3 March 2026
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EMADOC-1700519818-2967271
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Xolremdi (mavorixafor)
Treatment of WHIM syndrome
EU/3/19/2183

Sponsor: X4 Pharmaceuticals (Austria) GmbH

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Mavorixafor
Other name(s)	Antineoplastics; Antiretrovirals; Benzimidazoles; Diamines; Hydroquinones; Small molecules AMD 11070; AMD-070; X4P 001 RD; X4P-001-IO
International Non-Proprietary Name	Mavorixafor
Tradename	Xolremdi
Orphan condition	Treatment of WHIM syndrome
Sponsor's details:	X4 Pharmaceuticals (Austria) GmbH Hohenstaufengasse 9//Dg Innere Stadt 1010 Vienna Austria
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/3/19/2183
Post-designation procedural history	
Transfer of sponsorship	- Transfer from Voisin Consulting Life Sciences to Boyd Consultants Limited – EC decision of 26 July 2023 - 2nd transfer from Boyd Consultants Limited to X4 Pharmaceuticals (Austria) GmbH – EC decision of 18 December 2023
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Martin Mengel / Jayne Crowe
Applicant	X4 Pharmaceuticals (Austria) GmbH
Application submission	20 December 2024
Procedure start	23 January 2025
Procedure number	EMA/H/C/006496
Invented name	Xolremdi
Proposed therapeutic indication	Xolremdi is indicated in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes. 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/xolremdi
CHMP opinion	26 February 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Sine Buhl Naess-Schmidt
Sponsor's report submission	9 October 2025

COMP opinion (adoption via written procedure)	3 March 2026

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal 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 mavorixafor was considered justified based on clinical data demonstrating improvement in absolute neutrophil and leukocyte counts in patients;
- the condition is chronically debilitating due to recurring bacterial infections and cutaneous warts;
- the condition was estimated to be affecting less than 0.01 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 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 mavorixafor as an orphan medicinal product for the orphan condition: treatment of WHIM syndrome".

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

WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome is a rare congenital autosomal dominant primary immune deficiency disease, due to gain-of-function mutations of the CXCR4 chemokine receptor. It is characterised by neutropenia and an abnormal retention of mature neutrophils in the bone marrow (myelokathexis).

Most patients present with early onset recurrent bacterial and viral infections, and develop multiple cutaneous and genito-anal warts. Recently, Dermal fungoidodid have been reported for WHIM-syndrome patients (Strong, Dermatol Ther (Heidelb). 2025 May;15(5):1173-1179).

Lymphopenia is present in majority of patients, and immunophenotyping reveals very low numbers of B cells. Hypogammaglobulinemia may be present but is not correlated to the numbers of B cells. Patients have an increased risk of malignancy including HPV (human papilloma virus)-induced cancer and lymphoma, and the overall cancer risk has been estimated to be at 30% by the age of 40 years (ESID Clinical Working Party and Beaussant Cohen 2012).

The disease is linked to a variety of heterozygous gain-of-function (GOF) mutations in the C-terminus of the C-X-C chemokine receptor 4 (CXCR4), a master regulator of immune cell trafficking and homeostasis (Zmajkovicova 2022, Genes & Immunity (2022) 23:196–204)). The diagnosis is confirmed through genetic testing for the *CXCR4* mutation.

The approved therapeutic indication "Xolremdi is indicated in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes" falls within the scope of the designated orphan condition "treatment of WHIM syndrome".

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

Affected patients have chronic neutropenia and lymphopenia, which leaves them vulnerable to frequent viral and bacterial infections that may be severe and even life-threatening. Several of the complications are severe and potentially fatal, such as squamous cell carcinoma of the genital and anal region, chronic Eppstein-Barr virus infections leading to enhanced lymphoma risk, and in some subsets, bacterial meningitis, and sepsis/septicemia.

The disease is heterogenous regarding severity; While WHIM affected individuals may live well into adulthood, WHIM syndrome is considered a life-threatening condition. The prognosis for WHIM patients depends in part on early recognition of the disorder. The many chronic and debilitating aspects of the disease are acknowledged as well as the potential for life-threatening malignancies.

Number of people affected or at risk

At the time of initial orphan designation in 2019, the prevalence was agreed to be affecting less than 0.01 in 10,000 persons in the European Union. For the prevalence estimate in the maintenance of the orphan designation application, the sponsor's used data from national patient registries, structured reviews of the published biomedical literature, curated rare disease databases, and exploratory modelling approaches using real-world data.

Given the rarity of the disease, the sponsor relied on the prioritisation of registry-based epidemiological data as the most robust source for prevalence estimation.

The main source of the sponsor's assessment is the national French Severe Chronic Neutropenia Registry (FSCNR), established in 1993 (Haematologica. 2012;97(9):1312–9). In its 2011 report, the registry identified seven patients and one foetus with WHIM syndrome and calculated an incidence at birth of 0.23 per 1,000,000 live births (95% confidence interval: 0.0019–0.29 per 1,000,000) for the

period 1990–2006 (Beaussant-Cohen et al., 2012). This corresponds to approximately 0.0023 per 10,000 births. In the absence of evidence for ethnic or geographic clustering, the assumption that French registry estimates can be extrapolated to the broader European Union population is considered reasonable.

Complementary evidence was derived from systematic literature reviews. The Orphanet Report Series (October 2024) identified 65 cases worldwide, based on pooled data from registries, health institutes, MEDLINE searches, medical texts, grey literature, and expert consultation (Orphanet, 2024). The Orphanet database classifies WHIM syndrome as an orphan disease with a prevalence of <1 per 1,000,000 individuals (equivalent to <0.01 per 10,000) (Orphanet, 2025). This estimate aligns with earlier literature-based prevalence calculations.

A structured review conducted by the sponsor March 2018 identified 109 published case studies, including two cohort studies (Beaussant-Cohen et al., 2012; Dotta et al., 2016), yielding 88 distinct individual cases in addition to a 21-patient cohort described by Dotta et al. (2016). All reported cases between 1964 and 2018 were summarised (Ebrahim et al., 2018). A subsequent review identified 105 individuals reported in the biomedical literature through January 31, 2019, with diagnoses of myelokathexis, WHIM syndrome, or germline CXCR4 mutation (Heusinkveld et al., 2019). Although the absolute number of reported cases increased, the overall estimated prevalence remained <0.01 per 10,000 individuals, consistent with the earlier French registry estimate and the Orphanet supportive findings.

To explore potential underdiagnosis, an additional study employed an artificial intelligence/machine learning model applied to a US medical insurance claims database. This analysis identified between 1,803 and 3,718 individuals with a WHIM "look-alike" phenotype (Garabedian et al., 2021). Using the upper estimate and a US population of approximately 332 million in 2021 (US Census Bureau), the calculated prevalence would correspond to approximately 0.1 per 10,000 individuals. However, the model identified phenotypic similarity rather than clinically confirmed diagnoses, and diagnostic validation was not feasible. Therefore, the sponsor considers that this approach likely overestimates true prevalence. Nonetheless, it suggests that WHIM syndrome may be underdiagnosed in routine clinical practice. However, even under this conservative worst-case scenario, the estimated prevalence remains well below the orphan designation threshold.

In conclusion, the sponsor considers country-specific registry data to provide the most reliable basis for prevalence estimation. Extrapolation of French registry data led to a 2014 estimate of 0.0016 per 10,000 individuals in the European Union (approximately 80 patients). Updated French registry data in 2018 reported 14 confirmed cases, corresponding to a prevalence of approximately 0.002 per 10,000 inhabitants in France and an extrapolated estimate of approximately 106 patients in Europe. Literature-based reviews and Orphanet data support a prevalence of <0.01 per 10,000 individuals. Although AI-based modelling suggests possible underdiagnosis, even the highest projected estimates remain substantially below the regulatory threshold for orphan designation.

As the sources are limited and uncertainties remains, the Committee concluded the prevalence to be as less than 0.01 in 10,000 persons in the European Union.

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

Currently, treatment of WHIM syndrome patients is limited to incomplete management of infection risk: there is no approved treatment for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes

Available therapies that are applied in attempt to mitigate hematological defects and prevent infections are granulocyte colony stimulating factor (G-CSF) for the treatment of chronic neutropenia and intravenous or subcutaneous immunoglobulin (IVIG or SCIG). However, G-CSF does not increase lymphocytes, in contrast to Xolremdi (mavorixafor).

In addition, antibiotics and antiviral agents are used extensively in patients with WHIM syndrome to treat and prevent recurrent infections. Despite frequent administration, patients continue to experience frequent, recurrent, and severe infections, as these therapies do not address the underlying mechanism of disease (Kawai and Malech, 2009; Beaussant-Cohen et al., 2012).

However, none of these treatments are considered satisfactory methods.

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 3 March 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 WHIM syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.01 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to persistent bacterial, viral and fungal infections, including recurrent cutaneous and genital warts, with an increased risk of virus-associated malignancies;
- 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 Xolremdi, mavorixafor for treatment of WHIM syndrome (EU/3/19/2183) is not removed from the Community Register of Orphan Medicinal Products.