



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Nezglyal (5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride)
Treatment of adrenoleukodystrophy
EU/3/16/1770

Sponsor: Minoryx Therapeutics S.L.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

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1. Product and administrative information

Product	
Designated active substance	5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride
Other names	Nezglyal, leriglitazone, MIN-102; 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride Neuroprotectants; Small molecules; Thiazolidinediones
International Non-Proprietary Name	Leriglitazone
Tradename	Nezglyal
Orphan condition	Treatment of adrenoleukodystrophy
Sponsor's details:	Minoryx Therapeutics S.L. Calle Ernest Lluch 32 Tcm 2 08302 Mataro Barcelona Spain
Orphan medicinal product designation procedural history	
Sponsor/applicant	Minoryx Therapeutics S.L
COMP opinion	06 October 2016
EC decision	18 November 2016
EC registration number	EU/3/16/1770
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Fátima Ventura / Elita Poplavska
Applicant	Minoryx Therapeutics S.L.
Application submission	27 June 2025
Procedure start	17 July 2025
Procedure number	EMA/H/C/006693/0000
Invented name	Nezglyal
Proposed therapeutic indication	Nezglyal is indicated for the treatment of Cerebral Adrenoleukodystrophy (cALD) in males with Adrenoleukodystrophy (ALD) aged 2 to 12 years of age with Gadolinium (Gd) negative lesions in brain MRI, with a Neurological Functional Score (NFS) of 0 or 1 Further information can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Nezglyal
CHMP opinion	23 July 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Joao Rocha
Sponsor's report submission	19 February 2026

COMP discussion	14-15 July 2026
COMP opinion (adoption via written procedure)	24 July 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2016 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride was considered justified based on preclinical data demonstrating an improvement in motor control and a decrease in neuroinflammation;
- the sponsor has established that the condition is chronically debilitating and life threatening. Cerebral adrenoleukodystrophy is associated with rapid neurological deterioration, including behavioural abnormalities, seizures, spastic tetraplegia and dementia, and is usually fatal within several years of symptom onset. Adrenomyeloneuropathy is characterised by adrenal insufficiency and progressive motor impairment, often requiring walking aids or a wheelchair, with death occurring within approximately 20 years of symptom onset;
- the condition was estimated to be affecting less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride as an orphan medicinal product for the orphan indication: treatment of adrenoleukodystrophy.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Adrenoleukodystrophy (ALD) is a rare X-linked inherited neurodegenerative disorder that affects the brain, peripheral nerves, and adrenal glands. The disease is caused by mutations of the ABCD1 gene

resulting in loss of function of the encoded ALD protein (ALDP), an ABCD transporter located in the peroxisomal membrane. Deficiency of the ALDP impairs peroxisomal β -oxidation of very long-chain fatty acids (VLCFAs) leading to their toxic accumulation in plasma and tissues, particularly the myelin of the brain, spinal cord, adrenal glands and Leydig cells in the testes (Contreras et al., 1994; Ofman et al., 2010; van Roermund et al., 2008). Additionally, mutations in the ABCD1 gene could also cause changes in adhesion molecules and tight junctions in the brain endothelium, which increases BBB permeability independently of VLCFA accumulation (Musolino et al., 2015).

The disease could manifest as adult-onset chronic slow progressive adrenomyeloneuropathy (AMN), with spastic paresis, ataxia, bowel and bladder dysfunction, and peripheral neuropathy as main symptoms. The survival in adult-onset of symptoms is estimated as 20 years or more.

Childhood-onset disease is more generally severe, with a high risk of developing Cerebral ALD (cALD). Cerebral ALD is the most severe and life-threatening manifestation of ALD and is characterized by demyelinating brain lesions. All male patients with ALD are at risk of developing cALD from early childhood onwards, with disease onset typically occurring between 2 and 12 years of age, although cALD may also develop later in adulthood. Once cerebral lesions become active, cALD follows a rapidly progressive course, leading to acute neurological deterioration, severe disability, a vegetative state and death. Clinical manifestations include loss of voluntary movements, loss of communication, cortical blindness, dysphagia and incontinence. Following the onset of progressive cerebral disease, mean survival is approximately 3 to 4 years (Raymond et al., 2019), irrespective of age at onset, making cALD an end-of-life event.

Some patients may first present with primary adrenocortical insufficiency, leading to fatigue, weight loss, low blood pressure, and a distinctive darkening (hyperpigmentation) of the skin, without developing significant neurological manifestations in early disease stage.

The diagnosis is made by enhanced levels of VLCFA, albeit that no correlation has been established between the concentration of VLCFA and the different phenotypes of X-ALD. The diagnosis of AMN is confirmed by genetic counseling and genotyping. In some member states, neonatal screening is applied. More than 900 mutations have been reported thus far, but the correlation between geno- and pheno-type is yet not fully established (Engelen et al., Orphanet J Rare Dis. 2012 Aug 13;7:51).

Females may be either silent carriers or also develop AMN but later in life and with milder neurological manifestations, while they very rarely develop cALD.

The proposed therapeutic indication "Nezglyal is indicated for the treatment of cerebral Adrenoleukodystrophy (cALD) in males with Adrenoleukodystrophy (ALD) aged 2 to 12 years of age with Gadolinium (Gd) negative lesions in brain MRI, with a Neurological Functional Score (NFS) of 0 or 1" falls within the scope of the designated orphan condition "Treatment of adrenoleukodystrophy".

Intention to diagnose, prevent or treat

The medical plausibility is pending confirmation by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The sponsor claimed that since the time of the orphan designation, the chronically debilitating and life-threatening nature of cerebral adrenoleukodystrophy has remained unchanged. Progressive cALD continues to be associated with rapid neurological decline and death. No newly authorized therapies have been shown to substantially improve morbidity or mortality in patients affected by this condition. It is agreed by the COMP that the condition is chronically debilitating and life-threatening.

Number of people affected or at risk

At the time of the initial orphan designation in 2016, the prevalence of adrenoleukodystrophy in the European Union was estimated to be below 0.4 per 10,000 persons, based on available epidemiological literature and rare disease databases. The sponsor reassessed the prevalence of ALD by combining information from patient advocacy organisations, rare disease databases, and an updated systematic literature review of epidemiological studies published between 2016 and 2025, with particular emphasis on data generated through newborn screening (NBS) programmes.

The available European epidemiology data between 1993-2016 is summarized in **Table 1**. After adjusting the data to reflect a prevalence per 10,000 of the general population (assuming a 1:1 male to female ratio), sensitivity analyses were performed. As shown in the table, the mean and median estimates are smaller than 0.1 per 10,000.

Table 1. X-ALD prevalence from epidemiologic studies in EU

Country	Prevalence	Gender	Reference	Prevalence in general population
France	1:100,000	Males	Sereni et al., 1993	0.05:10,000
Germany	0.8:100,000	Both	Heim et al., 1997	0.08:10,000
Italy	3.6:100,000	Males	Di Biase et al., 1998	0.18:10,000
Netherlands	0.5:100,000	Males	van Geel et al., 1997	0.025:10,000
Norway	0.8:100,000	Both	Horn et al., 2013	0.08:10,000
UK	0.57:100,000	Both	Stellitano et al., 2016	0.057:10,000
				Mean = 0.0786:10,000 Median = 0.0685:10,000

The sponsor reviewed multiple NBS-derived incidences and cited the evidence review by Kemper et al. (2017) as the most relevant source for estimating prevalence in the EU.

Considering the newer newborn screening data and applying a conservative ("worst-case") approach, the sponsor concluded that the prevalence of ALD in the EU would be up to 1 per 10,000 persons.

The COMP accepted the prevalence estimate of less than 1/10,000, based on birth prevalence, which has increased after the introduction of neonatal screening in some regions. A more precise estimate based on birth incidence and disease duration was currently not considered feasible, as it is difficult to forecast which percentage of male patients will develop childhood or adult-onset adrenomyeloneuropathy (AMN) or the more detrimental cAMN phenotype based on a positive genetic neonatal screening.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

At the time of this review, there are no authorised medicinal products in the European Union for the treatment of (cerebral) adrenoleukodystrophy. Standard of care is limited to the treatment of adrenal insufficiency with gluco- and/or mineralo corticoid replacement therapy and gonadal insufficiency with hormonal substitution. For the neurological manifestation, limited symptomatic treatments are available for e.g. spasmolytics like baclofen, anti-seizure medications and treatment for neuropathic pain.

Several non-medicinal dietary products like Lorenzo's Oil and related product Aldixyl® are used in practice. Although Lorenzo's Oil reduced very long-chain fatty acids (VLCFAs) plasma levels in trials, its efficacy regarding disease progression has not been established in randomized trials.

Hematopoietic stem cell transplantation (HSCT) is currently recommended in international treatment guidelines, for selected patients with early-stage cerebral disease, at emerging signs of demyelination with gadolinium enhancement in magnetic resonance imaging (MRI) (MR severity score [Loes score] $\leq$ 9) (Engelen, 2022). In treatment guidelines, (bi-)annual screening of MRI is recommended in patients with childhood or adult-onset AMN. However, HSCT is not a pharmacological treatment and is associated with significant limitations, including procedure-related morbidity and mortality. There is a limitation of suitable donors.

In addition, HSCT is only recommended to a subset of patients, with emerging cerebral involvement in MRI, and is not generally performed in patients with adrenoleukodystrophy, because of its risks. Importantly, HSCT cannot be offered to patients once cerebral involvement has progressed beyond an early stage. As such, HSCT does not represent a satisfactory method for the treatment or prevention of cerebral adrenoleukodystrophy across the intended patient population.

Significant benefit

Not applicable.

4. COMP position adopted on 24 July 2026

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of adrenoleukodystrophy (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating. Adrenomyeloneuropathy is characterised by adrenal insufficiency and progressive motor impairment, often requiring walking aids or a wheelchair, with death occurring within approximately 20 years of symptom onset. Cerebral adrenoleukodystrophy is associated with rapid neurological deterioration, including behavioural abnormalities, seizures, spastic tetraplegia and dementia, and is usually fatal within several years of symptom onset.
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Nezglyal, 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride, leriglitazone for treatment of adrenoleukodystrophy (EU/3/16/1770) is not removed from the Community Register of Orphan Medicinal Products.