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Questions and answers on the review of medicines containing fibrates

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

The European Medicines Agency has completed a review of the safety and effectiveness of fibrates. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of fibrates continue to outweigh their risks but that they should not be used as 'first line' in the treatment of blood lipids (fats) disorders, such as high cholesterol, except in rare cases. This means that newly-diagnosed patients with blood lipid disorders should not be treated using these medicines in the first instance, unless they have very high levels of triglycerides (a type of fat). However, fibrates can be used in patients who cannot take statins (another type of medicine used to lower blood lipid levels).

What are fibrates?

Fibrates are a class of medicines that can be used to lower the level of lipids, such as cholesterol and triglycerides, in the blood. Blood lipid disorders are a risk factor of heart disease (such as heart attack and stroke) and fibrates are used to improve lipid levels in patients in whom dietary restrictions and exercise have not been enough.

Fibrates are 'PPAR agonists'. This means that they activate a type of receptor called the 'peroxisome proliferator activated receptor'. This receptor can be found in many cells throughout the body, where it is involved in breaking down dietary fat, especially triglycerides and cholesterol. When the receptors are activated, the break down of fats is accelerated, and this helps clear the blood of cholesterol and triglycerides.

Fibrates have been in use since the 1960s. Currently, four fibrates are available in the European Union:

- **Bezafibrate.** This medicine has been available since 1977. It is marketed mainly under the trade names Bezalip, Cedur, Eulitop and Befizal, as well as generic medicines. It is sold in Austria, Belgium, Cyprus, Finland, France, Germany; Greece, Hungary, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Spain, Sweden and the United Kingdom;
- **Ciprofibrate.** This medicine has been available since 1995. It is marketed mainly under the trade name Lipanor or Modalim, as well as generic medicines. It is sold in Belgium, Bulgaria,



Cyprus, the Czech Republic, Estonia, France, Greece, Hungary, Latvia, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia and the United Kingdom;

- **Fenofibrate.** This medicine has been available since 1975. It is marketed mainly under the trade name Lipanthyl, as well as generic medicines. It is sold in all EU Member States except Denmark and the Netherlands, as well as in Iceland and Norway;
- **Gemfibrozil.** This medicine has been available since 1981. It is marketed mainly under the trade name Lopid, as well as generic medicines. It is sold in Austria, Cyprus, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, the Netherlands, Portugal, Slovenia, Slovakia, Spain, Sweden and the United Kingdom.

These medicines have all been authorised via national procedures.

Why were fibrates reviewed?

In 2005, the CHMP's Pharmacovigilance Working Party (PhVWP) noted that there was limited evidence of the long-term benefit of fibrates in reducing cardiovascular risk, compared with the stronger evidence for statins (another type of medicines used for lowering blood cholesterol). As a result the working party undertook a review of the benefits and risks of all fibrates-containing medicines, on behalf of the medicines regulatory authorities of the countries where the medicines are marketed. The aim of the review was to establish how fibrates should now be used, taking into account their safety, their effectiveness in lowering lipid levels and the availability of other lipid-lowering medicines that were not around when fibrates were first used. Looking at the data, the PhVWP came to the conclusion that there were no new safety issues with fibrates and that fibrate-containing medicines still had a role to play in improving lipid levels, but that they should not be used as first-line treatment.

The conclusions of the PhVWP were transmitted to the companies that market fibrates, so that they could implement the changes recommended by the working party. However, a number of them questioned the restriction. Consequently, the UK medicines regulatory agency referred the matter to the CHMP on 20 October 2009, to carry out a full assessment of the benefit-risk balance of fibrates and to issue an opinion on whether the marketing authorisations for fibrates-containing medicines should be maintained or varied across the European Union.

Which data has the CHMP reviewed?

The CHMP looked at the information gathered by PhVWP during its review, as well as the responses provided by the companies to specific questions. The Committee also looked at the latest data from clinical studies including a trial looking at the effect of using fenofibrate as an 'add-on' to statins.

What are the conclusions of the CHMP?

The Committee endorsed the conclusions of the PhVWP that fibrates are still a safe option for lowering lipid levels, but that their use as first-line treatment is not justified. Fibrates should be used only when statins are contraindicated or not tolerated. However, the Committee noted that fibrates are more effective than statins in lowering triglyceride levels and therefore their use as a first-line treatment in patients with severe hypertriglyceridaemia (very high blood levels of triglycerides) is still appropriate.

The Committee also noted that there were new data for fenofibrate that supported a change to the PhVWP recommendations, based on the results of the add-on study. As a result, the Committee also allowed the use of fenofibrate together with a statin in some circumstances for patients at risk when using a statin on its own was not enough to completely control blood lipid levels.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of fibrates continue to outweigh their risks within these restrictions. The Committee recommended specific changes to the information to doctors and patients for [all four fibrates](#).

What are the recommendations for patients?

- Patients who are currently taking fibrates to lower their blood lipid levels should continue to do so. There are no new safety concerns with the medicines.
- However, patients taking a fibrate-containing medicine should arrange to see their doctor to check that the medicine is the most appropriate option to lower their blood lipid levels.
- Patients who have any questions should speak to their doctor or pharmacist.

What are the recommendations for prescribers?

- Doctors are reminded that fibrates should not be used as first-line treatment in patients with high lipid levels, except in specific groups:
 - patients with severe hypertriglyceridaemia;
 - patients for whom statins are contra-indicated or who cannot tolerate them.
- They should review the treatment of patients who are receiving fibrates to help control their lipid levels to ensure that the patient is receiving the most appropriate treatment.

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