26 May 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Ezmekly (mirdametinib)
Treatment of neurofibromatosis type 1
EU/3/19/2184

Sponsor: Springworks Therapeutics Ireland Limited

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Product and administrative information

Product	
Designated active substance(s)	N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-fluoro-4-iodo-phenylamino)-benzamide
Other name(s)	Aniline compounds; Anti-inflammatories; Antineoplastics; Benzamides; Immunotherapies; Small molecules PD0325901
International Non-Proprietary Name	Mirdametinib
Tradename	Ezmekly
Orphan condition	Treatment of neurofibromatosis type 1
Sponsor's details:	Springworks Therapeutics Ireland Limited Hamilton House 28 Fitzwilliam Place Dublin 2 Co. Dublin D02 P283 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Voisin Consulting S.A.R.L.
COMP opinion	20 June 2019
EC decision	25 July 2019
EC registration number	EU/3/19/2184
Post-designation procedural history	
Transfer of sponsorship	Transfer from Voisin Consulting Life Sciences to Springworks Therapeutics Ireland Limited – EC decision of 11 January 2004.
Sponsor's name change	Name change from Voisin Consulting S.A.R.L. to Voisin Consulting Life Sciences – EC letter of 12 October 2021.
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Karin Janssen van Doorn
Applicant	Springworks Therapeutics Ireland Limited
Application submission	24 July 2024
Procedure start	15 August 2024
Procedure number	EMA/H/C/0006460
Invented name	Ezmekly

Proposed therapeutic indication	Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above. 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/Ezmekly
CHMP opinion	22 May 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cécile Dop / Bozenna Dembowska-Baginska
Sponsor's report submission	27 February 2025
COMP discussion	13-15 May 2025
COMP opinion (adoption via written procedure)	26 May 2025

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2019 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-fluoro-4-iodo-phenylamino)-benzamide was considered justified based on non-clinical in vivo and preliminary clinical data showing a reduction in tumour size;
- the condition is life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia and increased risk of developing benign and malignant neoplasms;
- the condition was estimated to be affecting approximately 3 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 N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-

fluoro-4-iodo-phenylamino)-benzamide as an orphan medicinal product for the orphan condition: treatment of neurofibromatosis type 1".

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

Neurofibromatosis type 1 (NF1) is an autosomal dominant clinically heterogeneous neurocutaneous genetic disorder. It is caused by germline mutations in the NF1 tumour suppressor gene (17q11.2) and rarely by 17q11 microdeletion (only 5%), which encodes the tumour suppressor protein neurofibromin 1. Several thousand distinct pathogenic NF1 mutations have been identified in affected individuals. Neurofibromin 1 is a guanosine 5' triphosphate (GTP)ase activating protein that promotes the conversion of active Ras GTP to inactive Ras guanosine 5'diphosphate. NF1 therefore functions as a negative regulator of the Ras proto-oncogene, which is a key signalling molecule in the control of cell growth. NF1 mutation that leads to loss of function results in a failure to inactivate RAS, and can result in various tumour types, such as malignant or benign tumours. Approximately half of NF1 cases are familial, with complete penetrance, and the remainder are the result of de novo mutations.

NF1 is characterized by diverse and progressive cutaneous, neurological, skeletal, and neoplastic manifestations early in life and the associated morbidities can be severe. Neurofibromas are histologically benign nerve sheath tumours, which can be broadly grouped into dermal neurofibroma or plexiform neurofibromas (PN). While the dermal neurofibromas originate from terminal nerve branches in the skin and rarely develop before puberty, PNs typically grow deeper in the body along large nerves and plexuses and are present at birth. PNs grow the fastest during the first decade of life, and can cause pain, motor impairment and obstruction.

Clinical manifestations also include cognitive deficits, learning disabilities, headaches, and seizures, café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules, and osseous dysplasias.

The approved therapeutic indication "Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above" falls within the scope of the designated orphan condition "treatment of neurofibromatosis type 1".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review, treatment of neurofibromatosis type 1 is presented to the COMP to remain chronically debilitating and life-threatening disease. The clinical course can be debilitating due to pain, neurological and motor dysfunction, airway compromise, visual impairment, and/or disfigurement. The skin manifestations can be a psychological burden. In addition, individuals with NF1 are prone to develop benign or malignant tumours, such as sarcoma and gastrointestinal stromal tumours (GISTs). Optic pathway gliomas may cause delayed puberty and a short stature by pressuring on the hypothalamic region. NF1 is associated with an 8- to 15-year reduction in average life expectancy in both men and women, primarily due to malignant neoplasms and cardiovascular causes.

The COMP concluded that the condition remains life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia and increased risk of developing benign and malignant neoplasms.

Number of people affected or at risk

The sponsor has conducted a literature search with the aim to retrieve new articles that were published since the compilation of the original orphan designation application (i.e., from 01 Jan 2019 to 31 Dec 2024) and that could provide data enabling an update of the estimate of the number of NF1 patients in the EEA.

Pooled NF1 prevalence was 3.16 cases per 10,000 (1 in 3,164 [95%CI: 1 in 2,132-1 in 4,712]). This was derived from publications the sponsor drew from the public domain. Of these, 2 were exclusively done in patients with NF2, 8 exclusively in patients with NF1, and 2 studies included both patients with NF1 and patients with NF2. Concerning NF1 studies, 6 were in the EU (including 4 publications already mentioned in the original ODD: (Kallionpaa et al., 2018; Lammert et al., 2005; Poyhonen et al., 2000; Uusitalo et al., 2015) while 2 were from the United Kingdom, 1 from Israel, and 1 from Cuba. All these NF1 studies, except Uusitalo et al., provided prevalence rate (9 studies in total), and were included in the pooled prevalence estimate.

This was higher in studies that screened for NF1, compared to identification of NF1 through medical records (1 in 2,020 and 1 in 4,329, respectively). NF1 pooled birth incidence was 1 in 2,662 (95%CI: 1 in 1,968-1 in 3,601).

Different registries have been identified using internet search with the following keywords: 'registry', 'Neurofibromatosis', 'Neurofibromatosis type 1', 'NF1', 'von Recklinghausen' and using the registries listed in the Orphanet website. From the registries found, were excluded: registries with data anterior to 2000, non-EU registries and registries non-specific to NF1 (biobanks, cancer registries, transplant, neoplasm…). See Table 1 below.

Table 1. Overview of NF1 registries epidemiology data in Europe – Consulted on 17 Feb 2025

Country	Name of the registry	Data	Estimated prevalence
France	CERENEF – CEntre de REférence des NEurofibromatoses France	Prevalence: 1 in 4,000 Incidence: 1 in 3,000 births Reported in publications: (Lammert et al., 2005) (Germany), (Kallionpaa et al., 2018) (Finland), (Uusitalo et al., 2015) (Finland) *and non-EU articles*	= (1/4,000)*10,000 **= 2.5 per 10,000**

Country	Name of the registry	Data	Estimated prevalence
Hungary	Organization of the National Neurofibromatosis Register and areas of application	225 persons are registered in the system on NF Hungary and 37 patients belong to the NF National Register. Hungarian population*: 9,584,627 in 2024	=[(225+37)/ 9,584,627]*10,000 **= 0.27 per 10,000** This prevalence will not be considered in the conclusion as it is not considered representative of the Hungarian population.
Italy	ANF ODV: sostieni la ricerca sulla Neurofibromatosi	1 in 3,000 babies. At least 20,000 NF1 patients in Italy. Italian population*: 58,971,230 in 2024	= (20,000/58,971,230)*10,000 **= 3.4 per 10,000**

*Reference: Eurostat, consulted on 17Feb2025.
Abbreviations: NF: Neurofibromatosis; NF1: Neurofibromatosis type 1.

Table 2 summarises the updated prevalence estimate indicating the NF1 continues to meet the orphan drug designation statutory requirements.

It is worth emphasising that the sources of the data provided in the databases and registries were either not detailed (ANF ODV, databases), not representative (Hungarian register), or from previous publication (CERENEF). The Sponsor thus considers the original ODD and literature data published since 01 Jan 2019 as the most reliable sources to estimate the prevalence of NF1 in Europe in 2023.

Table 2. Summary of prevalence figures

Source	Prevalence rate (per 10,000)
Original ODD	1.3 to 2.9, with upper limit of 3
Literature	3.1 to 3.16
NF1 registries	2.5 to 3.4

Abbreviations: NF1: Neurofibromatosis type 1; ODD: orphan drug designation.

Conclusion

It is the Sponsor's position that the prevalence of NF1 in Europe ranges between 1.3 and 3.16 in 10,000, and that the upper limit is around **3.2 per 10,000 persons**.

According to Eurostat population provisional estimation, the latest estimation of the European Community population is 449,306,184 (Eurostat population break in time series, estimated, provisional for EU27 plus Iceland, Liechtenstein and Norway, in 2024). With a prevalence of 3.2 per 10,000, this would result in an estimated 143,778 individuals living with NF1 in the EEA.

The COMP accepted a prevalence of approximately **3 in 10,000**.

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

There is one medicinal product, Koselugo (selumetinib), authorised for the treatment of NF1 in general, or plexiform neurofibromas associated with NF1 specifically, in the EU.

- *Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.*
- *Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.*

Koselugo is only indicated for paediatric patients 3 years and older while Ezmekly covers a broader patient population, therefore Koselugo is not considered a satisfactory method of treatment and significant benefit will not be discussed.

Symptomatic treatments are pain analgesics including opioids and antiepileptics.

A recent European Guideline has emerged in 2023 supported by European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS), (Carton, C., Evans, D. G., Blanco, I., et al. (2023). ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1. EClinicalMedicine, 56, 101818. doi:10.1016/j.eclinm.2022.101818). Surgical removal is the primary treatment for neurofibromas and surgically amenable plexiform neurofibromas. However, most PNs are not amenable to complete resection due to encasement of, or close proximity to, vital structures. Permanent surgical complications (such as speech abnormalities, nerve palsies, and pain) following subtotal or partial PN resection have been reported in 18% of patients, with regrowth occurring in up to 55% of patients. Regrowth is most common in patients under age 10 years.

Although these guidelines do suggest several off-label strategies for the treatment of some NF1-related malignancies, these are based on incomplete evidence (such as carboplatin and vincristine, vinblastine, irinotecan, and bevacizumab for optic pathway glioma, ifosamide for MPNST (Malignant Peripheral Neve Sheath Tumour), or imatinib for GIST.

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 26 May 2025

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 neurofibromatosis type 1 (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia and increased risk of developing benign and malignant neoplasms;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Ezmekly.

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 Ezmekly, N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-fluoro-4-iodo-phenylamino)-benzamide, mirdametinib for treatment of neurofibromatosis type 1 (EU/3/19/2184) is not removed from the Community Register of Orphan Medicinal Products.