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 13.7 mg/mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral suspension contains 13.7 mg of leriglitazone (as hydrochloride).
One bottle (100 mL) contains 1 370 mg of leriglitazone (as hydrochloride).

Excipients with known effect

Each mL contains 80 mg sorbitol (E 420).
Each mL contains 2 mg sodium.
Each mL contains 1 mg sodium benzoate (E 211).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White, homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nezglyal is indicated for the treatment of Cerebral Adrenoleukodystrophy (cALD) in males with Adrenoleukodystrophy (ALD) aged 2 to 12 years with non-Gadolinium (Gd) enhancing lesions (i.e. Gd negative) in brain Magnetic Resonance Imaging (MRI), with a Neurological Functional Score (NFS) of 0 or 1.

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

Nezglyal is administered once daily. The recommended doses are based on height and body weight as shown below in Table 1 (children 2 to 5 years of age) and Table 2 (children 6 to 12 years of age).

Table 1: Recommended doses in mL for children 2 to 5 years of age

	Body weight (kg)						
Height (cm)	**9-10**	**11-13**	**14-16**	**17-20**	**21-26**	**27-32**	**33-41**
81-86	2	2.5	2.5	2.5	3	3	3.5
87-92	2	2.5	2.5	3	3	3.5	3.5
93-99	2.5	2.5	3	3	3	3.5	4
100-106	2.5	2.5	3	3	3.5	3.5	4
107-113	2.5	3	3	3.5	3.5	4	4
114-121	3	3	3	3.5	4	4	4.5
122-131	3	3	3.5	3.5	4	4.5	4.5

Table 2: Recommended doses in mL for children 6 to 12 years of age

	Body weight (kg)						
Height (cm)	**16-20**	**21-26**	**27-35**	**36-46**	**47-61**	**62-80**	**81-106**
107-113	3.5	4	4	4.5	5	5.5	6
114-121	3.5	4	4.5	5	5.5	6	6.5
122-129	4	4.5	4.5	5	5.5	6.5	7
130-138	4	4.5	5	5.5	6	6.5	7.5
139-148	4.5	5	5.5	6	6.5	7	7.5
149-158	4.5	5	5.5	6	6.5	7.5	8
159-170	5	5.5	6	6.5	7	8	8.5

Paediatric dose modifications
Checks on paediatric patients' growth are recommended every 6 months to adjust the dose, with monitoring of height and weight.

Dose modifications for hepatic function changes
Before initiation and during treatment, patients should be monitored for increased hepatic enzymes, with dose modifications according to the recommendations outlined in Table 3. Appropriate hepatic function tests should be performed in patients both prior to the initiation of treatment and monitored regularly during treatment (see section 4.4).

Table 3: Recommended Nezglyal dose discontinuation

Adverse reaction	**Severity**	**Recommended dose modifications**
Increased hepatic enzymes (see sections 4.4 and 4.8)	Alanine aminotransferase (ALT) > 3.0 times upper limit of normal (ULN) confirmed in 2 measurements. The second measurement should be performed within 3 to 5 days following the first elevated result.	Treatment should be suspended at the first measurement of a major increase until normalisation. After normalisation, consider resumption of treatment and continued monitoring of hepatic enzymes. If relapses in hepatic enzyme increase occur, the management should be repeated as above.

Missed dose
If a dose is missed, the patients should be advised not to take a double dose and to take the next dose as prescribed.

Special populations

Hepatic impairment
No data are available in subjects with hepatic impairment; therefore, the safety and efficacy of this medicinal product has not been established in those patients. The use in patients with mild, moderate and severe hepatic impairment (Child-Pugh classification groups A, B or C) is not recommended (see section 4.4).

Renal impairment
No data are available in subjects with renal impairment. Renal excretion plays a minor role in unchanged leriglitazone clearance and clinically relevant accumulation of leriglitazone or active metabolite M3 in mild renally impaired patients is unlikely. No dose adjustment is required for patients with mild renal impairment (glomerular filtration rate (GFR) = 60-89 mL/min).
However, the use in patients with moderate to severe renal impairment (GFR < 60 mL/min) is not recommended.

Paediatric population (children < 2 years of age)

The safety and efficacy of Nezglyal in children < 2 years of age have not been established. No data are available.

Method of administration

Oral use.

The suspension is administered once daily, preferably after breakfast at the same time of the day.
The bottle should be shaken well for about 30 seconds before each dose.

The suspension should be administered using the provided graduated oral syringe to measure the appropriate volume of suspension corresponding to the prescribed dose for the patient.

For further instructions on handling of the medicinal product see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to thiazolidinediones.

Cardiac failure or history of cardiac failure (NYHA stages I to IV) (see section 4.4).

4.4 Special warnings and precautions for use

Oedema/fluid retention and cardiac failure

Oedema events were observed very commonly in children (see section 4.8). Children had events typically of facial or periorbital oedema.

Oedema can start within 4 weeks of treatment, with the majority of patients experiencing the event within 24 weeks. Diuretics are not recommended for management of oedema as they may decompensate electrolyte balance in patients receiving corticosteroid hormone replacement for ALD associated adrenal insufficiency.

Oedema does not stabilise or resolve by dose reductions. In case of persisting or severe oedema, treatment withdrawal can be considered if the oedema is not tolerated. Patients should be informed to expect peripheral or facial oedema.

There are no data on the use of leriglitazone in patients with cardiac failure or a cardiac history and patients with risk factors for cardiac failure (see section 5.1). Use of leriglitazone in patients with cardiac failure or a cardiac history is contraindicated (see section 4.3).

Patients should be observed for signs and symptoms of fluid retention (assessment of jugular venous pressure and examination for hepatomegaly are recommended after treatment initiation) and cardiac failure (NYHA stages I to IV) or weight increase related with fluid retention; particularly those patients with risk factors for cardiac failure (NYHA stages I to IV) e.g. hypertension, coronary disease, valve disease, family history (see section 4.8).
Leriglitazone should be discontinued if clinically significant deterioration in cardiac status occurs.

Patients undergoing HSCT (Haematopoietic Stem Cell Transplantation)

Treatment with leriglitazone must be discontinued at least five days prior to initiating HSCT procedures, defined as the day of first administration of myeloablative conditioning medicinal products. The timing of discontinuation should be confirmed by the treating physician based on the planned conditioning regimen.

Monitoring of hepatic function

Hepatic enzymes should be checked prior to the initiation of therapy in all patients. Treatment should not be initiated in patients with increased baseline hepatic enzyme levels (Aspartate aminotransferase (AST) or ALT > 2 times the ULN), total bilirubin > 1.5 times ULN (unless due to Gilbert's syndrome), or with any other evidence of liver disease.

Following initiation of treatment, it is recommended that hepatic enzymes are monitored periodically; quarterly during the first 6 months and subsequently every 6 months. If ALT levels are increased to 3 times upper limit of normal during therapy, hepatic enzyme levels should be reassessed within 3 to 5 days following the first elevated result. If ALT levels remain > 3 times the upper limit of normal, treatment should be suspended. Treatment may be resumed after normalisation with continued monitoring of hepatic enzymes (see section 4.2).

Weight increase

Weight increase occurs in paediatric patients very commonly during treatment with leriglitazone (see section 4.8).

Long-term safety in the paediatric population

There is limited experience with leriglitazone in paediatric patients. Long-term safety data in this population are not available. The potential impact of leriglitazone on bone mineral density and growth in paediatric patients is unknown. When treating paediatric patients, appropriate clinical monitoring should be considered.

Bladder cancer

An increased risk of bladder cancer has been reported for pioglitazone in the treatment of type II diabetes. No bladder malignancies were reported for leriglitazone, however long-term safety data are limited.

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.

Risk of bone fractures

Although bone fractures have not been reported with leriglitazone in clinical trials to date, fractures are a recognized class effect of proliferator-activated receptor gamma (PPARγ) agonists due to effects on bone metabolism. Patients at increased risk of fracture should be monitored appropriately.

Diabetes mellitus type I and type II

The safety and efficacy in patients with type I or II diabetes mellitus have not been established. Leriglitazone should not be used in patients with blood-glucose-lowering treatments, due to the increased risk of hypoglycaemia. In diabetic patients, thiazolidinediones have been associated with reports of new-onset or worsening diabetic macular oedema, often accompanied by decreased visual acuity and peripheral oedema. Healthcare professionals should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Excipients with known effect

Sorbitol (E 420)
This medicinal product contains 8 000 mg sorbitol in each 100 mL which is equivalent to 80 mg/mL. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Sodium
This medicinal product contains 2 mg of sodium per mL, equivalent to 0.10% of the World Health Organization (WHO) recommended maximum daily intake of 2 g sodium for an adult.

Sodium benzoate (E 211)
This medicinal product contains 100 mg sodium benzoate in each 100 mL which is equivalent to 1 mg/mL.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting leriglitazone

No clinical drug-drug interaction studies have been completed with leriglitazone to date.

Leriglitazone is predominantly metabolised by cytochrome P450 (CYP2C8 and CYP3A4) and it is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

CYP2C8 and CYP3A inhibitors
Concomitant use of leriglitazone with strong and moderate CYP2C8 inhibitors (e.g. gemfibrozil) or strong and moderate CYP3A inhibitors (e.g. itraconazole, ketoconazole, clarithromycin, ritonavir, verapamil) is not recommended. Special care should be taken when inhibitors of both CYP2C8 and 3A4 are co-administered simultaneously with leriglitazone.

CYP2C8 and CYP3A inducers
Concomitant use of leriglitazone with CYP2C8 and/or CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin, phenobarbital) is not recommended.

Transporter interactions
No effect is expected on the absorption of leriglitazone when given concomitantly with P-gp or BCRP inhibitors, since the absolute oral bioavailability is high. P-gp and BCRP inhibitors are not expected to significantly increase the levels of leriglitazone in the brain.

Effect of leriglitazone on other medicinal products

Transporter interactions
The potential for inhibition of BCRP at the level of the intestine is unknown. Concomitant medicinal products being substrates of these transporters (including but not limited to lapatinib, methotrexate, rosuvastatin, topotecan, sulfasalazine) may increase their plasma concentrations and should be taken with caution.

Interactions with glucose-lowering medicinal products

No drug–drug interaction studies with antidiabetic medicinal products have been completed with leriglitazone to date. Leriglitazone increases insulin sensitivity, and therefore concomitant use with blood-glucose-lowering treatments (e.g. metformin, insulin, gliclazide, glimepiride or glibenclamide) may increase the risk of hypoglycaemia.

Leriglitazone should not be used in patients receiving blood-glucose-lowering medicinal products. If concomitant use is considered unavoidable, patients must be closely monitored for signs and symptoms of hypoglycaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Not applicable.

Breast-feeding

Not applicable.

Fertility

No human data on the effect of leriglitazone on fertility are available. In rats, there was no effect on fertility in males; however, an effect on fertility in females (reduced number of live embryos) was noted (see section 5.3)

4.7 Effects on ability to drive and use machines

Nezglyal has minor influence on the ability to drive and use machines. Increased lacrimation as well as oedema/swelling of the eyelid causing potential visual disturbances may occur following administration of leriglitazone (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of leriglitazone is based on clinical studies and additional clinical experience in paediatric patients with ALD.

In children (2 to 12 years of age), the most commonly reported adverse reactions during leriglitazone treatment were weight increased (8.7%), eyelid oedema (8.7%), leukopenia (8.7%) and neutropenia (8.7%) (see section 4.4).

Tabulated list of adverse reactions

The safety of leriglitazone in paediatric patients with ALD was evaluated in an open label Phase II study MT-2-02, of 23 patients, aged 2 to 12 years of age. The mean (SD) treatment duration was of 76.2 (48.91) weeks and the median was 57.9 (Min, Max 5.4, 192.1) (see section 5.1).

Adverse reactions in children (2 to 12 years of age) are listed in Table 4. Adverse reactions are classified according to MedDRA system organ class and frequency. Within each system organ class, adverse reactions are listed by frequency, based on the following frequency convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4: Adverse reactions

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Anaemia Differential white blood cell count abnormal International normalised ratio increased Leukopenia Lymphopenia Neutropenia Prothrombin level increased	Common
Metabolism and nutrition disorders	Weight increased Increased appetite	Common
Nervous system disorders	Headache	Common
Cardiac disorders	N-terminal prohormone brain natriuretic peptide increased	Common
Skin and subcutaneous tissue disorders	Night sweats	Common
General disorders and administration site conditions	Oedema*	Very common

*Oedema includes oedema peripheral, swelling face and eyelid oedema

Description of selected adverse reactions

Anaemia
Anaemia (including anaemia and iron deficiency anaemia) has been reported in patients from laboratory tests treated with leriglitazone (4.3% in children (2 to 12 years of age)). In some patients, laboratory findings were consistent with macrocytic changes (e.g. increased mean corpuscular volume or decreased mean cell haemoglobin concentration). Most events were reported within the first 48 weeks of starting treatment. These events were mild and asymptomatic.

Weight increase
Weight increase has been reported in 8.7% in children (2 to 12 years of age). Most events were reported within the first 24 weeks of starting treatment and were mild in severity.

Oedema and eyelid oedema
Oedema (including oedema and eyelid oedema) have been reported in patients treated with leriglitazone (17.4% patients in children (2 to 12 years of age)). Most adverse reactions were reported within the first 24 weeks of starting treatment and were all mild in severity in paediatric patients.

Paediatric population

There are no data available on the use of leriglitazone in patients under 2 years of age.

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, it is recommended that the patient is monitored with ECG, glucose and blood pressure assessments.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Various alimentary tract and metabolism products, ATC code: A16AX23

Mechanism of action

Leriglitazone is a selective peroxisome proliferator-activated receptor gamma (PPARγ) agonist. Leriglitazone decreases neuroinflammation through inhibition of NF-κB-mediated inflammatory signaling, protected neurons and astrocytes, and reduced microglia activation in *in vitro* models of cALD. It also reduced oxidative stress and promoted mitochondrial function in neural cell types. Leriglitazone decreased monocyte adhesion to endothelial cells in *in vitro* models related to blood-brain barrier. In an *in vivo* model of neuroinflammation relevant to cALD, leriglitazone caused a dose-dependent reduction in the clinical symptoms. Protective and restorative effects on myelination have been demonstrated in both *in vitro* and *in vivo* models.

Clinical efficacy

The efficacy of leriglitazone in the indicated population was assessed in an open-label study in paediatric male patients with cALD (MT-2-02; N=23).

Study MT-2-02

Study MT-2-02 was an open-label study in male paediatric patients aged 2 to 12 years old with cALD to assess the effects of leriglitazone (13.7 mg/mL) on disease progression prior to HSCT. Leriglitazone was administered once daily by oral use, initial doses were defined based on age and weight and then adjusted by pharmacokinetic results to achieve target exposure (170 mcg·h/mL). Treatment was continued up to week 96, unless discontinued earlier for HSCT. A total of 23 patients were enrolled, with the following age distribution: 7 patients aged 2–5 years and 16 patients aged 6–12 years; the mean age of the 23 patients was 7.7 years (SD 2.93); baseline variables are presented in the tables below. Patients were assigned to one of two populations at baseline: those with Gd negative brain lesions (population 1 – Gadolinium non-enhancing [Gd negative]; *n=9*) or those with Gd positive brain lesions (population 2 - Gadolinium enhancing [Gd positive]; *n=14*). At baseline, the Neurological Function Score (NFS) ranged from 0 to 1 in the overall population, and the MFD was 0 for all of the population.

Three patients from population 2 discontinued the study prior to week 24 and were therefore excluded from the evaluable set, as they could not provide the minimum required data to assess arrested disease. As a result, the evaluable set comprised 20 patients, including 9 patients from population 1 and 11 patients from population 2.

During the study, out of the 23 patients, 14 underwent HSCT or gene therapy (GT) (population 1, n=3; population 2, n=11).

Efficacy assessments were performed up to week 96 or up to the visit prior to HSCT, whichever occurred first.

The primary efficacy endpoint was the proportion of patients with clinically and radiologically arrested disease at week 96 or at the visit prior to HSCT based on the 10% disease arrest rate in natural history. Clinically and radiologically arrested disease ("arrested disease") was assessed using pre-specified criteria, defined as all of the following:

- Change from baseline in Neurological Function Score (NFS) ≤ 5 points;
- Absence of major functional disability (MFD);
- No evidence of lesion progression on MRI, including:
  - No conversion to gadolinium-enhancing (Gd+) lesions in population 1 (Gadolinium intensity score (GIS) score = 0);
  - Disappearance of persistent Gd+ lesions in population 2, defined as a change in GIS score from 1, 2, or 3 to 0, where persistent Gd+ lesions are defined as lesions present on ≥ 2 consecutive MRIs spanning a minimum of 6 months;
  - No significant growth of T2/FLAIR lesions compared with the previous MRI in either population, as assessed by central reading.

Secondary endpoints included sustained change from baseline for the NFS; change from baseline in Loes score and change from baseline in GIS..

At week 96 or the visit prior to HSCT, of 20 evaluable subjects, 7 (35%; 95% CI: 15.4, 100%) subjects fulfilled the arrested disease definition and the primary endpoint was met. The details of the primary endpoint are summarised in Table 5 for the population 1 cohort.

Table 5: MT-2-02 study. Primary endpoint results for the population 1 cohort

Primary endpoint (week 96 or visit prior to HSCT)	**n (%) (Evaluable set, n=9)**	**95% CI**
Arrested disease	**6 (66.7%)**	**29.9% - 100%**
Components arrested disease: 1 - NFS change ≤ 5	9 (100%)	66.4% - 100%
2 - Free of MFD	9 (100%)	66.4% - 100%
3 - Lack of lesion progression	6 (66.7%)	29.9% - 92.5%
3a - Gd negative (GIS=0)	6 (66.7%)	29.9% - 92.5%
3b - Absence significant growth	7 (77.8%)	40.0% - 97.2%

Sustained change from baseline in NFS was used to evaluate 15 domains of neurological function; 6 of these domains rate the most serious symptoms, summarised as MFD. In population 1, the median NFS was 0 at baseline and remained 0 at week 96 and at the visit prior to HSCT. No patient had a change in NFS of more than 1 point during the study, including those with follow-up beyond 96 weeks. All subjects remained MFD free and no subjects died while on treatment with leriglitazone, including those with follow-up beyond 96 weeks.

Change from baseline in Loes score was used to assess increase in lesion load over time. In population 1, the median Loes score was 2.0 at baseline. It remained stable in patients who continued on treatment to week 96 (median change from baseline 0), while for patients undergoing HSCT, the median change was 2 at the visit prior to HSCT.

Change from baseline in GIS was used to assess changes in Gd enhancement. In population 1, 6 out of 9 patients (66.7%) remained GIS=0 at week 96. In the three patients who progressed to Gd-enhancing lesions, GIS was 1 at the visit prior to HSCT.

Exceptional circumstances

This medicinal product has been authorised under 'exceptional circumstances'.
This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary

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 oral administration of leriglitazone 163.93 mg free form (+ intravenous administration of 91 mcg free form radiolabelled compound). Peak plasma concentrations are achieved 3 hours after administration. Proportional increases of the plasma concentration were observed for doses from 27.32 to 245.9 mg leriglitazone free form. Steady state is achieved after 4-5 days of dosing. Repeated dosing results in an accumulation factor of 1.7-1.8.

Distribution

Leriglitazone is bound to human plasma protein binding in a percentage of 96.4% and the blood to plasma ratio is 0.6. The volume of distribution is 35.3 L. Leriglitazone was detected in cerebrospinal fluid (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. M3 only passes the blood brain barrier to a very limited extent.

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. 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%. Leriglitazone and M3 are substrates of P-glycoprotein and BCRP.

Elimination

Following a single [^{14}C] labelled 163.93 mg leriglitazone dose, radioactivity is mainly excreted in urine (77%) and to a more limited extent via faeces (24%). In urine, leriglitazone was excreted predominantly as oxidised metabolites and glucuronide conjugates, with only trace amounts of unchanged leriglitazone and active metabolite M3. In faeces, leriglitazone was excreted mainly as a sulphated metabolite.

Following single oral administration of 180 mg leriglitazone hydrochloride + intravenous administration of 100 mcg ^{14}C-leriglitazone hydrochloride, the biliary excretion estimate in faeces is 21.3% for total radioactivity, and only small amounts as unchanged ^{14}C-leriglitazone or ^{14}C-M3. The elimination half-life of leriglitazone and M3 is approximately 22 h.
The measured clearance in humans is 0.976 L/h.

Special populations

Elderly
No data are available.

Hepatic impairment
No data are available.

Renal impairment
No data are available for patients with mild, moderate and severe renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity.

The repeated dose toxicological observations in mice, rats and dogs administered leriglitazone for up to 3, 6 and 9 months, respectively, were typical of excessive PPARγ activation. Namely, the studies showed decrease in red blood cells (RBC), increase in heart weight and increased fatty deposition and infiltration. In addition, in the chronic toxicity study in rats, an isolated subcutaneous malignant sarcoma was found in one male given the high dose At the NOAEL in the chronic toxicity study in rats, combined systemic exposure to unbound leriglitazone and its metabolite M3 was similar to that expected in patients.

Carcinogenicity

No carcinogenic potential was found in 2-year carcinogenicity studies in both species tested rat and mouse.

In a 2-year carcinogenicity study in Sprague Dawley (Crl:CD[SD]) rats treated with leriglitazone, no treatment-related neoplastic findings were observed. At the maximum tested doses in children, calculated safety margins were 0.63 and 1.50 for males and females, respectively, based on the combined exposure to unbound leriglitazone and M3.

In a 2-year mouse carcinogenicity study in CD-1 (ICR) - (Crl:CD1[ICR]) mice treated with leriglitazone, no treatment-related neoplastic findings were observed. At the maximum tested doses in children, calculated safety margins were 37.5 and 21.5 for males and females, respectively, based on the combined exposure to unbound leriglitazone and M3.

Reproductive and development toxicity

Embryofoetal development toxicity studies were performed in pregnant rats and rabbits and revealed a decrease in foetal body weight at the maximum tested doses (3.07 and 4.40-fold over the target clinical exposure in children, respectively, based on the combined exposure to unbound leriglitazone and M3). There were no teratogenic effects. At the maximum tested dose, adverse effects on female fertility and early embryonic development were reduced number of live embryos (10.8 embryos compared with 14.3 in the controls) due to a reduction in the mean number of corpora lutea and increases in the extent of pre- and post-implantation loss. Safety margins for these effects were estimated to be 2.7- times the target clinical exposure in children, based on the combined systemic exposure to unbound leriglitazone and its metabolite M3. No adverse effects for male fertility and male mediated effects on early embryonic development were observed at any dose evaluated.

Juvenile toxicity

In a juvenile rat study where rats were dosed from day 22 to 91 of age (equivalent to 2 years to adulthood in humans), the toxicological effects observed were similar to adult rats (NOAEL 25 mg/kg/day, 2.19-times the children target exposure, based on the combined systemic exposure to unbound leriglitazone and its metabolite M3), apart from slight effects on bone mineral density. There is no safety margin for this effect. Clinical relevance cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420)
Microcrystalline cellulose (E 460)
Carmellose sodium (E 466)
Saccharin sodium (E 954)
Sodium benzoate (E 211)
Sodium citrate (E 331)
Citric acid monohydrate (E 330)
Strawberry flavour
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

After first opening

Up to 66 days below 25 ºC.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

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 of 100 mL with a white polyethylene child-resistant cap packaged with a polyethylene oral dosing syringe of 12 mL graduated at every 0.5 mL.

Pack size of one bottle.

6.6 Special precautions for disposal and other handling

Handling

An oral dosing 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 syringe to ensure that the correct volume is administered.

Before each administration, the bottle should be shaken well for approximately 30 seconds.

The bottle should be placed on a horizontal, stable surface and the cap removed. The oral dosing syringe provided in the pack should be inserted into the bottle and used to withdraw the prescribed dose. The contents of the oral dosing syringe should then be administered directly into the patient's mouth.

After the patient has taken their daily dose, the bottle should be closed, and the oral dosing syringe washed with clean water and dried with a paper towel. The bottle and the oral dosing syringe should then be stored in the original package in order to protect from light.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2060/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Delpharm Huningue S.A.S.
26, Rue de la Chapelle 68330
Huningue
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): in order to further characterise the incidence of serious consequences of fluid	Annual reports (with annual re-assessment)

retention, including oedema, and long-term safety, including bone-safety, of leriglitazone in males with Adrenoleukodystrophy (ALD) aged 2 to 12 years with non-Gadolinium (Gd) enhancing lesions (i.e. Gd negative) in brain Magnetic Resonance Imaging (MRI), with a Neurological Functional Score (NFS) of 0 or 1, the MAH shall conduct and submit the results of study MT-4-01.	
In order to further characterize the efficacy of leriglitazone in males with Adrenoleukodystrophy (ALD) aged 2 to 12 years with non-Gadolinium (Gd) enhancing lesions (i.e. Gd negative) in brain Magnetic Resonance Imaging (MRI), with a Neurological Functional Score (NFS) of 0 or 1, the MAH shall conduct and submit the results of a multinational, multicentre, non-interventional study based on data from a patient registry, to collect long-term real-world effectiveness data on leriglitazone according to an agreed protocol.	Annually (with annual re-assessment)
In order to ensure adequate monitoring of safety and efficacy of leriglitazone in the treatment of males with Adrenoleukodystrophy (ALD) aged 2 to 12 years with non-Gadolinium (Gd) enhancing lesions (i.e. Gd negative) in brain Magnetic Resonance Imaging (MRI), with a Neurological Functional Score (NFS) of 0 or 1, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of leriglitazone.	Annually (with annual re-assessment)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nezglyal 13.7 mg/mL oral suspension
leriglitazone

2. STATEMENT OF ACTIVE SUBSTANCES

Each mL contains 13.7 mg of leriglitazone (as hydrochloride).
One bottle (100 mL) contains 1 370 mg of leriglitazone (as hydrochloride).

3. LIST OF EXCIPIENTS

Also contains sorbitol (E 420), sodium and sodium benzoate (E 211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
1 x 100 mL bottle
1 x 12 mL oral dosing syringe

5. METHOD AND ROUTES OF ADMINISTRATION

Oral use.
Shake well for 30 seconds before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening: Up to 66 days below 25 ºC.

Date of first opening: ____/_____/_____

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Minoryx Therapeutics S.L.
Av Ernest Lluch, 32, TCM3
08302 Mataró, Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2060/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nezglyal

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Nezglyal 13.7 mg/mL oral suspension
leriglitazone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 13.7 mg of leriglitazone (as hydrochloride).
One bottle (100 mL) contains 1 370 mg of leriglitazone (as hydrochloride).

3. LIST OF EXCIPIENTS

Also contains E 211, E 420 and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension.
100 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Shake well for 30 seconds before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening: Up to 66 days below 25 ºC.
Date of first opening: ____/_____/_____

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2060/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nezglyal

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Nezglyal 13.7 mg/mL oral suspension
leriglitazone

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of Section 4 for how to report side effects.

Read all of this leaflet carefully before giving this medicine to your child because it contains important information for you and your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of your child.
- If your child gets any side effects, talk to your child's doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nezglyal is and what it is used for
2. What you need to know before you use Nezglyal
3. How to take Nezglyal
4. Possible side effects
5. How to store Nezglyal
6. Contents of the pack and other information

1. What Nezglyal is and what it is used for

Nezglyal contains the active substance leriglitazone. It is part of a group of medicines known as peroxisome proliferator-activated receptor gamma (PPARγ) agonists.

Nezglyal is a treatment for a rare brain disease in boys called cerebral adrenoleukodystrophy (cALD).

Nezglyal is used in boys aged 2 to 12 years with cALD, who have brain lesions that do not show disruption of the blood brain barrier, referred as "Gd negative" lesions (these are areas that do not take up the contrast agent gadolinium and therefore do not light up on Magnetic Resonance Imaging (MRI)) and who have either no or mild clinical symptoms (meaning a Neurological Functional Score (NFS) of 0 or 1).

Cerebral adrenoleukodystrophy (cALD) is a form of an inherited disease called adrenoleukodystrophy in which fatty substances known as 'very long chain fatty acids' build up in tissues around the body, mainly in the brain, spinal cord and adrenal glands (two glands situated above the kidneys). In cALD, a build-up of these substances in the brain causes inflammation and destruction of the protective sheath (myelin) that insulates and helps signalling by nerve cells. This leads to brain lesions.

People with ALD may develop cALD in childhood. People can develop Gd negative lesions, with either no or mild clinical symptoms. These lesions can progress further to more serious disease which can be life-threatening.

The active substance in Nezglyal, leriglitazone, works by attaching to and activating a target (receptor) in the body known as PPARγ receptor. PPARγ receptors play a role in regulating the function of mitochondria (energy-producing structures in cells), how cells respond to oxidative stress (damage caused by toxic oxygen-containing molecules known as free radicals) and inflammation. Leriglitazone protects nerve cells from damage caused by cALD by reducing inflammation, improving the function of mitochondria and protecting against damage from free radicals.

2. What you need to know before you use Nezglyal

Do not use Nezglyal
- if your child is allergic to leriglitazone or any of the other ingredients of this medicine (listed in section 6).
- if your child is allergic to a type of medicine known as 'thiazolidinediones' such as pioglitazone (used to lower blood sugar levels in people with type 2 diabetes).
- if your child has or ever had heart failure.

Warnings and precautions
Talk to your child's doctor before giving Nezglyal to your child.

- Side effects with Nezglyal treatment have been reported more often during the first six months of treatment. In particular, side effects of weight gain and water retention leading to oedema with signs such as swelling of legs, feet or ankles. Your child's doctor will monitor this and your child's treatment with Nezglyal may be stopped if severe symptoms of oedema or cardiac failure occur.
- Some patients who experience water retention may develop heart failure. Inform your child's doctor as soon as possible if your child experiences signs of heart failure such as unusual shortness of breath, increased swelling of legs, feet, or ankles in spite of measures taken by the doctor, discomfort or swelling in the abdomen, trouble sleeping with breathlessness when lying flat in bed, chest pain or palpitations, frequent dry, hacking cough.
- Treatment with Nezglyal must be stopped at least 5 days before your child starts the conditioning medicines used in haematopoietic stem cell transplantation, a procedure where a patient's bone marrow is cleared of cells and replaced by stem cells to form new bone marrow.
- If your child has impaired liver function, their doctor will carefully consider whether this medicine is suitable for them and may wish to monitor them carefully.
- Inform your child's doctor immediately if you notice any blood in your child's urine or experience painful or difficult urination during treatment. Before giving Nezglyal to your child, your child will have a blood sample taken to check their liver function. This check may be repeated at regular intervals. Inform your child's doctor straight away if your child develops symptoms of liver disease such as unexplained nausea, vomiting or abdominal pain, weight loss, dark urine, or yellowing of the skin (jaundice).
- If your child has osteoporosis or are at risk of bone fracture, talk to their doctor. Medicines in the same class have been associated with an increased risk of broken bones. It is not known whether Nezglyal may affect bone development or bone strength in children. The doctor will monitor your child's growth and bone health during treatment.
- Nezglyal must not be used together with any blood-glucose-lowering medicines, because this may increase the risk of low blood sugar (hypoglycaemia). If your child has diabetes type 1 or 2 and is taking any anti-diabetic medicine, their doctor will carefully consider whether this medicine is suitable for them and may wish to monitor them carefully.
- If your child has a special type of eye disease called macular oedema (swelling of the back of the eye), their doctor may refer them for an eye examination and decide whether treatment should be continued.

Children under the age of 2 years
This medicine should not be given to children under the age of 2 years as it has not been tested in this age group.

Other medicines and Nezglyal
Tell your child's doctor if your child is taking, has recently taken or might take any other medicines.

The following medicines may increase the risk of side effects of Nezglyal:
- gemfibrozil (used to treat high cholesterol)
- itraconazole (used to treat fungal infections)

- clarithromycin (used to treat bacterial infections)
- metformin (used to treat diabetes) or other medicines that lower blood sugar, such as insulin, gliclazide, glimepiride or glibenclamide

The following medicines may reduce the effectiveness of Nezglyal:
- carbamazepine (used to treat certain types of seizures in people with epilepsy, pain in trigeminal neuralgia, or mania in bipolar disorder)
- rifampicin (used to treat certain bacterial infections, including tuberculosis)
- phenytoin (used to treat epilepsy)
- phenobarbital (used to treat epilepsy)

The following medicines may require special monitoring when taken with Nezglyal:
- rosuvastatin (used to treat high cholesterol)
- methotrexate (used to treat certain inflammatory diseases and some cancers)
- sulfasalazine (used to treat inflammatory bowel disease)

Your child's doctor will decide whether these medicines can be taken together and may monitor your child more closely.

Driving and using machines
This medicine may have minor influence on the ability to drive, ride a bicycle and use machines. If your child experiences side effects affecting their vision, they should not ride a bicycle or use machines until their vision is back to normal (see section 4 "Possible side effects").

Nezglyal contains sorbitol, sodium and sodium benzoate
This medicine contains 8000 mg sorbitol in each 100 mL which is equivalent to 80 mg/mL. Sorbitol is a source of fructose. If your child's doctor has told you that your child has an intolerance to some sugars or if your child has been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to their doctor before your child takes or receives this medicine.

This medicine contains 200 mg sodium (main component of cooking/table salt) in each 100 mL which is equivalent to 2 mg/mL. This is equivalent to 0.10% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 100 mg sodium benzoate in each 100 mL which is equivalent to 1 mg/mL.

3. How to take Nezglyal

Always give this medicine to your child exactly as your child's doctor has told you. Check with their doctor if you are not sure.

Treatment with this medicine should be started and supervised by a doctor experienced in the treatment of diseases that cause nerve cells to stop functioning properly.

Nezglyal is available as a suspension that is taken by mouth once daily.

The recommended daily dose will be calculated by your child's doctor based on your child's age, weight and height. Your child will need to attend regular appointments with their doctor to ensure they continue to receive the correct dose as they grow.

Give Nezglyal to your child at the same time every day, preferably after breakfast.

Your child's doctor or pharmacist will show you how to measure the correct dose. Use the dosing syringe which is provided with Nezglyal to measure your or your child's daily dose.

Instructions for use
- Always shake the bottle well for about 30 seconds before each dose.
- Put the bottle on a horizontal, stable surface and remove the cap.
- Insert the dosing syringe which is provided in the pack into the bottle and withdraw the recommended daily dose.
- Empty the contents of the oral dosing syringe into your child's mouth and make sure your child swallows the dose.
- After giving the dose to your child, close the bottle. Wash the oral dosing syringe with clean water and dry with a paper towel. Place the bottle and oral dosing syringe back in its original package in order to protect from light.

If you give more Nezglyal to your child than you should
If you accidentally give your child too much medicine, or if someone else or another child takes this medicine, talk to a doctor or pharmacist immediately and take this package leaflet with you.

If you forget to give Nezglyal to your child
If your child misses a dose, just carry on with the next dose as normal. Do not give a double dose to make up for a forgotten dose.

If your child stops taking Nezglyal
Nezglyal should be taken every day to work properly. Talk to your child's doctor before stopping this treatment.

If you have any further questions on the use of this medicine, ask your child's doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects are more common at the beginning of treatment and may require monitoring by your child's doctor.

The following side effects have been reported in children treated with Nezglyal:

Very common (may affect more than 1 in 10 people)
- Swelling due to fluid retention, including swelling of your child's lower legs, face and/or eyelids (oedema)

Common (may affect up to 1 to 10 people)
- Changes in blood tests, such as:
  - Low levels of red blood cells (anaemia)
  - Unusual balance of different types of white blood cells
  - Blood takes longer to clot (increased international normalised ratio (INR))
  - Low levels of white blood cells (leukopenia)
  - Low levels of lymphocytes, a type of white blood cell (lymphopenia)
  - Low levels of neutrophils, a type of white blood cell (neutropenia)
  - Increased levels of prothrombin (a protein required for the blood to clot)
  - Increased levels of a heart-related blood test marker (N-terminal prohormone brain natriuretic peptide)
- Increased appetite
- Weight gain
- Headache

– Night sweats

Reporting of side effects
If your child gets any side effects, talk to your child's doctor or surgeon. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Nezglyal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

After first opening: Use up to 66 days below 25 ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that your child no longer uses. These measures will help protect the environment.

6. Contents of the pack and other information

What Nezglyal contains
The active substance is leriglitazone (as hydrochloride).
Each mL of oral suspension contains 13.7 mg of leriglitazone (as hydrochloride).
One bottle (100 mL) contains 1 370 mg of leriglitazone (as hydrochloride).

The other ingredients are sorbitol (E 420), microcrystalline cellulose (E 460i) and carmellose sodium (E 466), saccharin sodium (E 954), sodium benzoate (E 211), sodium citrate (E 331), citric acid monohydrate (E 330), strawberry flavour, and purified water (see also section 2 'Nezglyal contains sorbitol, sodium and sodium benzoate').

What Nezglyal looks like and contents of the pack
Nezglyal is a homogenous, white oral suspension.
Hydrolytic class III amber glass bottle of 100 mL with a white polyethylene child-resistant cap packaged with a polyethylene oral dosing syringe of 12 mL graduated at every 0.5 mL.

Pack size of one bottle.

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This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Annex IV

Conclusions on the granting of the marketing authorisation under exceptional circumstances presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.