

Pharmacotherapeutic report, summary Pravastatin/fenofibrate (Pravafenix®) for the indication 'dyslipidaemia with high-concentration triglycerides'

Approved on 22 October 2012 by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Pravastatin/fenofibrate (Pravafenix®) capsule 40/160 mg

Registered indication.

Pravafenix® is indicated for the treatment of high coronary heart disease (CHD) -risk adult patients with mixed dyslipidaemia characterised by high triglycerides and low HDL-cholesterol levels whose LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy

Posology. 40 mg pravastatin and 160 mg fenofibrate (= 1 capsules) once daily per os (with the evening meal).

Mechanism of action. Pravastatin belongs to the group of statins and blocks the action of HMG-CoA-reductase, a liver enzyme involved in the production of cholesterol. Inhibiting this enzyme in the liver stimulates the LDL-receptors, thereby drawing LDL from the blood and reducing the total cholesterol. A response can be seen after one week and reaches its maximum after four to six weeks. Pravastatin has a limited effect on reducing the triglycerides and increasing the HDL-cholesterol.

Fenofibrate, which belongs to the class of fibrates, is not registered in the Netherlands as a monoprepate. Its effect on the lipid profile is mediated by alterations in the transcription – via PPAR- α ¹-activation – of genes that code for proteins which play a role in lipoprotein metabolism. The fibrates inhibit the synthesis of the VLDL-lipoprotein in the liver, as well as stimulating the degradation of VLDL (lipolysis). After taking the fenofibrate, one sees a sharp drop in triglycerides, a drop in LDL- and VLDL-cholesterol and an increase in HDL-cholesterol.

Summary of the therapeutic value

Intended effects. The set-up of the studies carried out in order to prove a difference in effect between pravastatin/fenofibrate and an optimum treatment with a statin in monotherapy (the standard treatment for this assessment) makes them unsuitable for the purpose. The included patients do not match the registered indication for the drug: their LDL-C had not (yet) been sufficiently managed, as it was >2.5 mmol/L. This means they had not been shown to have failed on an optimum treatment with statins. As a result the comparative treatment is not suitable for assessing the therapeutic value of the combination pravastatin/fenofibrate. The combination of pravastatin/fenofibrate shows in particular a reduction in the TG-levels with an incremental increase in HDL-C in comparison with pravastatin or simvastatin monotherapy, which is due to the fenofibrate. The effect of a reduction in the TG-level on cardiovascular morbidity and

¹ PPAR- α : peroxisome proliferator-activated receptor type alpha.
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mortality (long-term hard outcome measures) has not been demonstrated. For the above-mentioned reasons the CFH concludes that it is not possible based on the current studies to issue a substantiated statement on the favourable effects of the combination pravastatin/fenofibrate in comparison with a statin in monotherapy.

Unintended effects. Between 1 and 10% of the patients experience gastrointestinal side effects when using pravastatin/fenofibrate. The gastrointestinal side effects were nausea, stomach-ache, constipation, diarrhoea, flatulence and vomiting. Furthermore, headache was reported fairly frequently (9%). Side effects on muscles and the interstitial tissue system occurred in 0.1-1% of the patients and involved joint pain, muscular pain, back pain, muscular spasms and pain in the extremities. These side effects may be related to an interaction between pravastatin and fenofibrate. During the clinical studies no rhabdomyolysis or myopathy was reported. A more definitive statement on these unfavourable effects will only be possible after completion of the post-marketing studies requested by the EMA which may contribute to an improved definition of the safety profile.

Experience. Fenofibrate is not marketed in the Netherlands, but it has been marketed in the USA since 1994. Although a lot of experience has been gained with fenofibrate as a monopreparate, the same cannot be said of the combination drug pravastatin/fenofibrate.

Applicability. The applicability of pravastatin/fenofibrate is comparable with that of pravastatin 40 mg monotherapy. Pravastatin 40 mg is not the first-choice statin according to Dutch guidelines for treatment.

Ease of use. The ease with which pravastatin/fenofibrate can be used is comparable with that of pravastatin. The combination of both active ingredients pravastatin and fenofibrate in a single administrative form could promote therapy compliance. However, the disadvantage is that it is not possible to make individual adjustments in the dose of the two active ingredients.

Final conclusion. The use of pravastatin/fenofibrate to treat adult patients with an increased risk of coronary heart disease and who suffer from mixed dyslipidaemia characterised by high concentrations of triglycerides, low concentrations of HDL-cholesterol and sufficiently managed concentrations of LDL-cholesterol during treatment with pravastatin 40 mg monotherapy has a lower therapeutic value than treatment with pravastatin 40 mg or simvastatin 20 mg.

Specific detail. Fenofibrate is a fibrate that is not registered in the Netherlands.