Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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The combination of aliskiren (Rasilez) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been associated with adverse cardiovascular and renal outcomes in a recent large clinical trial (ALTITUDE). This combination is now contraindicated in: diabetic patients (type I or type II); and non-diabetic patients with an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2.

In all other patient groups, aliskiren in combination with an ACE inhibitor or an ARB is not recommended. Any use of aliskiren (either as monotherapy or in combination with other medicines) is no longer recommended in patients with severe renal impairment: eGFR <30mL/min (see article A1 for more information).

Following a review by the Commission on Human Medicines, the marketing authorisation (licence) for levothyroxine 100 microgram tablets manufactured by Teva has been suspended. The review examined reports of potential reduced efficacy when switching to Teva levothyroxine from other levothyroxine products and evidence of manufacturing difficulties (see article S1 for more information).

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Drug safety advice

A1 Aliskiren (Rasilez▼): risk of cardiovascular and renal adverse reactions—new contraindications and warnings

The combination of aliskiren (Rasilez▼) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been associated with serious adverse cardiovascular and renal outcomes in a recent large clinical trial (ALTITUDE). This combination is now contraindicated in:

- diabetic patients (type I or type II); and
- non-diabetic patients with an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2

In all other patient groups, aliskiren in combination with an ACE inhibitor or an ARB is not recommended.

Any use of aliskiren (either as monotherapy or in combination with other medicines) is no longer recommended in any patient with severe renal impairment: eGFR <30 mL/min per 1.73 m^2

Aliskiren inhibits the renin-angiotensin-aldosterone system (RAAS) by a direct effect on renin, blocking the conversion of angiotensinogen to angiotensin I. It has been licensed in the UK since 2007 for the treatment of essential hypertension at a dose of 150–300 mg once a day.

Early discontinuation of the ALTITUDE study

The ALTITUDE study (ALiskiren Trial In Type 2 diabetes Using cardiovascular and renal Disease Endpoints) was a 4-year, multicentre, randomised, placebo-controlled trial that looked at type II diabetic patients at high risk of cardiovascular and renal events who were randomised to receive either aliskiren 300 mg daily or placebo.

The study was designed to evaluate the effect of aliskiren on the risk of cardiovascular and renal events in these high-risk patients. All patients recruited into the trial were already taking either an ACE inhibitor or ARB, so those patients randomised to the aliskiren group received two agents that block the RAAS (dual RAAS block). In total, over 8600 patients were recruited into the study.

The ALTITUDE study was halted early in December 2011 following an interim analysis that showed:

- study patients were unlikely to benefit from aliskiren; and
- an increased incidence of non-fatal strokes, renal complications (including acute renal failure), hyperkalaemia and hypotension in patients randomised to the aliskiren group

In January 2012 prescribers were informed of the interim results of the ALTITUDE trial and advised that aliskiren in combination with an ACE inhibitor or an ARB is contraindicated in all diabetic patients.

Latest advice following a Europe-wide review

Further review of analyses from the ALTITUDE study, alongside all data from other studies and spontaneous reports of suspected adverse drug reactions now confirm a 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.

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Severe renal impairment

In addition, prescribers should note that use of aliskiren is no longer recommended in any patient with severe renal impairment—ie, an eGFR <30 mL/min per 1.73m^2, 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
- In patients who are taking an ACE inhibitor or an ARB, healthcare professionals should stop aliskiren and not initiate new treatment in:
    - diabetic patients; and
    - non-diabetic patients with an eGFR <60 mL/min per 1.73 m^2
- Aliskiren in combination with ACE inhibitors or ARBs is not recommended in any other patients. The benefits versus risks of continuing aliskiren treatment should be considered carefully
- If aliskiren is discontinued then alternative antihypertensive agents should be used as necessary
- Use of aliskiren (either as monotherapy or in combination with other medicines) is no longer recommended in patients with severe renal impairment—ie, eGFR <30mL/min per 1.73 m^2
- In all patients where aliskiren treatment is continued or initiated, eGFR and glucose tolerance should be monitored at appropriate intervals
- Please report suspected adverse reactions to aliskiren on a Yellow Card (www.mhra.gov.uk/yellowcard)

Further information
Prescribers are reminded of NICE guidelines for the management of hypertension published in August 2011 (http://guidance.nice.org.uk/CG127) and note that, at present, these guidelines do not recommend the use of aliskiren.

See also letter for healthcare professionals sent Feb 2012: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON146475

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Stop press

S1 Teva levothyroxine 100 microgram tablets: potential reduced efficacy—suspension of marketing authorisation

Following a review by the Commission on Human Medicines (CHM), the marketing authorisation (licence) for levothyroxine 100 microgram tablets manufactured by Teva has been suspended.

The CHM review examined sporadic reports of potential reduced efficacy when switching to Teva levothyroxine from other levothyroxine products and evidence of manufacturing difficulties. As a precautionary measure while investigations are ongoing, Teva has ceased manufacture and distribution of levothyroxine 100 microgram tablets. Only the Teva and Numark brands of this product are affected by the suspension.

Teva levothyroxine 100 microgram tablets will cease to be available in the UK within the next few weeks, and no further supplies of this product will be released for marketing. Teva is accepting returned stock via the normal channels if it is not required to meet patient needs*. Other levothyroxine 100 microgram products will continue to be available.

*Please liaise with your wholesaler or arrange for uplift via Teva's Customer Liaison team (0800 590 502) in the usual manner if you wish to return the Teva /Numark levothyroxine 100 microgram packs.

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Further information

Central Alerting System alert for the suspension of Teva levothyroxine 100 microgram tablets (issued Feb 16, 2012, see https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=101734)

MHRA press release on suspension of Teva levothyroxine: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON143688

Q&A document on Teva levothyroxine suspension: http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con143690.pdf

Advice for healthcare professionals:

- Prescribers should be alert to the possibility that a change in a patient's symptoms and TSH status may be attributed to switching to Teva product from another levothyroxine product
- Certain patient groups such as pregnant women, patients with heart disease, and patients receiving treatment with levothyroxine following treatment for thyroid cancer should be monitored closely. If taking Teva tablets, they should have an early appointment with their doctor for a clinical review and blood test
- The majority of patients will be able to continue with their medication and change to a different levothyroxine product at their next prescription
- Patients who experience a significant change in symptoms especially after switching should have their TSH status reviewed and their dose of levothyroxine adjusted accordingly
- You can report suspected lack of efficacy on a Yellow Card (www.mhra.gov.uk/yellowcard)

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Stop press

S1 **Unlicensed imported vitamin D (colecalciferol) capsules: potential peanut oil and soya oil allergens**

Vigantoletten and Dekristol vitamin D (colecalciferol) capsules are unlicensed medicines in the UK. However, they are legitimately imported and supplied in their original German language livery for the special needs of individual patients only on prescription under the direct responsibility of the prescriber. The German labelling of these products states that Vigantoletten capsules contain soya oil, and that Dekristol capsules contain arachis (peanut) oil. This is unlikely to be evident to non-German speakers. Healthcare professionals should be aware that these capsules contain potential allergens.

Furthermore, imported unlicensed vitamin D Osto D2 capsules from Canada and Drisdol capsules from the USA may pose a similar allergen risk. Although labelled in English, the products may not explicitly state that they contain soya oil.

Further information:

Drug safety information for Vigantoletten capsules: http://www.mhra.gov.uk/Publications/Safetywarnings/DrugAlerts/CON140798

Drug safety information for Dekristol capsules: http://www.mhra.gov.uk/Publications/Safetywarnings/DrugAlerts/CON140797

Unlicensed or off-label use of medicines: prescribers' responsibilities: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087990

Advice for healthcare professionals:

- Allergy to soya oil or arachis oil may lead to severe allergic reactions, including anaphylaxis
- These products are contraindicated in patients with relevant allergies. Doctors and pharmacists should enquire whether patients have any relevant allergies before supplying these medicines
- Importers are advised that prescribers must be made aware of this contraindication

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