16 February 2012
EMA/113677/2012[1]

Questions and answers on the review aliskiren-containing medicines

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

The European Medicines Agency has completed a review of aliskiren-containing medicines, following the early termination of a study investigating aliskiren. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of aliskiren-containing medicines continue to outweigh their risks but recommended changes to the product information for these medicines to restrict their use. In particular, aliskiren must not be prescribed in combination with other medicines called ACE inhibitors or ARBs to patients with diabetes or with moderate or severe kidney impairment. In addition, the combination is not recommended in all other patients.

What are aliskiren-containing medicines?

Aliskiren-containing medicines are used to treat essential hypertension (high blood pressure) in adults. 'Essential' means that the hypertension has no obvious cause.

Aliskiren is a renin inhibitor. It blocks the activity of a human enzyme called renin, which is involved in the production of a substance called angiotensin I in the body. Angiotensin I is converted into the hormone angiotensin II, which is a powerful vasoconstrictor (a substance that narrows blood vessels). By blocking the production of angiotensin I, levels of both angiotensin I and angiotensin II fall. This causes vasodilation (widening of the blood vessels), so that the blood pressure drops.

Eight aliskiren-containing medicines have been authorised in the European Union (EU) since 2007: Rasilamlo, Rasilez, Rasilez HCT, Rasitrio, Riprazo, Riprazo HCT, Sprimeo and Sprimeo HCT. Some of these medicines (Rasilamlo, Rasilez HCT, Rasitrio, Riprazo HCT and Sprimeo HCT) are combinations of aliskiren with other antihypertensive medicines. Aliskiren-containing medicines are available as tablets and marketed in all EU Member States, except Estonia, Latvia, Lithuania and Romania.

Why were these medicines reviewed?

On 19 December 2011, the marketing authorisation holder for aliskiren-containing medicines, Novartis Europharm Ltd., informed the Agency of its decision to terminate the ALTITUDE study early. The study

[1] Procedure numbers: EMEA/H/C/002073/A20/0016, EMEA/H/C/000780/A20/0063, EMEA/H/C/000964/A20/0026, EMEA/H/C/002017/A20/0001, EMEA/H/C/000853/A20/0069, EMEA/H/C/002420/A20/0015, EMEA/H/C/000851/A20/0067, EMEA/H/C/002421/A20/0011.

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was designed to determine whether aliskiren, on top of conventional antihypertensive treatment including an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), reduces the risk of disease and death from cardiovascular (heart and circulatory) or kidney problems in patients with type 2 diabetes and kidney impairment and/or cardiovascular disease.

Termination of the study was recommended by the independent Data Monitoring Committee overseeing it, because the results showed that there was no benefit from aliskiren in this study, and that patients treated with aliskiren together with an ACE inhibitor or ARB experienced a higher number of cardiovascular and kidney problems than patients given placebo. This particularly involved stroke, kidney complications, hyperkalaemia (high blood potassium levels) and hypotension (low blood pressure).

Consequently, on 20 December 2011 the European Commission asked the CHMP to assess the impact of the new safety data on aliskiren and to issue an opinion on whether the marketing authorisation for aliskiren-containing medicines should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed the available interim data from the ALTITUDE study, as well as interim data from other ongoing clinical studies and relevant data from completed studies with aliskiren. It also reviewed reports of side effects from post-marketing surveillance.

What are the conclusions of the CHMP?

On 22 December 2011, although the information available at the time was limited, the CHMP recommended, as a precautionary measure, that doctors should not prescribe aliskiren-containing medicines to diabetic patients in combination with ACE inhibitors or ARBs[2].

Since then, further data from the ALTITUDE study have become available. Although the CHMP noted that the final data from the ALTITUDE study are still awaited, it agreed that the interim results from this study, together with the other available data, provide evidence that aliskiren in combination with an ACE inhibitor or ARB could increase the risk of cardiovascular and kidney problems, even though the mechanism through which this may happen remains unclear.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefit-risk balance for aliskiren when used together with an ACE inhibitor or ARB is considered unfavourable in patients with diabetes or with moderate or severe kidney impairment. Therefore, the CHMP recommended that the product information for aliskiren-containing medicines be amended to contraindicate their use in combination in these patients.

The Committee also noted that although side effects such as hypotension, stroke and kidney complications were seen particularly in patients with diabetes or impaired kidney function, adverse outcomes cannot be excluded in other patients. Therefore, the Committee included a warning that the combination with an ACE inhibitor or ARB is not recommended in all other patients. A communication will be distributed to doctors at national level to inform them of the changes to aliskiren use.

The amended information to doctors and patients are detailed here.

[2] For more information, see: European Medicines Agency starts review of aliskiren-containing medicines following termination of ALTITUDE study.

What are the recommendations for prescribers?

- Doctors should prescribe aliskiren-containing medicines according to the amended product information and should review the treatment of patients taking aliskiren in combination with an ACE inhibitor or ARB at a routine appointment.
- Doctors should stop prescribing aliskiren-containing medicines to patients with diabetes (type 1 or type 2) or with moderate or severe kidney impairment who are taking an ACE inhibitor or an ARB.
- As the combination of aliskiren with ACE inhibitor or an ARB is not recommended in all other patients, doctors should carefully consider the benefits and risks of continuing aliskiren treatment in patients receiving these medicines.

What are the recommendations for patients?

- Patients should not stop any of their treatment before speaking to their doctor, because stopping antihypertensive medication without medical supervision can put them at risk.
- Patients are advised to discuss their treatment with their doctor at their next scheduled (non-urgent) appointment.
- Other ongoing clinical trials with aliskiren will continue. Patients who have any questions should make an appointment with the doctor who is treating them in the trial (investigator) to discuss their treatment.

A European Commission decision on this opinion will be issued in due course.

The current European public assessment reports for the eight aliskiren-containing medicines concerned by this referral (Rasilamlo, Rasilez, Rasilez HCT, Rasitrio, Riprazo, Riprazo HCT, Sprimeo, Sprimeo HCT) can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.