

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

(Fenofibrate)

Abbott Healthcare Products Ltd

IE/W/0007/pdWS/001

**Marketing Authorisation Holder:
Laboratoires Fournier S.A**

Rapporteur:	Ireland
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I. EXECUTIVE SUMMARY

This is an assessment of the data submitted by the MAH for Fenofibrate, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force 26 January 2007. Ireland is Rapporteur for this procedure.

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPAR α).

Based on the review of the presented paediatric data on the safety and efficacy, the Rapporteur considers that the results of these studies do not support an addition of paediatric posology.

SmPC changes are proposed in sections 4.2, 4.3 and 5.1.

Summary of outcome

- No change
- Change
- New study data:
- New safety information:
- Paediatric information clarified:

For Fenofibrate 67 mg and 100 mg capsules in sections 4.2 and 5.1.

For high dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets) in sections 4.2 and 4.3.

- New indication:

II. RECOMMENDATION

Based on the review of the provided paediatric data on the safety and efficacy, the Rapporteur considers that the results of these studies do not support an addition of paediatric posology.

Following changes to the SmPC are recommended:

For Fenofibrate 67 mg and 100 mg capsules

Section 4.2:

Paediatric population:

The safety and efficacy of Fenofibrate in children have not yet been established. Only limited paediatric data are available (see section 5.1). Therefore the use of fenofibrate is not recommended in paediatric subjects under 18 years.

Section 5.1

Limited paediatric data are available. The effects of fenofibrate in dyslipidemic children have been studied in two small clinical trials and in an open long-term surveillance registry with 76 hypercholesterolemic children aged 3 to 18 years receiving fenofibrate for 1 to 11 years. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of fenofibrate in dyslipidemic children.

Adverse events similar to those observed in adults have been reported in children: leucopenia, liver function test abnormal, rhabdomyolysis, renal failure, hepatitis, jaundice, myositis and rhabdomyolysis.

Overall, the safety and efficacy of fenofibrate in children and adolescents have yet not been established (see section 4.2).

The patient information leaflet should be updated accordingly.

For high dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets)

Section 4.2:

Paediatric population:

The safety and efficacy of fenofibrate in children and adolescents younger than 18 years has not been established. No data are available. Therefore the use of fenofibrate is not recommended in paediatric subjects under 18 years

The patient information leaflet should be updated accordingly.

III. INTRODUCTION

This is an assessment of data for Fenofibrate, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force 26 January 2007 which have not previously been submitted. Ireland is Rapporteur for this procedure.

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPAR α).

Fenofibrate has been approved in the treatment of hypercholesterolaemia and hypertriglyceridaemia alone or combined in patients unresponsive to dietary and other non-drug therapeutic measures (e.g. weight reduction or increased physical activity), particularly when there is evidence of associated risk factors.

However, further to the recent EU referral procedure on fibrates (October 2010), the CHMP recommended that fibrate-containing medicines should not be used as first-line treatment, except in patients with severe hypertriglyceridaemia and in patients who cannot use statins. For fenofibrate, the Committee noted additional new data and recommended that it can also be used together with a statin in some circumstances when a statin on its own has not been enough to completely control blood lipid levels.

Fenofibrate, as a standard formulation (100 mg and 300 mg capsules) was initially approved in 1975 in France. The bioavailability of the standard formulation was subsequently improved through a co-micronisation process leading to the development of the 67 mg and 200 mg micronised fenofibrate capsules. Then, a tablet formulation of micronised fenofibrate has become available with a greater bioavailability than the older capsule formulation. This 160 mg tablet is bioequivalent to the 200 mg capsule. In order to further reduce the dose administered to patients and to improve compliance, a no food effect formulation, based on particle size reduction using NanoCrystal® technology with a reduced dose of fenofibrate (145 mg and 48 mg tablets) was registered. The 145 mg fenofibrate tablet formulation is bioequivalent to the 160 mg tablet and to the 200 mg capsule.

Fenofibrate is currently registered in 25 Member States (except Denmark, Iceland, The Netherlands and Norway), either using Mutual Recognition Procedure (MRP) or national route.

The high dosage forms (fenofibrate 300 mg / 200 mg / 267 mg capsules, 160 mg /145 mg / 215 mg tablets) are not recommended for use or are contraindicated in children below age 18 due to a lack of safety and efficacy data. Only low strengths of fenofibrate (standard nonmicronised 100 mg capsules and the bioequivalent 67 mg micronised capsules) have obtained an indication in children in some European countries (France, UK, Poland, and Romania).

In these countries, the Summary of Product Characteristics (SmPC) includes the following statement in the section 4.2 of the SPC:

No comprehensive pediatric experience with fenofibrate is available to date. The precise type of hyperlipidaemia must be established by a genetic and biological study of the disorder whose hereditary nature (familial hyperlipidaemia) alone warrants an early treatment approach. It is recommended that treatment be initiated with a strictly controlled diet for a period of at least 3 months. If pharmacological therapy proves to be essential, for example in severe forms accompanied by clinical signs of atherosclerosis and/or xanthomatous deposits and/or in cases where the child's parents present with atheromatous cardiovascular symptoms before the age of 40, prescription of fenofibrate should only be made by a specialist.

For fenofibrate 100 mg capsules:

The maximum recommended dosage is 5 mg/kg/day (one capsule of fenofibrate 100 mg daily per 20 kg of body weight) in children 10 years of age or older.

For fenofibrate 67 mg capsules (bioequivalent to fenofibrate 100 mg capsules):

The maximum recommended dosage is one capsule of fenofibrate 67 mg daily per 20 kg of body weight) in children 10 years of age or older.

In Ireland no paediatric posology is included in the SPC for low strengths of fenofibrate (standard nonmicronised 100 mg capsules and 67 mg micronised capsules). The high dosage forms are contraindicated in children below age 18.

The MAH submitted 4 published paediatric studies for fenofibrate, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. 3 out of 4 studies have been performed in children with hyperlipidaemia.

A critical expert overview on fenofibrate pediatric data and a clinical expert statement have been also provided.

In addition a SmPC and PIL proposal for fenofibrate 67 & 100 mg capsules has been provided.
Please see section V (responses to queries and the assessment of responses)

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

The MAH submitted 4 published paediatric studies for fenofibrate:

- 1. Steinmetz J, Morin C, Panek E, Siest G, Drouin P. Biological variations in hyperlipidemic children and adolescents treated with fenofibrate. Clin Chim Acta. 1981 Apr 27;112(1):43=53.**
- 2. Chicaud P, Demange J, Drouin P, Debry G. Action of fenofibrate in hypercholesterolemic children. 18-month follow-up. La Presse médicale 1984; 13:417-419.**
- 3. Cree G.M et al. Insulin sensitivity and mitochondrial function are improved in children with burn injury during a randomized controlled trial of fenofibrate. Annals of Surgery 2007; 245:214-221.**
- 4. D. Gautier, J. Rouffy, P. Drouin, J. Rey. Assessment of long-term efficacy and safety of fenofibrate in hypercholesterolemic children and adolescents – Analysis of a long-term registry.**

In addition the MAH submitted:

- A SmPC and PIL proposal for fenofibrate 67 & 100 mg capsules
- A clinical expert statement
- A critical expert overview on fenofibrate pediatric data
- Safety data from post-marketing surveillance

2. Clinical studies:

1. Steinmetz J, Morin C, Panek E, Siest G, Drouin P. Biological variations in hyperlipidemic children and adolescents treated with fenofibrate. Clin Chim Acta. 1981 Apr 27;112(1):43=53.

➤ Description

This was an open-label, prospective study to assess the effect of fenofibrate given to hyperlipidemic children and adolescents.

➤ Methods.

- **Study design**

17 paediatric patients with hyperlipoproteinemia, Type IIa and with mixed, Type-IIb hyperlipoproteinemia were observed in the Diabetes Service for a maximum period of 18 months. Before any treatment was introduced, all patients were put on a low-lipid diet; those patients who were overweight were put on a low-caloric diet as well. After 3 to 6 months of dieting if the lipid levels were still too high, hypolipidemic treatment was introduced.

A blood sample were drawn before the beginning of the treatment and then after 3 months of treatment.

The long-term effect was evaluated in 10 patients after 6, 10, 12, 14 or 18 months of treatment.

- **Study population /Sample size**

17 patients aged 4 to 19 years participated in the study. Thirteen children had hyperlipoproteinemia, Type IIa and four had a mixed, Type-IIb hyperlipoproteinemia.

- **Treatments**

After 3 to 6 months of dieting if the lipid level was still too high, hypolipidemic treatment was given at the dose of 200 mg/day, with readjustment to 100 or 300 mg/day based on the lipid values and tolerance.

Assessor's comment:

In the study each patient received 200 mg/day of fenofibrate, irrespective of the body weight. Then the dose was readjusted to 100 or 300 mg/day.

➤ **Results**

- **Efficacy**

In the study, total cholesterol levels decreased from a baseline median level of 242 mg/dL (6.27 mmol/L) by -21% and triglycerides levels decreased from a median baseline of 68 mg/dL (0.77 mmol/L) by -38% after 3 months of treatment. There was no direct relation between the initial cholesterol concentration and the size of the change, and contrary to the effect on cholesterol, that on triglycerides seemed more pronounced when the concentrations of triglycerides were high before treatment (above 1.30 mmol/L). Nine patients were followed for at least 6 months and some of them up to 18 months. The changes observed after 3 months of treatment were also observed in these patients. In one patient triglyceride concentration increased, while his cholesterol concentration decreased by 39%.

- **Safety results**

The alanine aminotransferase (ALT) activity increased on average by 9 U/l. This important change was principally due to 4 patients, whose activity increased 2- to 5-fold and reached values higher than 30 U/l after 3 months of treatment. The aspartate aminotransferase (AST) activity increased in the same proportion (by 11 U/l). The increase was particularly large (greater than 80%) in the patients who had also a highly increased ALT activity.

Assessor's comment:

In some children an increase in aminotransferases was observed. No cases of hepatitis were reported. Changes in the uric acid, bilirubin and alkaline phosphatase levels were also observed.

2. Chicaud P, Demange J, Drouin P, Debry G. Action of fenofibrate in hypercholesterolemic children. 18-month follow-up. La Presse médicale 1984; 13:417-419.

➤ **Methods.**

• **Study design**

In the study 12 children (3 males, 9 females) from 4 to 16 years-old with hypercholesterolemia Type IIa were treated after a 3-month diet period with fenofibrate at the dose of 5 mg/kg/day. Long-term safety and efficacy data of fenofibrate were evaluated after 6, 12 and 18 months of treatment.

➤ **Results**

• **Efficacy**

In the study, total cholesterol levels decreased from a baseline median level of 283 mg/dL (7.32 mmol/L) by -24% after 12 months and by -17% after 18 months of treatment.

Assessor's comment:

In this study the dose of 5 mg/kg/day of fenofibrate was administered however it is not clear why this dose was chosen for children. No PK data have been provided.

In addition, it is noted that fenofibrate was administered as a first line treatment which is not in line with the recent CHMP recommendation.

3. Cree G.M et al. Insulin sensitivity and mitochondrial function are improved in children with burn injury during a randomized controlled trial of fenofibrate. Annals of Surgery 2007; 245:214-221.

➤ **Description**

In this study 21 children from 4 to 16 years-old with > 40% total body surface area burns were enrolled in a double-blind, prospective, first placebocontrolled randomized trial, and were treated with the recommended dose of 5 mg/kg/day of fenofibrate during 2 weeks.

Assessor's comment:

The objective of this study was to determine the mechanisms involved in insulin resistance immediately following burn trauma, and to determine the efficacy of PPAR- agonism for alleviating insulin resistance in this population therefore this study has limited value for an assessment of the safety and efficacy of fenofibrate when used in children for treatment of hyperlipidema.

4. D. Gautier, J. Rouffy, P. Drouin, J. Rey.

Assessment of long-term efficacy and safety of fenofibrate in hypercholesterolemic children and adolescents – Analysis of a long-term registry.

➤ **Description**

The long term registry data in 4 centres in France has been obtained retrospectively for 76 children (42 female, 34 male) from 3 to 18 years-old with dyslipidaemia Type IIa or IIb treated with fenofibrate during 10 to 132 months at the recommended dose of 5 mg/kg/day.

➤ **Methods**

- **Objective(s)**

The objective of this study was to evaluate the safety and efficacy of treatment with fenofibrate at the dose of 5 mg/kg/day in children with familial hypercholesterolemia.

- **Study design**

Data for the registry were extracted from hospital records of patients who began treatment with fenofibrate between 1973 and 1983. The treatment guidelines included a dietary period lasting between 3 and 6 months, followed by treatment with fenofibrate if the diet management was unsuccessful. The recommended dose of fenofibrate in children and adolescents was 5 mg/kg. Patients were seen at regular intervals for routine follow-up, including determination of lipid levels and assessment of tolerability of the medication.

Assessor's comment:

In this study fenofibrate at the dose of 5 mg/kg/day was administered to children.

In addition, it is noted that fenofibrate was administered as a first line treatment in patients with hypercholesterolemia which is not in line with the recent CHMP recommendation.

- **Study population /Sample size**

A total of 76 patients (42 Female and 34 Male, age 3-18 years) who began treatment with fenofibrate when they were less than 18 years of age were included in the analyses.

- **Treatments**

Capsules of non-micronized fenofibrate of 50 mg and 100 mg. The recommended dose in children was 5 mg/kg per day. The starting daily dose of fenofibrate ranged from 50 to 400 mg. The dose of fenofibrate could be increased or decreased by the clinician according to the biological and clinical results. Patients were treated from 10 to 132 months.

- **Outcomes/endpoints**

Efficacy: Mean plasma concentration and % change in total cholesterol and triglycerides after 6, 12, 18, 24, 36 months of treatment with fenofibrate and at the last visit in comparison with baseline was determined.

Safety: Mean and % change in vital signs (weight and blood pressure), as well as in biological parameters (white blood cell count, red blood cell count, platelet count and hemoglobin, total bilirubin, creatinine, uric acid, urea and glucose) was assessed. Changes in transaminases AST/ALT, gammaGT, alkaline phosphatase and creatine phosphokinase were recorded.

➤ **Results**

- **Efficacy**

At entry into the study, all patients except one with borderline high cholesterol (177 mg/dl), had elevated cholesterol levels (> 200 mg/dl) and 44% had levels greater than 300 mg/dl.

After 12 months of treatment, about 25% of patients had total cholesterol less than 200 mg/dl and 92% had total cholesterol less than 300 mg/dl. Triglycerides levels during treatment were maintained around a median value of 50 mg/dl from a baseline of 60 mg/dl. The reduction of triglycerides was relatively mild in this population of familial hypercholesterolemic children (from -11.1% at 12 months and -15.9% at the end of the follow-up).

Assessor's comment:

The majority of patients showed some response to treatment however after 12 months of treatment only 25% of patients had total cholesterol less than 200 mg/dl.

- **Safety**

Adverse events: Twenty three adverse events were reported in 14 patients of the 76 included in the registry (18.4%).

The most frequently reported adverse events were in the digestive system [eight adverse events (35%) reported in 7 patients (9%)] followed by the cardiovascular system [five adverse events (22%) reported in 4 patients (5%)] and by skin and appendages [four adverse events (17%) in three patients (4%)]. Although the relationship with fenofibrate was not documented for most events, one adverse event (anemia) was considered to be related to the treatment. Two of the digestive events (constipation and hemorrhoids) were reported to be related to concomitantly administered colestipol.

Assessor's comment:

In the study the most frequently reported adverse reactions in children were from the digestive system which is also observed in adults as per SPC.

In relation to cardiovascular system peripheral vascular disorder, aortic stenosis, arteritis and ECG abnormalities were reported.

In relation to skin and subcutaneous tissue system urticaria and alopecia were reported. These adverse reactions are listed in the SPC for fenofibrate.

Asthenia was also reported which is in line with the SPC for fenofibrate.

Biochemistry: On treatment determinations of ALT revealed transient elevations > 3 x normal in eleven patients, three of whom had normal determinations at baseline. AST elevation > 3x normal occurred in seventeen patients, only two patients of whom had normal determinations at baseline.

Fenofibrate treatment was discontinued in one patient after two years of treatment due to persistently elevated transaminase determinations. This patient began treatment with an ALT determination of 1.7x normal, and experienced a peak level of 4.8x normal approximately 8 months after beginning treatment.

Out of 46 patients who had GGT measured on at least one occasion during treatment, only 7 had a moderate elevation of GGT (maximum 3.5x normal).

One male patient presented with a significant elevation of alkaline phosphatase up to 723 U/l after 4 years of follow-up without concomitant elevation of total bilirubin or transaminases. The treatment was continued for another 2 years with a return toward normal value.

CPK was measured at least once in 38 patients over the course of the follow-up. Two patients had abnormal values above 130 U/l at baseline and 5 presented with isolated CPK elevation during the course of the treatment. No elevation of CPK exceeded 5 times the upper normal limit.

Hematology: White blood cell counts were reduced after 18 months of treatment versus baseline with a mean decrease of 12% after 36 months of treatment. Only two patients had determinations below $3.0 \times 10^3/\text{mm}^3$: one of these returned to levels above $3.0 \times 10^3/\text{mm}^3$ with continued treatment, while the second appeared to be an isolated determination at the end of 6 years of treatment. Similarly, a slight decrease in red blood cell counts and hemoglobin was also observed at each time point versus baseline.

Platelet counts did not reveal any clinically significant mean or individual changes.

Height and weight changes in males and females: Treatment with fenofibrate did not alter growth in these patients based on height/weight charts versus age for the reference population.

Assessor's comment:

An increase in transaminases, changes in the haemoglobin level and white blood cell count observed in the study are also reported in adults.

3. Safety data from post-marketing surveillance

The undesirable effects reported to the company's safety database with a data lock point of 31 December 2010 have been analyzed and provided for assessment.

Children between 2 and <12 years of age:

Seventeen Individual Case Safety Reports (ICSRs) were identified, five of them serious. In all ICSRs 21 terms were identified, 5 of them serious.

- The serious terms were as follows: leucopenia (n=2), liver function test abnormal (n=1), rhabdomyolysis (n=1) and renal failure (n=1).

Of the seventeen ICSRs the outcome was as follows:

- In seven cases the patients recovered completely. Six cases were with unknown outcome, in one case the events were abating and in two cases the patient had not yet recovered. In one case the patient died.

FR-SOLVAY-00007016089 is an authority report on a 7 year-old boy with obesity (50 kg)

who presented an acute renal failure with hyperkalaemia, hypernatraemia and hemoconcentration after one week of hospitalisation to reduce weight. During the week he received fenofibrate, benfluorex hydrochloride, levothyroxin sodium for hypothyroidism from the third day and furosemide. The boy developed cardiac arrest and died. According to health authorities, the patient presented a severe renal insufficiency not correctly treated and related to dehydration and treatment with high dose furosemide.

The fatal outcome of the case is most probably related to insufficient treatment of the renal failure and to the dehydration. The role of fenofibrate which was probably received prior to hospitalization is difficult to assess in this case. The post mortem fenofibric acid level of 9 mg/L was normal.

Children between 12 and 18 years of age:

Eleven ICSRs were identified, five of them serious.

In all ICSRs 16 terms were identified, 6 of them serious.

- The serious terms were as follows: hepatic function abnormal (n=1), hepatitis (n=1), jaundice (n=1), overdose (n=1), myositis (n=1) and rhabdomyolysis (n=1).

Of the eleven ICSRs the outcome was as follows:

- In six cases the patients recovered completely. In three cases the outcome was unknown and in two cases abating.

In addition, an attempt was undertaken to estimate the exposure data for fenofibrate using IMS data in France, Germany, Italy, Spain, UK and US. It can be concluded that the exposure in this age group is quite limited.

It is to be noted that all doses of fenofibrate were prescribed i.e. not only the recommended standard non-micronised dose of 100 mg or the micronised dose of 67 mg.

From the few available safety data, presented above, the MAH concluded that the differences between the undesirable effects observed in children 2 years of age and above and those observed in adults cannot be determined.

Assessor's comment:

The safety data from post-marketing surveillance have been provided. Adverse reactions observed in children seem to be similar to those observed in adults however the final conclusions cannot be drawn due to the limitation of the paediatric data (small numbers, lack of controls). Cases of hepatitis, myositis, rhabdomyolysis have been reported.

V. RESPONSES TO QUERIES AND THE ASSESSMENT OF RESPONSES:

1. The MAH should provide the English translation of the study Chicaud P, Demange J, Drouin P, Debry G. Action of fenofibrate in hypercholesterolemic children. 18-month follow-up. La Presse médicale 1984; 13:417-419.

Company answer:

The English translation of this study has been provided.

Assessor comments:

English translation of this study has been submitted.

2. The MAH should provide justification for the dose of 5 mg/kg/day and provide the relevant PK data , if available.

Company response:

The dose of 5 mg/kg fenofibrate daily was proposed for the treatment of hyperlipidemia in children on an empirical basis since no specific pharmacokinetic study was performed in children.

In 1977, P. Drouin et al1 reported the effect of fenofibrate 100 to 300 mg daily in 30 young patients aged 7 to 19 years with heterozygous familial hypercholesterolemia treated for one year. These investigators who first treated children and adults with the same condition derived this dose per kilogram on the basis of the adult dose which was 300 mg of standard non micronized fenofibrate for 60 kg.

This dose of 5 mg/kg was given as a 50 mg capsule for 10 kg body weight or a 100 mg capsule for 20 kg body weight.

With the development of new formulations of fenofibrate with an improved bioavailability leading to halve the daily dose of fenofibrate, this expression in mg/kg could be misleading. Indeed, in the double-blind, placebo-controlled study by Cree et al² published in 2007 in children with burn injury, which used the 160 mg tablet formulation, the dose used of 5 mg/kg corresponds to the double of the usual dose. There were no observed adverse events from the medication in this 2-week study in 21 children aged 4 to 17 years and weighing 20 kg or more.

This is the reason why, in some European countries, the recommended dose in children is one 67 mg micronized fenofibrate capsule per 20 kg body weight (the 67 mg formulation being the most frequent low dose formulation registered in Europe, and being bioequivalent to the standard non-micronized fenofibrate 100 mg formulation).

The proposed dosage scheme should be the following:

one fenofibrate 67 mg micronized capsule daily with a meal if body weight is 20 to 39 kg,
two fenofibrate 67 mg micronized capsules daily with a meal if body weight is 40 to 59 kg,
or three fenofibrate 67 mg micronized capsules daily with a meal if body weight is 60 kg or more.

In European countries where only the 100 mg standard non-micronized fenofibrate capsule is registered, the proposed dosage scheme should be:

one fenofibrate 100 mg capsule daily with a meal if body weight is 20 to 39 kg,
two fenofibrate 100 mg capsules daily with a meal if body weight is 40 to 59 kg,
or three fenofibrate 100 mg capsules daily with a meal if body weight is 60 kg or more.

Assessor comment:

No specific pharmacokinetic study was performed in children. The dose of 5 mg/kg fenofibrate daily was proposed for the treatment of hyperlipidemia in children on an empirical basis.

The MAH has proposed to include paediatric posology in section 4.2 of the SPC. However the provided data are considered insufficient to include a specific indication for children and adolescents in section 4.1 and a specific paediatric posology in section 4.2 of the SPC.

3. It is noted that fenofibrate was administered as a first line treatment in patients with hypercholesterolemia which is not in line with the recent CHMP recommendation. The MAH should discuss this in the context of the current recommendation on managing lipid problems in children.

Company response:

The data about fenofibrate treatment in children were obtained at a time where statins were not available on the market and where fenofibrate was the most effective treatment to reduce total cholesterol levels.

Fenofibrate has been initially approved in the treatment of hypercholesterolaemia and hypertriglyceridaemia alone or combined (Types IIa, IIb, IV dyslipidaemias, as well as Types III and V dyslipidaemias although only a few patients have been treated during clinical trials) in patients unresponsive to dietary and other non-drug therapeutic measures (e.g. weight reduction or increased physical activity), particularly when there is evidence of associated risk factors.

During the recent European referral procedure on fibrates (October 2010), the CHMP recommended specific changes to the therapeutic indications of fenofibrate to apply in adult patients.

The new indications are the following:

Fenofibrate is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the treatment of:

- severe hypertriglyceridemia with or without low HDL cholesterol,
- mixed hyperlipidemia when a statin is contraindicated or not tolerated,
- mixed hyperlipidemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.

Consequently, according to the recent CHMP recommendation, we consider that in children only the first two indications above are relevant for fenofibrate use, namely severe hypertriglyceridemia and hypercholesterolemia when a statin is contraindicated or not tolerated. The third indication covers rare instances in children where there is no data available for fenofibrate use in co-administration with a statin in this specific population.

Assessor comment:

It is noted that in all submitted studies fenofibrate was given as a first line treatment in paediatric patients with dyslipidemia (mostly in patients with familial hypercholesterolemia).

No studies have been performed in children with mixed hyperlipidemia when a statin is contraindicated or not tolerated (at the time statins were not available on the market).

Information in relation to changes in the triglyceride level in this treated patient population is also very limited.

As highlighted above the submitted data are considered insufficient to include a specific indication for children and adolescents in section 4.1 and a specific paediatric posology in section 4.2 of the SPC.

4. The MAH should provide background information on why the high dosage forms (fenofibrate 300 mg / 200 mg / 267 mg capsules, 160 mg /145 mg / 215 mg tablets) are contraindicated in children below age 18 (lack of data? other safety reasons? or these formulations are not suitable for dosing requirements in children?).

Company response:

The high dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets) are either not recommended for use or contraindicated in children below age 18 as no comprehensive safety or efficacy data exist in this type of patients and consequently these formulations are not suitable for dosing requirements in this population.

Assessor comment:

As per the MAH response the high dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets) are contraindicated in children as no studies have been performed with these dosage forms in children (no safety or efficacy data exist).

However, in line the SPC guideline, lack of data alone should not lead to a contraindication.

Therefore, the contraindication should be removed from section 4.3 of the SmPC and section 4.2 should be updated with the following wording:

Section 4.2

Paediatric population:

The safety and efficacy of fenofibrate in children in children and adolescents younger than 18 years has not been established. No data are available. Therefore the use of fenofibrate is not recommended in paediatric subjects under 18 years.

5. The MAH should propose the relevant wording for section 5.1 of the SPC for fenofibrate 67 mg and 100 mg capsules. The limitations of the currently available paediatric data should be highlighted. In addition the MAH should discuss if the any safety paediatric data could be included in section 4.4 and 4.8 of the SPC without a specific recommendation for the use in children.

Company response:

The following changes to the SmPC(s) are proposed:

Fenofibrate 67 mg capsules:

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Children: see sections Posology and Method of Administration, Special Warnings and Precautions for use.

4.2. Posology and Method of Administration

Children: Prescription of <Tradename> 67 mg should only be made by a specialist (see section Special Warnings and Precautions for use).

It is recommended that <Tradename> 67 mg is initiated with a strictly controlled diet for a period of at least 3 months in children where the precise type of hyperlipidaemia warrants an early treatment approach.

The maximum recommended dosage is one capsule of <Tradename> 67 mg daily per 20 kg of body weight in children 10 years of age or older.

Assessor comment:

As highlighted above the submitted data are considered insufficient to include a specific indication for children and adolescents in section 4.1 and a specific paediatric posology in section 4.2 of the SPC.

The proposed wording to section 4.1 and 4.2 cannot be accepted. Instead the following wording is proposed by the Rapporteur:

Section 4.2:

Paediatric population:

The safety and efficacy of Fenofibrate in children have not yet been established. Only limited paediatric data are available (see section 5.1). Therefore, the use of fenofibrate is not recommended in paediatric subjects under 18 years.

4.4. Special Warnings and Precautions for Use

Children: no long term safety data of fenofibrate in children in comparative trials is available. In an open long-term surveillance registry the growth of children was not modified. Spontaneous adverse events reported to date did not indicate that the tolerance profile of fenofibrate in children differed from the one observed in adults.

It is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and thereafter periodically.

Assessor comment:

The available data seems to indicate that that the tolerance profile of fenofibrate in children does not differ from the one observed in adults, however no definitive conclusion can be drawn (the data are too limited). In these circumstances the proposed wording to section 4.4 cannot be accepted.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

.../...

Children: No comprehensive paediatric experience with fenofibrate is available to date. The effects of fenofibrate in children have been studied in three small clinical trials (Steinmetz 1981, Chicaud 1984, and Cree 2007) and in an open long-term surveillance registry with 76 hypercholesterolemic children aged 3 to 18 years receiving for 1 to 11 years 5 mg/kg/day fenofibrate. The data showed that the lipid-lowering effects of fenofibrate in dyslipidemic children are comparable to the ones observed in adults with no difference in the safety profile.

Assessor's comment:

The following wording is recommended by Rapporteur as it better reflects limitations of the currently available paediatric data:

Section 5.1

“Limited paediatric data are available. The effects of fenofibrate in dyslipidemic children have been studied in two small clinical trials and in an open long-term surveillance registry with 76 hypercholesterolemic children aged 3 to 18 years receiving fenofibrate for 1 to 11 years. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of fenofibrate in dyslipidemic children.

Adverse events similar to those observed in adults have been reported in children: leucopenia, liver function test abnormal, rhabdomyolysis, renal failure, hepatitis, jaundice, myositis and rhabdomyolysis.

Overall, the safety and efficacy of fenofibrate in children and adolescents have yet not been established (see section 4.2).”

References to the study performed Cree G.M et al. was removed as this study was performed in children with burn injury.

FENOFIBRATE 100 MG CAPSULES
SmPC proposal

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Children: see sections Posology and Method of Administration, Special Warnings and Precautions for use.

4.2 Posology and Method of Administration

Children: Prescription of <Tradename> 100 mg should only be made by a specialist (see section Special Warnings and Precautions for use).

It is recommended that <Tradename> 100 mg is initiated with a strictly controlled diet for a period of at least 3 months in children where the precise type of hyperlipidaemia warrants an early treatment approach.

The maximum recommended dosage is one capsule of <Tradename> 100 mg daily per 20 kg of body weight in children 10 years of age or older.

Assessor comment:

As highlighted above the submitted data are considered insufficient to include a specific indication for children and adolescents in section 4.1 and a specific paediatric posology in section 4.2 of the SPC.

The proposed wording to section 4.1 and 4.2 cannot be accepted. Instead the following wording is proposed by the Rapporteur:

Section 4.2:

Paediatric population:

The safety and efficacy of Fenofibrate in children have not yet been established. Only limited paediatric data are available (see section 5.1). Therefore, the use of fenofibrate is not recommended in paediatric subjects under 18 years.

4.4. Special Warnings and Precautions for Use

Children: no long term safety data of fenofibrate in children in comparative trials is available. In an open long-term surveillance registry the growth of children was not modified. Spontaneous adverse events reported to date did not indicate that the tolerance profile of fenofibrate in children differed from the one observed in adults.

It is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and thereafter periodically.

Assessor comment:

The available data seems to indicate that the tolerance profile of fenofibrate in children does not differ from the one observed in adults, however no definitive conclusion can be drawn (the data are too limited). In these circumstances the proposed wording to section 4.4 cannot be accepted.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

.../...

Children: No comprehensive paediatric experience with fenofibrate is available to date. The effects of fenofibrate in children have been studied in three small clinical trials (Steinmetz 1981, Chicaud 1984, and Cree 2007) and in an open long-term surveillance registry with 76 hypercholesterolemic children aged 3 to 18 years receiving for 1 to 11 years 5 mg/kg/day fenofibrate. The data showed that the lipid-lowering effects of fenofibrate in dyslipidemic children are comparable to the ones observed in adults with no difference in the safety profile.

Assessor's comment:

The following wording is recommended by Rapporteur as it better reflects limitations of the currently available paediatric data:

Section 5.1

Limited paediatric data are available. The effects of fenofibrate in dyslipidemic children have been studied in two small clinical trials and in an open long-term surveillance registry with 76 hypercholesterolemic children aged 3 to 18 years receiving fenofibrate for 1 to 11 years. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of fenofibrate in dyslipidemic children.

Adverse events similar to those observed in adults have been reported in children: leucopenia, liver function test abnormal, rhabdomyolysis, renal failure, hepatitis, jaundice, myositis and rhabdomyolysis.

Overall, the safety and efficacy of fenofibrate in children and adolescents have yet not been established (see section 4.2).

References to the study performed Cree G.M et al. was removed as this study was performed in children with burn injury.

VI RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The MAH submitted 3 published studies on the use of fenofibrate in children with hypaelipdemia. None of the studies was randomised or controlled. The age of children participating in these studies ranged from 3 years to 18 years however the exact number of children in each age category has not been provided.

It has to be noted that in all submitted studies Fenofibrate was given to children (mostly with familial hypercholesterolemia) as a first line treatment.

As per the recent CHMP recommendation, fenofibrate should not be used as a first-line treatment, except in patients with severe hypertriglyceridaemia and in patients who cannot use statins

No studies have been performed in children with mixed hyperlipidemia when a statin is contraindicated or not tolerated (at the time statins were not available on the market). Information in relation to changes in the triglyceride levels in this patient population is also very limited.

In one study 200 mg/day of fenofibrate, irrespective of the body weight, was given to children. Then the dose was readjusted to 100 or 300 mg/day. In other studies the dose of 5 mg/kg/day was administered.

No pharmacokinetic data have been provided and the dose of 5 mg/kg/day was chosen on an empirical basis. In addition there is no formulation currently available which allows for an administration of fenofibrate per kilogram of body weight.

No studies on the effect of fenofibrate on the growth and sexual maturation and endocrine function have been performed.

The safety data from post-marketing surveillance have been provided. Adverse reactions observed in children seem to be similar to those observed in adults however the final conclusions cannot be drawn due to the limitation of the paediatric data (small numbers, lack of controls). Cases of hepatitis, myositis, rhabdomyolysis have been reported.

It is the Rapporteur's opinion that the submitted data provide some supportive evidence for the use of fenofibrate in children however they are insufficient to update section 4.2 of the SPC.

The MAH proposed to update sections 4.1, 4.2 and 4.4 of the SPC for Fenofibrate 67 mg and 100 mg capsules and include recommendations for the use in children.

However, it is the Rapporteur's opinion that the scientific data for children submitted by the MAH as a part of this procedure are not sufficiently robust to support this proposal.

The Rapporteur considers that only some information can be added to section 5.1 of the SmPC of these two forms (*see section VII. recommendation*).

The high dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets) are contraindicated in children as no studies have been performed with these high dosage forms in this population (no safety or efficacy data exist).

However in line the SPC guidelines, lack of data alone should not lead to a contraindication. Therefore the contraindication should be removed from section 4.3 of the SmPC and section 4.2 should be updated with the following wording:

Section 4.2

Paediatric population:

The safety and efficacy of fenofibrate in children and adolescents younger than 18 years has not been established. No data are available. Therefore the use of fenofibrate is not recommended in paediatric subjects under 18 years.

During procedure comments were received from two MS(s) Both MS(s) agreed with the overall conclusions of the Rapporteur.

The UK has agreed with the overall conclusions of the Rapporteur and also agrees with the proposed changes to SmPC section 4.2 of the high dose fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets). However for low dose fenofibrate 67mg micronised capsules, in the absence of any new safety concerns, the UK intends to maintain the existing posology granted Nationally by the MHRA.

VII. RECOMMENDATION

Based on the review of the provided paediatric data on the safety and efficacy, the Rapporteur considers that the results of these studies do not support an addition of paediatric posology.

Following changes to the SmPC are recommended:

For Fenofibrate 67 mg and 100 mg capsules

Section 4.2:

Paediatric population:

The safety and efficacy of Fenofibrate in children have not yet been established. Only limited paediatric data are available (see section 5.1). Therefore, the use of fenofibrate is not recommended in paediatric subjects under 18 years

Section 5.1

Limited paediatric data are available. The effects of fenofibrate in dyslipidemic children have been studied in two small clinical trials and in an open long-term surveillance registry with 76

hypercholesterolemic children aged 3 to 18 years receiving fenofibrate for 1 to 11 years. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of fenofibrate in dyslipidemic children.

Adverse events similar to those observed in adults have been reported in children: leucopenia, liver function test abnormal, rhabdomyolysis, renal failure, hepatitis, jaundice, myositis and rhabdomyolysis.

Overall, the safety and efficacy of fenofibrate in children and adolescents have yet not been established (see section 4.2).

Patient information leaflets should be updated accordingly.

For high dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets)

Section 4.2:

Paediatric population:

The safety and efficacy of fenofibrate in children in children and adolescents younger than 18 years has not been established. No data are available. Therefore, the use of fenofibrate is not recommended in paediatric subjects under 18 years

Patient information leaflets should be updated accordingly.