CYP3A4 is unknown but might be similar to fluconazole (3).

Of the statins, atorvastatin and simvastatin are metabolised by CYP3A4 (9,10). Fluvastatin is metabolised by multiple alternative CYP450 pathways and so its metabolism is relatively insensitive to CYP3A4 and CYP2C9 inhibition (11). Rosuvastatin undergoes limited metabolism by CYP2C9, and to a lesser extent by CYP3A4, CYP2C19 and CYP2D6 (12). Pravastatin is not metabolised to a clinically significant extent by the CYP450 system (13).

The Medicines and Healthcare products Regulatory Agency (MHRA) acknowledges the potential for interaction between some of the statins and azole antifungals. It issued guidance in January 2008 advising that prescribing of potent inhibitors of CYP3A4, such as itraconazole and ketoconazole, should be avoided with atorvastatin and simvastatin; they did not discuss moderate inhibitors (14).

### What data are available to support an interaction between azoles and statins?

#### Miconazole

There do not appear to be any reports of an interaction between miconazole and any of the statins. However, like fluconazole, miconazole is an inhibitor of CYP3A4 and CYP2C9, and might be expected to interact in a similar way (3,4).

#### Fluconazole

- ◆ **Fluvastatin** - administration of fluconazole to 12 healthy subjects, who took a single dose of fluvastatin, resulted in an increase in the area under the curve (AUC) of fluvastatin by 1.8-fold (15).

- ◆ **Rosuvastatin** - administration of fluconazole to 14 healthy subjects resulted in a very small rise in AUC and plasma concentrations of rosuvastatin (4). No clinically significant adverse effects were reported (4).
- ◆ **Atorvastatin** - myopathy and rhabdomyolysis resulting in multiple organ failure and death occurred in a patient taking atorvastatin and fluconazole. The patient was previously taking pravastatin and fluconazole. Within one week of switching to atorvastatin he developed dyspnoea, myopathy, rhabdomyolysis and renal failure and later died; an interaction between the two drugs was considered the most likely cause of rhabdomyolysis (4).
- ◆ **Simvastatin** - a patient taking simvastatin developed generalised muscle weakness, brown urine and elevated serum creatinine kinase one week after starting fluconazole. Two similar cases of rhabdomyolysis have been reported in patients taking simvastatin and fluconazole. In both cases rhabdomyolysis resolved after discontinuing fluconazole (4).

#### Itraconazole

- **Fluvastatin** - administration of itraconazole to 10 healthy volunteers did not affect the pharmacokinetics of fluvastatin, apart from a small increase in its half-life (4,16).
- **Rosuvastatin** - concomitant administration of itraconazole and a single dose of rosuvastatin resulted in a 1.4-fold rise in rosuvastatin plasma levels (12).
- **Atorvastatin** - co-administration of itraconazole and a single dose of atorvastatin resulted in a 3.3-fold rise in atorvastatin plasma levels (9).
- **Simvastatin** - studies have shown itraconazole increases the AUC of simvastatin by 18.6-fold (17). High interpatient variability puts certain patients at much greater risk than others (17). Six case reports describe rhabdomyolysis in patients taking simvastatin after starting itraconazole (4). Symptoms started within two to three weeks of concurrent use (4).

#### Ketoconazole

- **Simvastatin** - five cases of rhabdomyolysis have been reported in patients taking simvastatin, which developed between seven days and four weeks after starting ketoconazole (4).

#### What are the implications of using miconazole oral gel in patients taking statins?

There are no data available that confirm concomitant use of miconazole and any of the statins results in a clinically significant interaction. The basis for the manufacturer's contraindication appears to be extrapolation from reports of interactions between other azoles and statins. Interactions are theoretically possible with all statins except pravastatin, but are unlikely, especially with fluvastatin and rosuvastatin for which metabolism via CYP3A4 is less important (9-13).

#### Pravastatin

Patients taking pravastatin can use miconazole oral gel as no interaction is expected (4,13).

#### Fluvastatin

Fluvastatin is metabolised by multiple CYP450 pathways, however not predominantly by CYP3A4 (11,17). Theoretically, fluvastatin is less likely to interact with miconazole (11,17). The manufacturer for fluvastatin states that metabolism is relatively insensitive to CYP450 inhibition (11).

Patients taking fluvastatin can use miconazole oral gel. If used together, patients should be advised to report any signs of myopathy and possible rhabdomyolysis (i.e. unexplained muscle pain, tenderness, weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately (4).

#### Rosuvastatin

Rosuvastatin undergoes limited metabolism. Approximately 10% is metabolised, principally by CYP2C9, and by CYP2C19, CYP3A4 and CYP2D6 to a lesser extent. The manufacturer of

rosuvastatin states that drug interactions resulting from CYP450-mediated metabolism are not expected (12).

Patients taking rosuvastatin can use miconazole oral gel. However, they should be advised to report signs of myopathy and possible rhabdomyolysis (i.e. unexplained muscle pain, tenderness, weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately (4).

### Atorvastatin

Atorvastatin is metabolised by CYP3A4, and concomitant use of miconazole and atorvastatin may increase atorvastatin levels (2,9,18).

The concomitant use of atorvastatin and miconazole should be avoided if possible. Cases of rhabdomyolysis have been reported with fluconazole, and as miconazole has the potential to interact similarly (4), prescribers should consider the benefits of treatment versus the risk of using the combination. If miconazole oral gel must be used, it may be prudent to temporarily withhold atorvastatin to avoid possible adverse effects but the patient's GP must be involved in this decision. If concurrent use is unavoidable then a lower dose of atorvastatin should be considered and the patient monitored for toxicity (4,9)

Patients taking atorvastatin and miconazole oral gel should be advised to report any signs of myopathy and possible rhabdomyolysis (i.e. unexplained muscle pain, tenderness, weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately (4). If long-term antifungal treatment is needed, it would seem safer to prescribe a non-azole antifungal agent for patients taking atorvastatin.

### Simvastatin

Simvastatin is a substrate of CYP3A4 (10). The SmPC for miconazole oral gel (*Daktarin*) contraindicates co-administration of miconazole oral gel and simvastatin due to the risk of myopathy and rhabdomyolysis (1). If miconazole oral gel must be used, simvastatin must be temporarily stopped but the patient's GP must be involved in this decision.

### Prescribing issues

As the SmPC for miconazole oral gel (*Daktarin*) contraindicates the co-administration of drugs metabolised by CYP3A4, miconazole is not licensed for use in patients taking atorvastatin, fluvastatin, rosuvastatin or simvastatin. However, if no suitable alternative exists it may be necessary to prescribe miconazole in combination with a statin. Prescribers should be aware that by doing this they will be prescribing *Daktarin* outside of the product licence and will take responsibility for their decision to do this should any adverse effects occur. If adverse effects do occur, these should be reported to the MHRA via the [Yellow Card Scheme](#).

### Summary

- ◆ Miconazole is an azole antifungal which inhibits CYP450 isoenzymes CYP2C9 and CYP3A4. It is absorbed systemically from the oral gel preparation and has the potential to raise plasma levels of drugs metabolised by these isoenzymes, increasing the risk of adverse effects.
- ◆ The Summary of Product Characteristics for miconazole oral gel (*Daktarin*) contraindicates co-administration of miconazole with drugs that are metabolised by CYP3A4, including fluvastatin, rosuvastatin, atorvastatin and simvastatin.
- ◆ There are no reports describing interactions between miconazole and any of the statins.
- ◆ **Pravastatin** - patients taking pravastatin can use miconazole oral gel. Pravastatin is not metabolised by CYP450 isoenzymes therefore no interaction is expected.

- ◆ **Fluvastatin and rosuvastatin** - these undergo limited CYP450 metabolism therefore a clinically significant interaction is unlikely. Miconazole oral gel could be used with caution provided patients are monitored for adverse effects.
- **Atorvastatin** - the concomitant use of atorvastatin and miconazole should be avoided if possible. If miconazole oral gel must be used, it may be prudent to temporarily withhold atorvastatin to avoid possible adverse effects but the patient's GP must be involved in this decision. If concurrent use is unavoidable then a lower dose of atorvastatin should be considered and the patient monitored for toxicity.
- **Simvastatin** - the SmPC for miconazole oral gel (Daktarin) contraindicates co-administration of miconazole oral gel and simvastatin due to the risk of myopathy and rhabdomyolysis. Simvastatin must be temporarily stopped if miconazole is prescribed; the patient's GP must be involved in this decision.
- Any patient taking a statin (other than pravastatin) who is given miconazole oral gel should be warned to watch for signs of myopathy (i.e. unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately.

### Limitations

There are no data for drug interactions with miconazole and azoles. All data available are for azoles other than miconazole.

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### Quality Assurance

#### Prepared by

Emily Westwood. North West Medicines Information Centre, 70 Pembroke Place, Liverpool, L69 3GF.

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#### Checked by

Helen Edmondson, Emma Parker and Joanne McEntee. North West Medicines Information Centre, 70 Pembroke Place, Liverpool, L69 3GF.

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#### Search strategy

1. Embase 1974 to date – (exp MICONAZOLE/ AND (exp “HYDROXYMETHYLGLUTARYL COENZYME A REDUCTASE INHIBITOR”/ OR “ATORVASTATIN CALCIUM”/ OR exp FLUINDOSTATIN/ OR “PRAVASTATIN SODIUM”/ OR “ROSUVASTATIN CALCIUM”/ OR exp SIMVASTATIN/)) for information added since 01/01/14. Limit humans.
2. Embase 1974 to date – (exp “CYTOCHROME P450”/ AND (exp FLUCONAZOLE/ OR exp ITRACONAZOLE/ OR exp KETOCONAZOLE/ OR exp CLOTRIMAZOLE/ OR exp MICONAZOLE/ OR exp VORICONAZOLE/ OR exp “PYRROLE DERIVATIVE”/)) for information added since 01/01/14. Publication type: review. Limits: English language and humans.
3. Medline 1946 to date – (exp MICONAZOLE/ AND (exp “HYDROXYMETHYLGLUTARYL COENZYME A REDUCTASE INHIBITORS”/ OR exp ATORVASTATIN/ OR exp FLUVASTATIN/ OR exp PRAVASTATIN OR exp “ROSUVASTATIN CALCIUM”/ OR SIMVASTATIN/)) for information added since 01/01/14.

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