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Avaglim EMEA/H/C/000675/A20/0029
Avandamet EMEA/H/C/000522/A20/0063

Questions and answers on the suspension of rosiglitazone-containing medicines (Avandia, Avandamet and Avaglim)

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

The European Medicines Agency has completed a review of rosiglitazone-containing medicines at the request of the European Commission, following reports of an increase in the risk of cardiovascular problems with rosiglitazone. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that, at present, the benefits of rosiglitazone do not outweigh its risks, and that the marketing authorisation for all rosiglitazone-containing medicines should be suspended across the European Union (EU). The suspension means that, within the next few months, Avandia, Avandamet and Avaglim will no longer be available in all EU Member States.

The suspension will remain in place unless convincing data are provided that identify a group of patients in whom the benefits of the medicines outweigh their risks.

What is rosiglitazone?

Rosiglitazone-containing medicines are used in type 2 diabetes, a disease in which the pancreas does not make enough insulin to control the level of glucose in the blood or when the body is unable to use insulin effectively. They are available as tablets containing rosiglitazone on its own (Avandia) or as tablets where rosiglitazone is combined with other anti-diabetes medicines, metformin hydrochloride in Avandamet and glimepiride in Avaglim.

Rosiglitazone belongs to the class 'thiazolidinediones'. These antidiabetic substances work by attaching to receptors called 'PPAR receptors' in fat, muscle and liver cells, making them more sensitive to insulin, which means that the body makes better use of the insulin it produces. As a consequence, the blood glucose is reduced and this helps to control diabetes.

Avandia has been authorised in the EU since 11 July 2000, Avandamet since 20 October 2003 and Avaglim since 27 June 2006. Avandia and Avandamet are marketed in all Member States as well as Norway, Iceland and Liechtenstein. Avaglim is marketed in Belgium, Austria, Denmark, Germany, Greece, Hungary, Iceland, Italy, the Netherlands, Romania, Slovakia, Spain and Sweden. The medicines are made by GlaxoSmithKline.

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Why were rosiglitazone-containing medicines reviewed?

Since Avandia's first authorisation, rosiglitazone has been recognised to be associated with fluid retention and an increased risk of heart failure. The issue was discussed during the initial assessment of Avandia, and the authorisation granted clearly stated that patients with heart failure or a history of heart failure should not be prescribed rosiglitazone. The medicine was to be used only in patients whose diabetes did not respond satisfactorily to treatment with other anti-diabetes medicines. In addition, the company agreed to carry out further cardiovascular studies.

Over the years, the Agency has been monitoring the cardiovascular safety of rosiglitazone-containing medicines closely, and has reviewed the results of the cardiovascular studies carried out by the company, as well as data from other information sources and from the published literature. As a result, the use of these medicines has been further restricted, with new warnings and clear restrictions on the use of the medicines in patients with ischaemic heart disease (disease of the heart caused by failure in the blood supply)[1].

The number of prescriptions for rosiglitazone has declined significantly since 2007 reflecting the prescribers' awareness of these safety issues and the latest labelling restrictions.

In June 2010, two further scientific articles became available suggesting that Avandia may be linked to an increased risk of heart problems[2]. This triggered a formal review by the CHMP to assess the new information and its impact on the risk benefit balance of rosiglitazone-containing medicines, and to issue an opinion on whether the marketing authorisation for rosiglitazone-containing medicines should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The Committee looked at all the data available for rosiglitazone, and in particular, at the information that had become available since the last review of the medicines (in March 2010). This included the new publications as well as data from the Food and Drugs Administration (FDA) in the United States of America, including the results of meta-analyses. The CHMP also consulted a group of experts in diabetes and cardiovascular diseases and patients' representatives.

What are the conclusions of the CHMP?

Looking at the latest data, the Committee noted that the data added to previous concerns with rosiglitazone and indicated an increased cardiovascular risk. The Committee noted that the evidence of this increased risk, coming from a variety of sources (observational studies, published literature and short-term trials), had accumulated to the extent that the benefits of rosiglitazone-containing medicines could no longer outweigh their risks.

In view of the restrictions already in place on the use of rosiglitazone, the Committee could not identify additional measures that would reduce the cardiovascular risk.

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[1] The outcome of the reviews carried out in 2007 and 2008 are available on the Agency's website:
2007:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000143.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1
2008:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000385.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1

[2] Graham DJ *et al*. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA doi:10.1001/jama.2010.920; Nissen SE *et al*. Rosiglitazone revisited. An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med doi:10.1001/archinternmed.2010.207.

The Committee therefore recommended that the marketing authorisations be suspended until the company can supply convincing data to identify a patient population in which the clinical benefits of rosiglitazone-containing medicines clearly outweigh their risks.

What is happening with clinical trials with rosiglitazone-containing medicines?

Decisions on whether clinical trials should continue or not are made by individual Member States at a national level. The CHMP is of the opinion that clinical trials with rosiglitazone-containing medicines should be reviewed on a case-by-case basis to establish, in the context of this suspension, whether the trials should continue, taking into account the disease and the population under study.

Patients currently in a rosiglitazone clinical trial should make an appointment with the doctor who is treating them in the trial (investigator) to discuss their treatment.

What are the recommendations for patients?

- Patients who are currently taking rosiglitazone-medicines should make an appointment with their doctor to discuss suitable alternative treatments. Rosiglitazone-containing medicines will no longer be available in pharmacies as soon as the suspension of the marketing authorisations becomes effective. This is expected within the next few months.
- Patients must not stop their medication without talking with their doctor.
- Patients who have any questions should speak to their doctor.

What are the recommendations for prescribers?

- Doctors should stop prescribing rosiglitazone-containing medicines. Patients who are currently receiving rosiglitazone should be reviewed in a timely manner to amend their treatment.
- The Committee is not recommending any specific alternative to rosiglitazone. When switching, doctors will select among other anti-diabetes medicines the most appropriate alternative based on the individual patient's needs.

What are the recommendations for pharmacists?

- Pharmacists should be aware that rosiglitazone-containing medicines will soon no longer be available. They should advise patients presenting with a prescription for Avandia, Avandamet or Avaglim to speak to their doctor so that their treatment can be discussed and amended as needed.

A European Commission decision on this opinion will be issued in the next few weeks.

The current European public assessment reports for Avandia, Avandamet and Avaglim can be found on the Agency's website ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports:

- Avandia
- Avandamet
- Avaglim

Procedure start date:	9 July 2010
Scientific Advisory Group meeting:	19 July 2010
Discussion at CHMP:	19-22 July 2010
Company written responses provided on:	9 August 2010
Discussion at extraordinary CHMP:	8 September 2010
Oral explanations:	20 July 2010; 20 September 2010
Opinion date:	22 September 2010