



### **Aliskiren – New contraindications and warnings due to the risks of cardiovascular and renal adverse reactions (Brands include Rasilez, Rasilez HCT, Rasilamlo)**

Aliskiren is an antihypertensive agent which inhibits the renin-angiotensin-aldosterone system through a direct effect on renin. It has been licensed for use across the EU since 2007.

A review of aliskiren-containing medicines was initiated by the European Medicines Agency (EMA) in December 2011 after the ALTITUDE study was terminated early on the basis of preliminary interim analyses. The ALTITUDE study (ALiskiren Trial In Type 2 diabetes Using cardiovascular and renal Disease Endpoints) was a 4-year, randomised, placebo-controlled trial that included patients with type II diabetes and renal impairment and/or cardiovascular disease. The study was designed to evaluate the effect of aliskiren on the risk of cardiovascular and renal events in these high-risk patients and participants received aliskiren or placebo in addition to either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

The interim analysis showed that study patients were unlikely to benefit from aliskiren and there was a higher incidence of non-fatal strokes, renal complications (including acute renal failure), hyperkalaemia and hypotension in patients in the aliskiren group. In December 2011, healthcare professionals were informed of the interim results of the trial and advised that aliskiren use in combination with an ACE inhibitor or an ARB was contraindicated in all diabetic patients.

Further review of analyses from the ALTITUDE study, alongside data from other studies and spontaneous reports, confirmed the risk of adverse outcomes (hypotension, syncope, stroke, hyperkalaemia, and changes in renal function including acute renal failure) when aliskiren is combined with ACE inhibitors or ARBs, especially in diabetic patients and those with impaired renal function. Although less evidence is available for other patient groups, adverse outcomes cannot be excluded and therefore the combination is not recommended for any patient.

In addition, use of aliskiren is no longer recommended in any patient with severe renal impairment (GFR <30 ml/min per 1.73m<sup>2</sup>) irrespective of whether it is used in combination with an ACE inhibitor or an ARB, another antihypertensive, or as monotherapy. This recommendation is based on an analysis of postmarketing surveillance data that showed an increased risk of renal adverse events and hyperkalaemia with aliskiren in this patient group.

#### **Advice for healthcare professionals**

- Prescribers should review the treatment of all patients taking aliskiren in combination with an ACE inhibitor or an ARB at a routine appointment.
- Treatment with aliskiren-containing medicines should be discontinued (or not initiated) in diabetic patients, or non-diabetic patients with renal impairment (GFR < 60ml/min/1.73m<sup>2</sup>) who are taking an ACE inhibitor or an ARB.
- Aliskiren in combination with ACE inhibitors or ARBs is not recommended in any other patient groups.
- Use of aliskiren (either as monotherapy or in combination) is no longer recommended in patients with severe renal impairment (GFR <30ml/min per 1.73 m<sup>2</sup>).
- The benefits and risks of continuing aliskiren treatment should be considered carefully at the individual patient level.
- Alternative antihypertensive treatment should be considered as necessary.

#### **Key Message**

**Use of aliskiren in combination with ACE inhibitors or ARBs is contraindicated in:**

- diabetic patients (type I or type II); and
- non-diabetic patients with renal impairment (GFR <60ml/min per 1.73m<sup>2</sup>).

**In all other patient groups, the combination is not recommended.**

**Use of aliskiren is no longer recommended in any patient with severe renal impairment.**

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## Proton pump inhibitors – Small increased risk of bone fractures with long term use in patients with risk factors

Proton pump inhibitors (PPIs) are indicated in the treatment of gastric and duodenal ulcers, NSAID-associated ulcers, gastro-oesophageal reflux, Zollinger-Ellison syndrome and in combination with antibacterial therapy for eradication of *Helicobacter pylori*. Some products are indicated for short term use to treat reflux symptoms in adults (see individual SPCs on [www.imb.ie](http://www.imb.ie) for full details of licensed indications).

Following the publication of several pharmacoepidemiological studies, the Pharmacovigilance Working Party (PhVWP) reviewed data from clinical trials and observational studies investigating the risk of fracture with use of proton-pump inhibitors (PPIs).<sup>1-10</sup> The evidence from the pharmacoepidemiological studies and meta-analyses of these studies<sup>11,12</sup> suggested that there is a modest increase in fracture overall (by 10-40%), and specifically hip fracture (by 10-50%) and spine fracture (by 30-80%)<sup>3</sup>. There were inconsistencies between studies in terms of the magnitude of the risk and the duration of time-to-event. PPIs increased the risk of hip fracture significantly after exposure of at least 1 year, 2 years and 7 years respectively in three studies<sup>1,8,3</sup>. Two meta-analyses<sup>11,12</sup> of the published pharmacoepidemiological studies reported adjusted odds ratios of 1.20 (95% CI 1.11–1.30) and 1.29 (95% CI 1.18–1.41) for any fracture, 1.23 (95% CI 1.11–1.36) and 1.31 (95% CI 1.11–1.54) for hip fracture, 1.50 (95% CI 1.32–1.72) and 1.56 (95% CI 1.31–1.85) for spine fracture.

The primary studies varied with respect to the potential confounders that were adjusted for. Age, sex and concomitant medication were amongst the variables included in the adjustments. Some studies lacked information on important potential confounders such as smoking, alcohol abuse, body mass index and calcium and vitamin D exposure. One study<sup>4</sup>, which excluded subjects with potential risk factors for fractures, did not find an association between PPI use and increased risk of fracture.

It was concluded that there is a small increased risk of hip, wrist and spine fractures, predominantly in the elderly or in those with other recognised risk factors, especially if PPIs are used in high doses and over

prolonged periods of time (> 1 year). The majority, but not all of the studies showed a small increased risk of fractures, however in view of the extensive usage of PPIs, it was considered that information on the risk should be included in the product information where authorised for longer term use.

Use of PPIs obtained over-the-counter without prescription was not examined in these studies and the evidence was not considered sufficiently robust to indicate an increase in risk for PPI-containing medicinal products available without prescription, as these are only authorised for short-term use.

Several potential pathophysiological mechanisms of PPIs could have a role in increasing the risk of bone fractures including effects on calcium balance, magnesium balance, vitamin D and parathyroid hormone levels, and inhibition of vacuolar H<sup>+</sup>-ATPase and its effects on bone turnover. However, there is currently no unequivocal pharmacological explanation for the increased risk of fractures.

### Advice to Healthcare Professionals

- Long term use of PPIs (>1 year), especially at high doses is associated with a modest increase in the risk of fractures predominantly in the elderly and those with other recognised risk factors.
- Observational studies suggest that PPIs may increase the overall risk of fracture by 10 to 40%. Some of this increase may be due to other risk factors.
- Patients at risk of osteoporosis should receive care according to current clinical guidelines and should have an adequate intake of vitamin D and calcium.

#### Key Message

**Proton pump inhibitors, especially if used at high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in those with other recognised risk factors.**

1. The active substances included in this review were esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole. See [www.imb.ie](http://www.imb.ie) for authorised product names and SPCs for these products.

References available upon request from the Irish Medicines Board

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## Oral Methotrexate – Risk of unintentional overdose due to medication errors

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Oral methotrexate is indicated in the treatment of active rheumatoid arthritis, adult psoriasis and in a number of oncological indications, with differing dosage regimens for the respective indications (see section 4.2 of the Summary of Product Characteristics (SPC) available on [www.imb.ie](http://www.imb.ie)).

For rheumatology and dermatology indications, methotrexate should be administered as a once weekly dose only. The patient and/or carers should be informed of the risks associated with overdose and the need to adhere to once weekly dosing. For these indications, it is also suggested that the day of intake should be specified on the prescription and dispensing label.

Medication errors resulting in inadvertent overdose due to erroneous daily intake of the weekly dose have been reported in Ireland and elsewhere. The IMB has also received reports of strength confusion resulting in error between the 10 mg and 2.5 mg tablets. The IMB would like to remind healthcare professionals of the need for vigilance when prescribing, dispensing, administering and counselling patients and/or carers in relation to methotrexate, particularly following initiation of treatment, a change in the dose, or a change in the tablet strength usually taken.

In the context of experience across the EU in relation to this issue, the PhVWP of the EMA recently reviewed this issue to consider possible additional, regulatory actions to further minimise the risk of medication error with oral methotrexate.

The review of relevant, reported cases indicated that serious adverse drug reactions, some of which were fatal, occurred particularly due to the haematological toxicity of methotrexate. The root causes of the medication errors ranged from prescribing and administration errors (mainly for hospitalised patients) to errors in self-administration (by patients at home, either inadvertently, or by misunderstanding the medication schedule).

The PhVWP recommended that the product information (SPC and Package Leaflet) be updated to emphasize the need for adherence to once weekly dosing for rheumatology and dermatology indications and to include warnings on the risks of overdose (in particular the risks of haematological and gastrointestinal reactions).

### Advice to Healthcare Professionals

- Methotrexate, for dermatology and rheumatology indications, should be taken as a single once weekly dose.
- Prescribers are advised to specify the day of intake on the prescription for clarity.

- Cases of overdose, sometimes fatal, due to erroneous daily intake instead of weekly intake have been reported. In these cases, symptoms commonly reported are haematological and gastrointestinal reactions.
- Healthcare professionals should ensure that the patient and/or their carer understands the prescribed therapy, including the dose and frequency, with any treatment changes highlighted. Great care should be taken to give and repeat clear instructions on dosage.
- Patients and/or carers should also be informed of the potential risk of serious adverse reactions in the case of overdose and of the signs and symptoms of toxicity.
- Any adverse drug reactions suspected to be related to a medication error with methotrexate should be notified to the IMB in the usual way.

#### Key message

**Methotrexate for oral use in rheumatology and dermatology indications should be taken once a week only.**

**Patients and/or carers should be informed of the risk of overdose due to erroneous daily intake of the weekly dose.**

**Healthcare professionals should also be aware of the risk of error due to strength confusion.**

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## Miconazole oral gel (Daktarin oral gel) – Interaction with warfarin

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Miconazole is a broad spectrum imidazole antifungal known to inhibit CYP3A4/2C9 enzymes when administered systemically. Miconazole oral gel can be absorbed to a sufficient extent to affect warfarin metabolism and hence increase its anticoagulant effect by inhibiting these cytochrome P450 enzymes. The product information for **Daktarin Oral Gel** advises that the anticoagulant effect should be carefully monitored if warfarin is used at the same time.

The IMB has received reports of drug interaction between miconazole oral gel and warfarin resulting in clinically significant international normalised ratio (INR) increases. As miconazole oral gel is available without a prescription, prescribers and pharmacists are reminded to inform patients taking warfarin about the potential for interaction with miconazole oral gel.

#### Key Message

**Clinically significant increases in the INR of patients who have been stabilised on warfarin can occur following concomitant use of miconazole oral gel. The anticoagulant effect of warfarin should be carefully monitored if miconazole oral gel and warfarin are used at the same time.**



## Children's liquid paracetamol medicines\* – New dosage instructions

New dosage instructions will be included on the product information supplied with liquid paracetamol medicines for paediatric use in order to ensure that children get the most effective amount of paracetamol for their age and to optimise the safe use of these products. The IMB recommendations represent a refinement of the existing paediatric posology for these products rather than a response to any safety concern.

1. Paediatric posology for liquid oral formulations of paracetamol will be altered to a posology based on narrower age bands with a single dose per band.
2. Liquid paracetamol medicines for paediatric use should be administered with a suitable measuring device to assist accurate administration.

### Rationale and background to the recommendations

Paediatric paracetamol dosage can be calculated in mgs per kg body weight for individual patients however this is not always practical for parents to manage at home. The new doses recommended by the IMB more closely match amounts based on body weight by introducing narrower age bands, and by defining a single dose per age band, which increases between age bands stepwise by 2.5 ml.

### Implementation of the updated dosage instructions

Medicines with the new dosage information will begin to be introduced to pharmacies over the coming months. In the meantime, as this is not a safety issue, the IMB is advising parents and carers to follow the instructions on the current product information. Parents should be reminded that the dosing interval and the maximum daily dose recommended on the packaging should never be exceeded and that no other paracetamol-containing medicine should be administered.

## Advice to Healthcare Professionals

There are two different strengths of liquid paracetamol formulations for children, the changes apply to both.

### Infant paracetamol suspension (120 mg/5ml)

Under the current dosage instructions, liquid paracetamol-containing medicines (**120mg/5ml**) have two single age bands ranging from 3 months to 1 year and from 1 year to 6 years. In the updated instructions, there will be four separate age bands as follows:

Child's Age	How Much	How often (in 24 hours)
3-6 months	2.5 ml	4 times in 24 hours
6-24 months	5 ml	4 times in 24 hours
2-4 years	7.5 ml	4 times in 24 hours
4-6 years	10 ml	4 times in 24 hours

### Paracetamol six plus suspension (250 mg/5ml)

For liquid paracetamol-containing medicines for children aged over 6 years (250mg/5ml), the following new age bands and doses will apply:

Child's Age	How Much	How often (in 24 hours)
6-8 years	5 ml	4 times in 24 hours
8-10 years	7.5 ml	4 times in 24 hours
10-12 years	10 ml	4 times in 24 hours

This information was recently communicated to healthcare professionals, a copy of [the communication](#) is available on [www.imb.ie](http://www.imb.ie). The communication should be highlighted to relevant pharmacy staff, where appropriate.

\* The updates apply to single-constituent oral liquid paracetamol medicines for paediatric use. A list of medicines affected is available on [www.imb.ie](http://www.imb.ie) along with the updated SPCs for the relevant medicines.

## Direct Healthcare Professional Communications published on the IMB website since the last Drug Safety Newsletter

Product	Safety Issue
<a href="#">Vitreliis (boceprevir)</a>	Interaction with ritonavir-boosted HIV protease inhibitors.
<a href="#">Aliskiren-containing medicines (Rasilez, Rasilez HCT, Rasilamlo)</a>	New contraindications and warnings.
<a href="#">Brinavess (Vernakalant)</a>	Recommendations for monitoring blood pressure and heart rate during and after vernakalant infusion.
<a href="#">Benlysta (belimumab)</a>	Risk of hypersensitivity and infusion reactions.
<a href="#">Onglyza (saxagliptin)</a>	Association with serious hypersensitivity reactions and acute pancreatitis.