DRAFT 1.3

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Nezglyal 13.66 mg/mL oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral suspension contains 13.66 mg of leriglitazone equivalent to 15 mg of leriglitazone hydrochloride.

Excipients with known effect
Each mL contains 80 mg sorbitol (E420).
Each mL contains 2 mg sodium.
Each mL contains 1 mg sodium benzoate (E211).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

White, homogeneous suspension with strawberry flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nezglyal is indicated for the treatment of ambulatory adrenoleukodystrophy (ALD) in adult male patients with early stage myeloneuropathy, and paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD).

4.2 Posology and method of administration

Nezglyal should be initiated and monitored by a physician with experience in the management of neurodegenerative diseases.

Posology

Adults (≥ 18 years)
The recommended starting dose is 10 mL once daily. After 1 month from initiation of treatment the dose should be increased to 12 mL except in cases of moderate to severe edema or weight gain or increased liver enzymes in which case the dose will be maintained at 10 ml. (Table 1).

Dose modifications

Following initiation of therapy dose modifications are possible at any time in case of adverse events not controlled by other specific measures, upon clinical judgement. After adverse event resolution, the dose may be increased again (see Table 1 below).

Table 1: Recommended Nezglyal Dose Modifications

Adverse reaction	Severity	Recommended Dose Modifications
Moderate – severe oedema and/or weight gain	Moderate - Severe	Decrease the reference dose (*) by increments of 2 ml.to a minimal dose of 8 ml After resolution, the reduced dose may be increased again up to the reference dose
Increased liver enzymes	ALT >3.0 times ULN confirmed in 2 measurements	Treatment should be suspended until normalization. After normalization, consider resumption of treatment and continued monitoring of liver enzymes.

(*) Reference dose is defined as either the starting dose of 10 mL, or the dose of 12 mL

Special populations

Women
Nezglyal has not yet been studied in women with ALD. Currently available data are described in section 5.2.

Elderly
No difference in posology is anticipated for patients over 65 years of age (see section 5.2). Data are limited, but generally, safety was similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with Nezglyal.

Renal impairment
No data are available for patients with hepatic impairment (see section 5.2).

Hepatic impairment
Nezglyal has not been investigated in patients with moderate to severe hepatic impairment (Child-Pugh classification groups B or C).

Children (2 to < 12 years) and adolescents (12 to < 18 years)
The recommended daily doses in children and adolescents, are as follows (Table 2):

Table 2: Recommended doses in mL for children

Age (years)	Dose (mg/kg per day)	Dose (mL/kg per day)
2-5	2.6	0.17
≥ 6-11	2.4	0.16
12-17 (*)	2.2	0.15

(*) The starting dose cannot be greater than 10 ml.

Method of administration

Oral use. The suspension is administered by means of a graduated dosing syringe.

The suspension can be taken with or without food.

The bottle should be shaken well (for about 30 seconds) before each dose. For further instructions on handling of the product, see section 6.6.

4.3 Contraindications

Nezglyal is contraindicated in patients with:

- Hypersensitivity to thiazolidinediones.
- Cardiac failure or history of cardiac failure (NYHA stages I to IV).
- History of cancer, except surgical resection and without signs of recurrence for at least 5 years.
- Type 1 or type 2 diabetes.

4.4 Special warnings and precautions for use

Weight gain

Weight gain with thiazolidinediones (TZD) may be associated with an increase in subcutaneous adipose tissue and a concomitant decrease in visceral fat. There is evidence of weight gain during treatment with leriglitazone, which in the initial stage may be due to fluid retention and later may be associated with fat accumulation.

Patients should be advised to adhere to a calorie-controlled diet and weight monitoring (see section 4.8).

Dose modifications are recommended (see section 4.2).

Oedema/fluid retention

Fluid retention and oedema are known class effects of TZD. There is evidence of oedema during Nezglyal treatment.

Diuretics are recommended as the first line measure for oedema management. Dose modifications are recommended if oedema is not controlled with diuretics or where diuretics contraindicated (see section 4.2). The administration of a diuretic should be carefully considered in the context of the patient's overall clinical status, i.e., whether adrenocortical insufficiency is present, and co-medication, i.e., whether the patient receives corticosteroids, aldosterone or other medication that may interfere with electrolyte balance. Diuretics with a low potential to interfere with serum electrolytes are preferred. Most recent laboratory results for electrolyte status should be considered to decide on the treatment of choice. The patient should be educated to avoid situations that disturb electrolyte balance such as dehydration or drinking excessive amounts of plain water and should be monitored for signs and symptoms of electrolyte imbalance like fatigue and confusion.

Fluid retention and cardiac failure

Patients should be observed for signs and symptoms of oedema and heart failure or weight gain related with fluid retention; particularly those patients with risk factors for heart failure (i.e., hypertension, coronary disease, valve disease, family history, etc.) (see section 4.8).

Leriglitazone should be discontinued if clinically significant deterioration in cardiac status occurs.

Bladder cancer

Increased risk of bladder cancer has been reported for some TZD used in the treatment of type 2 diabetes. While no increased risk of bladder cancer has been observed in clinical studies with leriglitazone, risk factors for bladder cancer should still be assessed before initiating leriglitazone treatment (risks include: age, smoking history, frequent urinary infections, permanent bladder catheter, exposure to some occupational or chemotherapy agents e.g., cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting treatment.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Monitoring of liver function

Liver enzymes should be checked prior to the initiation of therapy with Nezglyal in all patients. Treatment should not be initiated in patients with increased baseline liver enzyme levels (AST or ALT

> 2 times the upper limit of normal), total bilirubin >1.5 times ULN (unless due to Gilbert's syndrome), or with any other evidence of liver disease.
Following initiation of therapy with Nezglyal, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 times upper limit of normal during therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times the upper limit of normal, therapy should be suspended. Treatment may be resumed after normalization with continued monitoring of liver enzymes, and a dose modification should be considered (see section 4.2). If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with leriglitazone should be guided by clinical judgement pending laboratory evaluations. If bilirubin increases or clinical signs such as jaundice are observed, treatment with Nezglyal should be discontinued.

Information about excipients

Sorbitol
Nezglyal contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Sodium
This medicinal product contains 24 mg sodium per 12 mL dose, equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Sodium benzoate
This medicinal product contains 12 mg sodium benzoate (E211) per 12 mL dose.

4.5 Interaction with other medicinal products and other forms of interaction

Nezglyal should be used with caution during concomitant administration of cytochrome P450 (CYP) 2C8 and CYP3A inhibitors (e.g., gemfibrozil and itraconazole) or CYP3A inducers (e.g., carbamazepine) (see sections 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Nezglyal in pregnant women. Results in animals indicate that foetal growth was reduced after treatment with leriglitazone at the high dose but there were no effects on foetal morphology (external, visceral, or skeletal) at any dose (see section 5.3).
Nezglyal is not recommended during pregnancy.

Breast-feeding
It is unknown whether leriglitazone/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Nezglyal should not be used during breast-feeding.

Fertility
There was no effect on sexual maturation in male or female rats dosed through puberty. Despite reduced number of corpus luteum and some evidence for asynchronous cycles in the ovary, there were no permanent effects on mating or fertility (see section 5.3). No effects on human fertility are expected.

4.7 Effects on ability to drive and use machines

Nezglyal has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Nezglyal in ALD patients with AMN was evaluated in the Phase II/III study MT-2-01 (ADVANCE), a randomized, double-blind, placebo-controlled 2-year study, in which 77 patients were randomized to leriglitazone and 39 patients to placebo in a 2:1 ratio. Patients receive an individualized daily dose to achieve a leriglitazone plasma target exposure (AUC_{tau}) of 200 µg·h/mL (± 20%).

The most commonly reported adverse reactions during Nezglyal treatment were weight increase (70.1 %), oedema peripheral (63.6 %), and lacrimation increase (18.2 %) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are listed in Table 2. They are classified according to MedDRA body system organ class and frequency. Within the system organ classes, adverse events are listed under headings of frequency (number of patients expected to experience the adverse reaction), using the following categories: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Adverse events reported in 2% of patients or more overall in the safety set and with higher frequencies in leriglitazone group than in placebo group have been defined as ADRs.

Table 2: Adverse Reactions

MedDRA SOC	**MedDRA Preferred Term**	**Frequency**
Blood and lymphatic system disorders	Anaemia Macrocytosis	Common
Metabolism and nutrition disorders	Hypercholesterolaemia Increased appetite	Common
Eye disorders	Lacrimation increased	Very Common
	Eyelid oedema Swelling of eyelid	Common
Musculoskeletal and connective tissue disorders	Joint swelling	Common
Renal and urinary disorders	Nocturia	Common
General disorders and administration site conditions	Oedema Oedema peripheral	Very Common
	Fatigue Peripheral swelling	Common
Investigations	Weight increased	Very Common
	Blood creatinine phosphokinase increased Haemoglobin decreased	Common

Description of selected adverse reactions

Anaemia
Within the SOC blood and lymphatic system disorders, the event anemia was reported most frequently in Nezglyal group (leriglitazone: 10 patients [13%], placebo: 1 patient [2.6%]). Within the SOC investigations, the event haemoglobin decreased was reported most frequently in Nezglyal group (leriglitazone: 6 patients [3.9%], placebo: 0 patients). Most events were reported within the first 48 weeks of starting treatment. The reports of anaemia are considered secondary to haemodilution. These events were generally mild, recovered throughout the study and no actions regarding treatment had to be taken.

Lacrimation increased
Within the SOC eye disorders, the event lacrimation increased was reported exclusively in Nezglyal group (14 patients [18.2%]). Most events were reported within the first 24 weeks of starting treatment. Most of the events were of mild severity with intermittent frequency and dose reduction was recommended only in a few cases.

Weight gain
Within the SOC investigations, the event weight increased was reported most frequently in Nezglyal group (leriglitazone: 54 patients [70.1%], placebo: 9 patients [23.1%]). Most events were reported within the first 24 weeks of starting treatment and were mild in severity and manageable with diuretics and / or dose reductions and usually did not require discontinuation of treatment.

Oedema peripheral
Within the SOC blood and lymphatic system disorders, the event oedema peripheral was reported most frequently in Nezglyal group (leriglitazone: 49 patients [63.6%], placebo: 7 patients [17.9%]) Most of the events were reported within the first 24 weeks of starting treatment and were mild and manageable with diuretics and / or dose reductions and usually did not require discontinuation of treatment.

Paediatric population

There are no data available on the use of Nezglyal in patients under 2 years of age. For children aged 2 to 12 years, there are data on 13 patients with cALD from ongoing study MT-2-02 (NEXUS). Eight of the thirteen patients (61.5%) have experienced at least 1 TEAE, of which 97.2% were mild and 2.7% were moderate in severity. TEAE considered related to the study drug were observed in 3 patients (23%) and were eyelid oedema, swelling of the face (all mild) and night sweat (moderate). In none of the cases actions regarding the study drug were needed. Data are limited, but generally, it can be considered that safety profile is similar to adult patients.

Tabulated list of adverse reactions for paediatrics

The safety of Nezglyal in paediatric patients with cALD aged 2 to 12 years is under evaluation in the ongoing study MT-2-02 (NEXUS), an open-label, multi-centre study in male paediatric patients with cALD to assess the effects of Nezglyal on disease progression. Patients received an individualized daily dose to achieve a leriglitazone plasma target exposure (AUC_{tau}) of 170 µg·h/mL (± 20%).

Safety database of the interim analysis at week 24 of the ongoing NEXUS study (n=16), 7 ADRs were reported in 4/16 patients (25%). There were two events of eyelid oedema (12.5%). Another 5 events were reported each in 1 patient (6.25%): increased appetite, headache, weight increased, swelling face and night sweats. This last event was considered moderate in severity, while all other events were assessed as mild.

Adverse reactions in paediatric population are listed in Table 10.

Table 10: Adverse reactions in paediatrics

MedDRA SOC	MedDRA Preferred Term	Frequency
Eye disorders	Eyelid oedema	Very Common
General disorders and administration site conditions	Swelling face	Common
Investigations	Weight increased	Common
Metabolism and nutrition disorders	Increased appetite	Common
Nervous system disorders	Headache	Common
Skin and subcutaneous tissue disorders	Night sweats	Common

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of overdose, symptomatic and general supportive measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned.

Mechanism of action

Leriglitazone activates the human peroxisome proliferator-activated receptor (PPAR) gamma receptor. Leriglitazone activates key genes that counteract oxidative stress, mitochondrial dysfunction and neuronal death, stimulate mitochondrial biogenesis, and suppress genes that induce inflammation (nuclear factor kappa-light-chain-enhancer of activated B cells [NfKβ] pathway), thus preventing axonal degeneration, demyelination and neuroinflammation.

Pharmacodynamic effects

In vitro, leriglitazone was able to protect motor neurons and astrocytes survival and decreased microglia activation induced by several toxic agents relevant to diverse neurodegenerative pathologies; *in vivo*, in adrenomyeloneuropathy (AMN) models it reversed motor dysfunction in the *Abcd1/Abcd2* double knock-out mice model and restored mitochondrial expression of genes associated with biogenesis and function and reduced oxidative damage and reversed proinflammatory status in rodent spinal cord tissue. Biomarker changes recorded in preclinical models upon leriglitazone administration correlate with reversal of disease progression and with natural history data in AMN patients.

Leriglitazone reduced endothelial cell activation, monocyte adhesion and inflammatory activation in an *in vitro* model of the blood brain barrier (BBB) of ALD, therefore protecting the initial BBB disruption thought to be a key step in the development of cALD. Moreover, leriglitazone decreased the levels of inflammatory cytokines and chemokines in monocyte-derived macrophages from AMN patients. Leriglitazone also increased myelin debris clearance and increased myelination and oligodendrocyte survival *in vitro*, thus promoting remyelination and was active in *in vivo* models of demyelination/remyelination (cuprizone induced). In inflammatory models, leriglitazone decreased the neurological disability in the experimental autoimmune encephalomyelitis (EAE) neuroinflammatory mouse model.

Clinical efficacy

Study MT-2-01 (Part 1; ADVANCE) was a randomized, double-blind, placebo-controlled 2-year safety and efficacy study in adult male patients with AMN; diagnosed with ALD based on genetic testing and with clinical evidence of spinal cord involvement. 77 patients were randomized to leriglitazone and 39 patients to placebo in a 2:1 ratio. Patients completing the 2-year double-blind part (Part 1) are offered an optional long-term extension with open-label treatment with leriglitazone (Part 2). Patients received an individualized daily dose to achieve a leriglitazone target plasma exposure (AUC_{tau}) of 200 µg·h/mL (± 20%).

Baseline demographic characteristics were similar for patients in the leriglitazone and placebo groups, except for mean years since onset of myelopathy symptoms which was slightly longer in the placebo group (leriglitazone 10.6 years, placebo 12.8 years). Cerebral involvement, white matter brain abnormalities were present in approximately 50% of the patients in both groups. Patients at cardiac risk were excluded from study participation (i.e., previous or current history of congestive heart failure or reduced left-ventricular ejection fraction, or other clinically significant cardiac abnormalities on echocardiogram).

The primary endpoint, change from Baseline in the 6-minute walk test (6MWT), was not met in the overall population. Patients on active treatment as well as those on placebo showed little progression in 6MWT and there was no difference between treatment groups.

Radiological progression of cerebral lesions was less frequent in the leriglitazone group than in the placebo group (3.9% vs 20.5%, 95% CI of proportion difference -0.32 to -0.05, p=0.007). Six patients, all in the placebo group, were independently reported by sites as having clinically progressed to the cALD phenotype (15.4%, 95% CI of proportion difference -0.30 to -0.06, p=0.001) Such results were aligned across radiological, clinical and biomarker-based observations. These results are of major clinical value as onset of cALD precedes a rapid decline leading to vegetative state or death with a mean survival of 3.4 years.

All body sway parameters in stances with eyes closed favoured leriglitazone. In the condition with 'eyes closed, feet apart' (EC-FA), the least square (LS) mean difference between treatment groups was -1.049 mm (95% CI -2.8 to 0.7, p=0.234) in total body sway amplitude, -3.776 mm (95% CI -6.3 to -1.3, p=0.004) in anteroposterior body sway amplitude and -0.250 mm (95% CI -1.9 to 1.4, p=0.762) in mediolateral body sway amplitude. In the condition with EC-FT, the LS mean difference between treatment groups was -2.374 mm (95% CI -4.6 to -0.2, p=0.036) in total body sway amplitude, -2.536 mm (95% CI -5.5 to 0.5, p=0.096) in anteroposterior body sway amplitude and -5.587 mm (95% CI -9.3 to -1.9, p=0.003) in mediolateral body sway amplitude. These results indicate that treatment with Nezglyal provides clinically meaningful benefits by preserving the balance deterioration in these patients.

On the Severity Score System for Progressive Myelopathy (SSPROM), there was a trend towards greater decline from baseline to week 96 in severity scores (indicating greater disability) in the placebo group than in the leriglitazone group (LS mean difference 2.3; 95% CI –0.3 to 4.9; p=0083). On the Expanded Disability Status Scale (EDSS) step, there was a trend towards greater increase from baseline to week 96 in disability scores (indicating greater disability) in the placebo group than in the leriglitazone group (LS mean difference –0.3; 95% CI –0.7 to 0.0; p=0.085). The EDSS ambulation showed no difference between the groups. On the European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L), there was a trend towards greater decline with placebo than with leriglitazone (LS mean difference 0.0; 95% CI –0.0 to 0.1; p=0.11). Improvement at week 96 in the Clinician Global Impression – Improvement scale (CGI-I) was reported for five patients (6.5%) in the leriglitazone group and for zero patients with placebo (95% CI of proportion difference -0.03 to 0.14, p=0.093).

Natural history of adrenomyeloneuropathy is non-linear in terms of ambulation and patients decline significantly in the first 10 years of disease i.e. early stage myeloneuropathy with a slowing of decline thereafter. For early stage myeloneuropathy patients the 6MWT favoured the leriglitazone group compared to the placebo group (a LS means difference 38.3; 95% CI -4.7 to 81.3; p=0.08). The same analysis with the EDSS step and EDSS ambulation showed a greater worsening in the placebo group compared to the leriglitazone group (LS means difference -0.7 and -1.9;95% CI -1.3 to -0.01 and -3.0 to -0.7; p=0.047 and 0.002, respectively). The EQ-5D-5L also showed a greater trend in patients with early disease (LS means difference 0.1; 95% CI -0.004 to 0.2; p=0.059.

Paediatric population

Clinical efficacy

Study MT-2-02 (NEXUS Study) is an open-label study in male paediatric patients aged 2 to 12 years old with cALD to assess the effects of leriglitazone on disease progression. Patients were assigned to one of two populations: those without gadolinium (Gd) enhancement (population 1) or those with Gd enhancement (population 2) at baseline.

The primary efficacy endpoint is the proportion of patients with clinically and radiologically arrested disease at week 96. A pre-specified assessment of arrested disease has been conducted up to 13 enrolled patients reached week 24, including the evaluation of study continuation criteria defined as

lesion growth deceleration without clinical progression or disease arrest. Key secondary endpoints are Sustained change from baseline for the Neurological Functional Scale (NFS); change from baseline in Loes score; change from baseline in Gadolinium Intensity Score (GIS); overall survival for patients not undergoing haematopoietic stem cell transplant (HSCT) and number of patients meeting HSCT criteria.

The study is currently on-going with 23 enrolled patients. At baseline, Loes score, lesion volume, and total NFS were similar for both populations. Eleven patients were evaluable with 24 weeks of data and comprised the interim analysis set. All the 11 evaluable subjects remained clinically stable (free of Major Functional Disability and stable NFS at Week 24 (95% CI: 71.5, 100) and 5 out of 11 showed arrested disease (95% CI: 16.7, 76.6). All patients who have not undergone HSCT (n=10) are alive. 5 patients met HSCT criteria at week 24, 2 patients underwent HSCT post week 24, both with stable lesions but persistence of Gd enhancement. Neurofilament light chain concentrations stabilized in most patients following a parallel profile to lesion volume change. Matrix metalloproteinase-9 concentrations decreased in all patients.

The European Medicines Agency has deferred the obligation to submit the results of studies with leriglitazone in one or more subsets of the paediatric population in the treatment of ALD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration in humans, leriglitazone is rapidly absorbed showing an absolute bioavailability of 91.1% after a single dose of 180 mg radiolabelled compound. Peak plasma concentrations are achieved 3 hours after administration. Proportional increases of the plasma concentration were observed for doses from 30 to 270 mg leriglitazone hydrochloride. Steady state is achieved after 5 days of dosing. Repeated dosing results in an accumulation factor of 1.7-1.8. Absorption is not influenced by food intake.

Distribution

The estimated volume of distribution in humans is 0.29 L/kg. Leriglitazone is bound to human plasma protein in a percentage of 98%. Leriglitazone was detected in CSF from human volunteers 4 hours on Day 8, at 188 ng/mL and 332 ng/mL after the last dose of 135 and 270 mg leriglitazone hydrochloride, respectively. It approximately corresponds to the 2% of total plasma concentration of leriglitazone.

Biotransformation

Leriglitazone undergoes hepatic metabolism predominantly via CYP2C8 and CYP3A4.

M3 is the main metabolite of leriglitazone, and it is formed by dehydrogenation of the alcohol function, mainly by CYP2C8. In human volunteers, leriglitazone represents 60 to 65% of total medicine related material (2-24 h) in plasma and the main metabolite M3 represents 30 to 35%.

Metabolite profiling indicated, two abundant radio peaks were detected which could be assigned to the parent compound leriglitazone (P1) and the M3 metabolite (P2), which is an oxidized analogue of the parent compound. In urine, eleven abundant radio peaks were detected. The main metabolite in urine was a demethylated analogue which is oxidized to a carboxylic acid. Seven peaks could be identified as glucuronic acid conjugates and one sulphate conjugate. Two further metabolites were a reduced and a deaminated and oxidized analogue of the parent compound. In faeces homogenate samples, six abundant radio peaks were detected. The most abundant signal could be assigned to a sulphated metabolite followed by unchanged leriglitazone. One further metabolite could be assigned to a demethylated analogue which is oxidized to a carboxylic acid.

Elimination

Radiolabelled ^{14}C-leriglitazone administration in an absolute bioavailability/ human absorption, distribution, metabolism and excretion (ABA/hAME) study in human volunteers showed that the main route of excretion was in urine from 73.9% to 80.7% and in faeces from 20.6% to 27.6%. Very small amounts of the drug were excreted in urine as unchanged leriglitazone (0.4% of the administered oral dose) and as M3 (< 0.02%), and 5.1% was excreted in faeces as unchanged ^{14}C-leriglitazone and 0.3% of the administered dose was excreted in faeces as ^{14}C-M3.

Special populations

Elderly
No data are available.

Patients with hepatic impairment
No data are available.

Patients with renal impairment
No data are available for patients with moderate and severe renal impairment.

Paediatric population

There are no data available on the use of leriglitazone in patients under 2 years of age. For children aged 2 to 12 years, there are pharmacokinetic data from 16 patients with cALD from ongoing study MT-2-02 (NEXUS) and generally, pharmacokinetic properties were similar between paediatric patients and adult patients treated with leriglitazone.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

The toxicological observations in rats and dogs administered leriglitazone hydrochloride for 6 and 9 months were typical of excessive PPAR gamma activation, i.e., heart weight increase and oedema. No additional toxicological findings were observed.

Embryofoetal development toxicity studies were performed in pregnant rats and rabbits and leriglitazone showed to be not teratogenic at any tested dose (highest doses above the target clinical exposure) and that foetal growth was reduced after treatment with leriglitazone at the high dose but there were no effects on foetal morphology (external, visceral, or skeletal) at any dose. Adverse effects on female fertility and early embryonic development were limited to the maximum dose of 50 mg/kg/day, as demonstrated by fewer live embryos on Day 13 of gestation due to a reduction in the mean number of corpora lutea and slight increases in the extent of pre- and post-implantation loss. No adverse effects for male fertility and male mediated effects on early embryonic development were observed at any dose evaluated.

The genotoxic potential of leriglitazone was evaluated in a comprehensive battery of in vivo and in vitro genotoxicity assays. The combined weight of evidence from these studies suggests that leriglitazone does not pose a genotoxic concern.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Microcrystalline cellulose (E460)

Carmellose sodium (E466)
Saccharin sodium (E954)
Sodium benzoate (E211)
Sodium citrate (E331)
Citric acid monohydrate (E330)
Strawberry flavour
Citric acid monohydrate 0.2M solution
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After the first opening: 66 days. Store below 25°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Hydrolytic class III amber glass bottle with a white polyethylene child-resistant cap.
Pack size of 1 x 100 mL bottle.

The pack includes a polyethylene oral dosing syringes of 12 mL graduated every 0.5 mL.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

An oral syringe of 12 mL is provided for accurate measurement of the prescribed dose. It is recommended that the healthcare professional advises the patient or carer how to use the oral syringes to ensure that the correct volume is administered.

After the patient has taken their daily dose, the bottle should be closed, and the syringe(s) washed with clean water and dried with a paper towel. The bottle and the syringe(s) should then be stored in the original packaging.

7. MARKETING AUTHORISATION HOLDER

Minoryx Therapeutics S.L.
Av Ernest Lluch, 32, TCM3
08302 Mataró, Barcelona
Spain
Tel: +34 93 544 14 66
Fax: + 34 93 0160119
info@minoryx.com

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu