2. SYNOPSIS

NAME OF COMPANY: Laboratoires Fournier S.A.
NAME OF FINISHED PRODUCT: Non-micronized fenofibrate
NAME OF ACTIVE INGREDIENT: FENOFIBRATE

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<tr>
<th>INDIVIDUAL STUDY TABLE REFERRING TO PART .......... OF THE DOSSIER</th>
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<tbody>
<tr>
<td>Volume: Page: (FOR NATIONAL AUTHORITY USE ONLY)</td>
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Title of the study: Assessment of long-term efficacy and safety of fenofibrate in hypercholesterolemic children and adolescents—Analysis of a long-term registry.

Investigators: Removed for privacy reasons


Studied period (years): October 12, 1973 (date of first enrolment) to January 20, 1988 (date of last completed)
Objectives: To evaluate the safety and efficacy on total cholesterol and triglycerides after 6, 12, 18, 24, and 36 months of treatment with fenofibrate at the dose of 5 mg/kg/day in children with familial hypercholesterolemia.

Methodology: Data for the registry were extracted from hospital records for 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 in controlling the patients' dyslipidemia. The recommended dose of fenofibrate in children and adolescents was 5 mg/kg. Patients were to be seen at regular intervals for routine follow-up, including determination of lipid levels and assessment of tolerability of the medication.

Number of patients (planned and analyzed): This was a retrospective analysis of all data collected from a registry. Thus, there was no prospective target population. A total of 76 patients who began treatment with fenofibrate when they were less than 18 years of age were included in the analyses.

Diagnosis and main criteria for inclusion: Patients included in the study were children and adolescents with familial hypercholesterolemia who were less than 18 years of age when they began treatment with fenofibrate.

Test product, dose and mode of administration: 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.

Duration of treatment: Patients were treated from 10 to 132 months.

Reference: C FEN 73 01 FR 02 02
Version: FINAL
Edition date: February 2002
Statistical methods: No statistical tests were carried out. All analyses used descriptive methods.

Efficacy results: At entry into the study, all patients except one with borderline high cholesterol (177 mg/dl), had elevated cholesterol levels (> 200 mg/dl) according to NCEP standards, 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. The reduction of total cholesterol was stable over time varying from −21.1% after 12 months to −17.5% at the end of the follow-up. 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).

Safety results:

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 colestepl.

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 x 10³/mm³; one of these returned to levels above 3.0 x 10³/mm³ 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.

Conclusion: Data from this survey indicated that long-term treatment with fenofibrate at an average dose of 5 mg/kg is well tolerated in children and adolescents of both genders with familial hypercholesterolemia aged 3 to 18 years at the initiation of the treatment. The major adverse events related to fenofibrate were elevation of AST/ALT. Clinical acceptability was satisfactory and the treatment did not alter growth in these children and adolescents.

Date of report: February 20, 2002