European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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QUESTIONS AND ANSWERS ON THE BENEFITS AND RISKS OF ROSIGLITAZONE AND PIOGLITAZONE

As part of its continuous monitoring of medicines, the European Medicines Agency (EMEA) has reviewed the available information on the benefits and risks of rosiglitazone and pioglitazone.

The EMEA's Committee for Medicinal Products for Human Use (CHMP) has concluded that both medicines' benefits continue to outweigh their risks. However, it recommended that patients with 'ischaemic heart disease' (reduced blood supply to the heart muscle) should only be prescribed rosiglitazone after careful evaluation of their individual risk. In addition, it should only be used in combination with insulin in exceptional cases and under close supervision.

These changes will be introduced to rosiglitazone's prescribing information. No changes were needed for pioglitazone's prescribing information, which already includes appropriate warnings on the use of the medicine with insulin.

The Committee concluded that further information needed to be gathered in studies, in order to increase the level of certainty over the effects of the two medicines.

What are rosiglitazone and pioglitazone?
Rosiglitazone and pioglitazone are antidiabetic medicines that belong to the class 'thiazolidinediones'. These types of medicine are commonly known as 'glitazones'. Rosiglitazone (available as Avandia) and pioglitazone (available as Actos) have been licensed in the European Union (EU) since 2000[1]. Both medicines are also available in combination tablets that include other antidiabetic medicines[2].

Rosiglitazone and pioglitazone are both used to treat adult patients who have type 2 diabetes (also known as non insulin-dependent diabetes), particularly in those who are overweight. The medicines can be used on their own or in combination with metformin or a sulphonylurea (other types of antidiabetic medicine) or with both metformin and a sulphonylurea. Pioglitazone can also be used in combination with insulin. Neither rosiglitazone nor pioglitazone should be used in patients with a history of heart failure.

Type 2 diabetes is a disease in which the pancreas does not make enough insulin to control the level of glucose (sugar) in the blood or when the body is unable to use insulin effectively. Thiazolidinediones make cells in the fat, muscle and liver 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, which helps to control type 2 diabetes.

Why has the EMEA reviewed the medicines?
During the first half of 2007, as part of its continuous monitoring of the safety of medicines, the CHMP became aware of new information on these medicines' side effects. This included information on the risk of bone fractures (broken bones) in women taking them, and, in patients taking rosiglitazone, a possible risk of ischaemic heart disease. Because this raised concerns over the benefit-

[1] Pioglitazone is also licensed as Glustin, but this product is not marketed in the EU.
[2] Rosiglitazone is also available in Avandamet (with metformin) and Avaglim (with glimepiride). Pioglitazone is also available in Competact (with metformin) and Tandemact (with glimepiride).

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risk balance of both rosiglitazone and pioglitazone, in May 2007 the CHMP decided to carry out a full re-assessment of the benefits and risks of these medicines.

Which data has the CHMP reviewed?
The review included all available information on the benefits and risks of rosiglitazone and pioglitazone, focusing on their effects on the heart. This included information from clinical trials, 'meta-analyses' looking at the results of a number of studies taken together, as well as information from epidemiological studies (studies of the causes and distribution of diseases in the population), data provided by the companies that make the medicines, and reports of side effects seen in patients taking them.

The review was carried out by the CHMP in collaboration with the EMEA's Pharmacovigilance Working Party.

What were the conclusions of the CHMP?
The CHMP concluded that the benefits of both rosiglitazone and pioglitazone in the treatment of type 2 diabetes continue to outweigh their risks. The Committee did note that rosiglitazone treatment seemed to be associated with an increased risk of ischaemic heart disease, but this did not seem to be linked to an increased risk of death.

The Committee also concluded that taking rosiglitazone at the same time as insulin may be linked to an increase in the risk of fluid retention and heart disease.

Therefore, the CHMP recommended that, in patients who have ischaemic heart disease or who have had it in the past, rosiglitazone should only be used after careful evaluation of each patient's individual risk. These changes should be introduced to the prescribing information for rosiglitazone-containing medicines in forthcoming regulatory procedures. The Committee also recommended that rosiglitazone should only be used in combination with insulin in exceptional cases and under close supervision.

No changes to the prescribing information for products containing pioglitazone were necessary. The information for these products already contains appropriate warnings on the safety of pioglitazone.

The Committee concluded that further information needs to be gathered, in order to increase the level of scientific knowledge on the two medicines. It will review the results of currently ongoing studies, and also recommended that additional studies be performed.

What is the advice to patients and prescribers?
- Doctors should prescribe rosiglitazone- and pioglitazone-containing medicines according to the latest prescribing information.
- Patients who are taking rosiglitazone or pioglitazone and have questions or concerns should talk to their doctor or pharmacist.