Review Article
Advancements in Life Sciences – International Quarterly Journal of Biological Sciences

ARTICLE INFO

Date Received: 30/07/2024;
Date Revised: 01/09/2024;
Available Online: 15/10/2024;

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How to Cite:
Imran M, Alshammari AK, Alhamad KR, Alghamdi MA, Alghareeb MA et al., (2024). Mavorixafor: A spotlight on the clinical aspects and prospects of the first USFDA-approved treatment for the primary immunodeficiency WHIM syndrome. Adv. Life Sci. 11(4): 726-732.

Keywords:
Mavorixafor; WHIM syndrome; Cancer; Immunodeficiency; Patent; Prospect

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Mavorixafor: A spotlight on the clinical aspects and prospects of the first USFDA-approved treatment for the primary immunodeficiency WHIM syndrome

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Abstract

WHIM syndrome (WHIMS) is an extremely rare, severe, and potentially fatal genetic condition that affects the immune system, leading to warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM). Effective therapy for WHIMS requires regular monitoring, medical intervention, and a collaborative approach to treatment. Due to the limited therapeutic options, addressing WHIMS is an unmet medical need. The United States Food and Drug Administration (USFDA) recently granted approval for mavorixafor as the first treatment for WHIMS. This review focuses on the pharmacological characteristics, clinical investigations, associated inventions, and prospects of mavorixafor. The literature for this article was searched on PubMed, reputable websites (USFDA and X4 Pharmaceuticals) and free patent databases like Espacenet. WHIMS is distinguished by severe neutropenia and hypogammaglobulinemia, which increases the risk of developing cancer. Mavorixafor enhances the movement of neutrophils and lymphocytes from the bone marrow (BM) to the bloodstream. Hence, it could be beneficial for managing medical illnesses characterized by a decrease in the quantity of neutrophils and lymphocytes in the bloodstream. X4 Pharmaceuticals has submitted patent applications for the utilization of mavorixafor in the treatment of diverse cancer types, inflammatory ailments, B-cell dysfunction, Waldenstrom's macroglobulinemia, and primary immunodeficiency disorders. This suggests that mavorixafor can effectively treat various disorders either alone or when used in conjunction with other medications. It will be intriguing to observe the future approvals of mavorixafor for various disorders.

Introduction

Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome (WHIMS) a primary immunodeficiency and genetic condition that is extremely uncommon, severe, and life-threatening [1]. It is distinguished by potentially critical neutropenia, recurrent acute and chronic infections (respiratory tract, ear and skin infections), hypogammaglobulinemia, an amplified danger of bacterial meningitis, and human papillomavirus (HPV) infection with linked extremity and anogenital warts, as well as a greater risk of malignancy. WHIMS patients may also progress to end-organ damage such as bronchiectasis, bronchiectasis and hearing damage from the infections [2,3]. Gain-of-function mutations in the Cysteine-X-cysteine chemokine receptor 4 (CXCR4) gene cause WHIMS. These mutations unusually extend the interaction between CXCR4 and Chemokine Ligand 12 (CXCL12, the ligand of CXCR4). As a consequence, mature myeloid and lymphoid cells are retained in the BM, and transferring into the bloodstream is changed [4,5]. An imbalanced interaction between CXCR4 and CXCL12 leads to a significant decrease in blood neutrophils, lymphocytes, and immunoglobulins [2,3]. Individuals afflicted with WHIMS have a heightened vulnerability to infection and frequently suffer from recurring bacterial infections. Additional clinical symptoms of WHIMS encompass the presence of warts and, in certain instances, the development of cervical cancer as a consequence of HPV infection [6,7]. Recurrent bacterial infections, particularly severe lung infections, resulting in respiratory and cardiac failure, are the primary reason for illness and mortality in patients with WHIMS [2,3]. Effective therapy for WHIMS requires regular monitoring, medical intervention, and a collaborative approach to treatment. Due to the limited therapeutic options, addressing the treatment of WHIMS is considered an unmet medical need [2,3] (Figure 1).

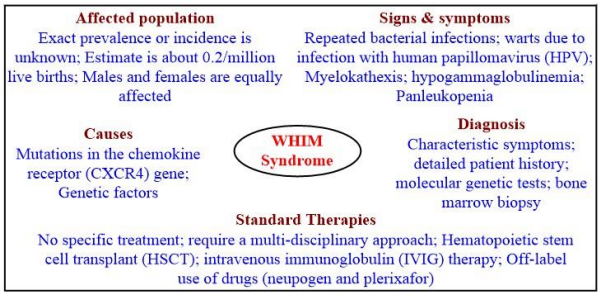

Figure 1: Causes, symptoms, diagnosis and therapies for WHIMS [1-5].

There were no USFDA-approved drugs for the treatment of WHIMS till April 25, 2024 [8,9]. On April 26, 2024, the USFDA approved mavorixafor as the first treatment for WHIMS (Table 1) [8,10].

Drug (Proprietary Name; Applicant; Therapeutic class)	Dosage Form (Route; Strength; Status)	Exclusivity Data*	Indication
Mavorixafor (Xolremdi; X4 Pharmaceuticals; CXCR4 antagonist)	Capsule (Oral; 100 mg; Prescription drug)	New Chemical Exclusivity expiring on April 26, 2029; Orphan Drug Exclusivity expiring on April 26, 2031	Treatment of WHIMS (≥ 12 years of patients)

*Period during which the second company cannot gain drug approval from the USFDA.

Table 1: Information about the USFDA-approved mavorixafor product [8-10].

This review spotlights the pharmacological characteristics, clinical investigations, associated inventions, and prospects of mavorixafor. This article differs from the earlier reviews concerning new updates on pharmaceutical aspects, spotlighting patent literature on mavorixafor and suggesting foreseeable inventions of mavorixafor. This article would be useful to scientific teams working on developing treatments for WHIMS and associated disorders.

Methods

Literature search and selection criteria

The literature for this article was searched on PubMed, authentic websites (X4 Pharmaceuticals and USFDA) and free patent databases (Espacenet) utilizing different keywords (mavorixafor, Xolremdi, X4P-001, and AMD-070). The articles, USFDA reports, authentic webpages and patent literature explicitly providing pharmaceutical and clinical data information about mavorixafor were segregated and included for writing this review.

Discussion

Mavorixafor

General information

Mavorixafor (Figure 2; Synonyms: Xolremdi, X4P-001, AMD-070; Chemical Formula: $C_{21}H_{27}N_5$; Chemical class: Aminoquinoline; Molecular weight: 349.48; CAS Registry Number: 558447-26-0) is an optically active and hygroscopic small synthetic compound. Mavorixafor has one chiral carbon, and its S-isomer is approved by the USFDA to treat WHIMS [11,12].

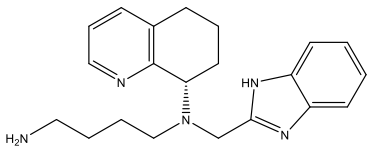

Figure 2: Chemical structure of mavorixafor [11,12].

The marketed Xolremdi immediate-release capsule product encompasses 100 mg of mavorixafor and many

inactive excipients, including sodium lauryl sulfate, microcrystalline cellulose, colloidal silicon dioxide, sodium stearyl fumarate, dibasic calcium phosphate dihydrate, and croscarmellose sodium. The hard capsule shell is built up of gelatin, titanium dioxide and FD & C Blue Number 2 colour [11,12].

Clinical trials

The clinical trial information about mavorixafor was searched on USFDA documents, clinicaltrial.gov (Accessed on July 25, 2024) and PubMed utilizing different keywords (mavorixafor = 6 hits; Xolremdi = 0 hits; X4P-001 = 10 hits; AMD-070 = 8 hits) [8,9,13-21] (Table 2).

NCT Number (Other IDs; Title Acronym; Sponsor; Location)	Conditions (Intervention; Allocation; numbers enrolled; Purpose)	Phase (Status; Start date; Completion date; Last update)
NCT02680782 (X4P-001-REGA; None; X4 Pharmaceuticals; United States)	Healthy (Mavorixafor; Randomized; 15; Treatment)	1 (Terminated; January 2016; February 2016; December 2018)
NCT02823405 (X4P-001-MELA; X4P-001-MELA; X4 Pharmaceuticals; United States)	Melanoma (Mavorixafor and Pembrolizumab; Not applicable; 16; Treatment)	1 (Completed; September 2016; March 2018; July 2020)
NCT02667886 (X4P-001-RCCA; None; X4 Pharmaceuticals; United States)	Clear Cell Renal Cell Carcinoma (Mavorixafor and axitinib; Randomized; 74; Treatment)	1/2 (Completed; January 2016; March 2022; March 2023)
NCT02923531 (X4P-001-RCCB; None; X4 Pharmaceuticals; United States)	Clear Cell Renal Cell Carcinoma (Mavorixafor and Nivolumab; Not applicable; 9; Treatment)	1/2 (Terminated; December 2016; August 2018; December 2022)
NCT04154488 (X4P-001-104; None; X4 Pharmaceuticals; United States)	Neutropenia (Mavorixafor; Not applicable; 43; Treatment)	1/2 (Active; October 2020; July 2025; May 2024)
NCT05103917 (X4P-001-201; None; Abbisko Therapeutics; China)	Triple Negative Breast Cancer (Mavorixafor; Not applicable; 24; Treatment)	1/2 (Unknown; July 2021; May 2023; November 2021)
NCT03005327 (X4P-001-MKKA and 2016-005028-26; None; X4 Pharmaceuticals; United States and Australia)	WHIMS (Mavorixafor; Not applicable; 8; Treatment)	2 (Completed; December 2016; June 2022; September 2023)
NCT03995108 (X4P-001-103, 2019-001153-10 and 4WHIM; None; X4 Pharmaceuticals; Spain and United States)	WHIMS (Mavorixafor and placebo; Randomized; 31; Treatment)	3 (Active; October 2019; December 2024; May 2024)
NCT04274738 (X4P-001-204 and 2019-003909-95; None; X4 Pharmaceuticals; United States)	Waldenstrom's Macroglobulinemia (Mavorixafor and Ibrutinib; Not applicable; 16; Treatment)	1 (Completed; April 2020; October 2022; November 2022)
NCT06056297 (X4P-001-110; None; X4 Pharmaceuticals; Georgia)	Neutropenia (Mavorixafor and placebo; Randomized; 150; Treatment)	3 (Recruiting; July 2024; August 2026; July 2024)

Table 2: Clinical trial information about mavorixafor [8,9,13-21].

The efficacy of mavorixafor in patients with WHIMS was demonstrated through enhancements in absolute neutrophil count (ANC) and absolute lymphocyte count (ALC), as well as a decreased susceptibility to infections, as indicated by NCT03995108 [15,16]. The study also found that mavorixafor did not provide any advantage compared to a placebo in the management of warts. Likely factors contributing to this flop include a limited number of participants, variations in the severity and distribution of warts, and the potential inadequacy of mavorixafor's impact on the immune coordination to effectively treat warts. Nevertheless, the expert committee from the USFDA recommended the approval of mavorixafor because of its advantages above the risks. The adverse reactions mostly consist of mild to moderate adverse effects that are generally tolerable and can be monitored [15,16].

Pharmacology

Mavorixafor is an oral CXCR4 antagonist. It works by blocking the attaching of the CXCR4 to CXCL12 (a ligand of CXCR4). The CXCR4- CXCL12 assembly is involved in the movement and targeting of white blood cells (leukocytes) to and from the BM. WHIMS's patients experience an increase in the functional mutations in the CXCR4 receptor gene, ensuing in heightened sensitivity to CXCL12 and the storing of leukocytes in the BM [8,9,12,14-16,22] (Figure 3).

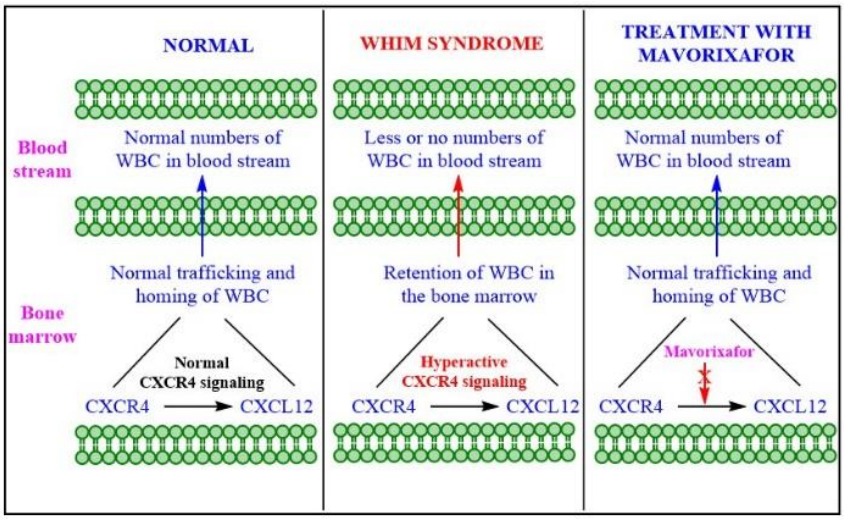

Figure 3: Mechanism of mavorixafor.

Mavorixafor suppresses the reaction to CXCL12 in both normal and altered CXCR4 variations linked to WHIMS. The administration of mavorixafor leads to enhanced movement of lymphocytes and neutrophils from the BM to the bloodstream [8,12]. The information about important pharmacological parameters of mavorixafor is provided in Table 3.

Parameter	Summary
Dosing regimen	Weight > 50 kg: 400 mg orally per day; Weight ⩽ 50 kg: 300 mg orally per day; Administer after overnight fast (or empty stomach) and at least half an hour before the meal
Absorption	C_{max} = 2.8 hours; T_{max} =1.9 to 4 hours
Volume of distribution	768 L; Plasma protein binding (*in vitro*) = > 93%
Metabolism	CYP3A4 and CYP2D6 are primary metabolizing enzymes
Elimination	Terminal half-life = 82 hours; Clearance = 62 Liter/hour; Excretion is mainly though feces (61.0%) and urine (13.2%)
Adverse effects	Thrombocytopenia; epistaxis; rash; rhinitis; pityriasis; dizziness; vomiting
Warning	Mavorixafor can cause embryo-fetal toxicity
Contraindication	No co-administration with CYP2D6-dependent drugs
Toxicity/Overdose	The fertility and carcinogenicity investigations are yet to be performed; tubular degeneration/atrophy was detected in the tests of dogs
QT prolongation	Mavorixafor leads to QTc interval prolongation
Use in special populations	Not recommended for lactating mothers and geriatric patients
Drug/Food Interactions	Strong CYP3A4 inhibitors (itraconazole and midazolam), CYP2D6 substrates (dextromethorphan) and P-gp substrates (digoxin) increase mavorixafor exposure. High-fat meals decrease the absorption by about 66%
Renal/Hepatic impairment	Not recommended for severe cases of hepatic/renal impairment due to lack of study in these patients

Table 3: ADME-Toxicity parameters of mavorixafor [8,9,12,14-16].

Development timeline

The development time of mavorixafor is provided in Figure 4.

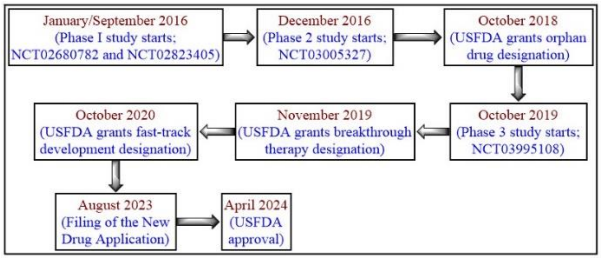

Figure 4: Development phases of mavorixafor [8,14-16].

Inventions

Different keywords (mavorixafor, Xolremdi, X4P-001, and AMD-070) were used to search the important patents related to mavorixafor utilizing the free patent database (Espacenet, Accessed on July 25, 2024) [23-25].

US10548889B1 (X4 Pharmaceuticals; Patented Case) claims a mavorixafor composition comprising some mavorixafor analogs useful for treating disorders associated with CXCR4, including WHIMS and various cancers [26]. One of the advantages of this composition is its utilization as transdermal patches.

US10610527B2 (X4 Pharmaceuticals; Patented Case) relates to a method of treating WHIMS by mavorixafor, wherein the dose of mavorixafor ranges from 20-600 mg/day [27]. The claimed dose provides significant treatment outcomes with low side effects.

US10953003B2 (X4 Pharmaceuticals; Patented Case) discloses a composition (a stable capsule with a high dissolution rate) comprising mavorixafor and other pharmaceutical ingredients for treating disorders associated with CXCR4, including WHIMS [28].

US11045461B2 (X4 Pharmaceuticals; Patented Case) unveils a mavorixafor composition for treating WHIMS comprising an aldehydic analog of mavorixafor in an amount of 0.001-0.5% w/w of the mavorixafor composition [29].

US11219621B2 (X4 Pharmaceuticals; Patented Case) reveals a method for treating WHIMS with a dose of about 200-600 mg of mavorixafor daily in a single/divided dose [30]. The claimed dose provides significant treatment outcomes with low side effects.

US11357742B2 (X4 Pharmaceuticals; Patented Case) claims a method for treating refractory advanced renal cell carcinoma with mavorixafor in synergistic combination with axitinib [31].

WO2023240259A1 (X4 Pharmaceuticals; New patent application) covers a method of treating inflammatory condition (various types of arthritis) with an effective dose of mavorixafor [32].

WO2023240258A1 (X4 Pharmaceuticals; New patent application) discloses a method of treating a B-cell disorder with a synergistic combination of a CXCR4 inhibitor (mavorixafor), an IL-6 modulator (tocilizumab) and a targeted B-cell therapy (ibrutinib) [33].

WO2023172640A1 (X4 Pharmaceuticals; New patent application) covers a treatment of Waldenstrom's macroglobulinemia (WM) with a synergistic combination of mavorixafor and a BTK inhibitor (tirabrutinib) [34].

WO2023107689A1 (X4 Pharmaceuticals; New patent application) claims a method for treating a primary immunodeficiency with a CXCR4 inhibitor (mavorixafor) [35].

US2023014231A1 (X4 Pharmaceuticals; Under examination) relates to the treatment of neutropenia (chronic, cyclic or congenital) with an effective amount of mavorixafor [36].

Mavorixafor is a recently USFDA-approved first and transformational milestone drug for WHIMS. The drug demonstrated a reduction in the symptoms of WHIMS and an improvement in the patient's condition during clinical studies [8-10]. Mavorixafor is a CXCR4 antagonist. Multiple functions have been verified for CXCR4 in human illnesses, including cancer,

Alzheimer's disease, different types of arthritis, HIV, rheumatoid arthritis and pulmonary fibrosis [26,32,37-39]. Mavorixafor has been investigated clinically for its anticancer potential, including hematologic malignancies, renal cancer and solid tumours (Table 2) [40]. Mavorixafor enhances immune functions by mobilizing immune cells (neutrophils and lymphocytes) from the BM to the bloodstream. These properties of mavorixafor make it a suitable investigational candidate for treating diverse diseases [35].

X4 Pharmaceuticals is the innovator company of mavorixafor. X4 Pharmaceuticals has filed patents for treating cancer with the combination of mavorixafor with other anticancer drugs [33,34] (Table 2). Some patent applications exist claiming general aspects of mavorixafor, for example, WO2023059903A1 (claims process for making mavorixafor) [41], WO2023212244A1 (generically claims a method of treating 5HT2A mediated conditions with mavorixafor in combination with other drugs) [42], US2023190769A1 (generically claims a method of treating coronavirus infection with mavorixafor in combination with other drugs) [43], and CN115252790B (generically claims a double-targeting multifunctional nano delivery system comprising mavorixafor) [44]. There is a scope for exploring the combinations of mavorixafor with other drugs to provide synergistic combinations for treating cancer, immunodeficient patients, and conditions with CXCR4 malfunctioning. The authors believe that there is a scarcity of mavorixafor-based inventions. A patent can be granted for various types of research work [45-47]. The authors anticipate more patent filings related to various types of mavorixafor-based inventions (new dosage forms, indication for new diseases, analogs of mavorixafor, salts, polymorph, cocrystals, etc.) in future.

Despite the promising profile, there exist some areas that need to be explored. Recurrent microbial infections are the primary reason for illness and mortality in patients with WHIMS [2,3]. Additionally, mavorixafor did not provide any advantage compared to a placebo in the treatment of warts [15,16]. These aspects necessitate developing an effective combination of suitable antibiotics/antiviral agents and mavorixafor to treat WHIMS and its associated ailments. Mavorixafor has shown immunomodulatory effects [35]. Accordingly, it may be assessed as a cancer prevention therapy or as an immunomodulator. Many important toxicity studies (carcinogenicity, mutagenicity, hepatotoxicity, genetic toxicity, etc.) have not yet been well established (Table 2 and Table 3) for mavorixafor. Additionally, the pharmacokinetics of mavorixafor have not been investigated in patients who have severely impaired renal or hepatic function or who have reached the end stage of renal disease. Further, the safety and tolerability of mavorixafor among some populations (pregnant/lactating women and old people of > 65 years) have not been done. Some, but insufficient drug interaction studies on mavorixafor have been reported [48,49]. However, additional drug interaction studies are also required to be conducted. The study of drug resistance has become a crucial area in the field of pharmaceutical and medical sciences. This is primarily due to the increasing problem of drug resistance. The knowledge acquired from drug resistance research is crucial in directing the development of advanced medications and in devising efficient treatment strategies to address drug resistance and enhance patient outcomes [1-3,14-16]. The clinical studies of mavorixafor have been performed on a limited number of WHIM patients [14-16]. These studies are not sufficient to inform about the mechanism of developing mavorixafor resistance. Accordingly, mavorixafor-based drug resistance studies are also advocated.

Conclusion

Mavorixafor is a breakthrough therapy for WHIMS. It has considerable potential in various treatment fields, especially for uncommon genetic illnesses, immunodeficiency disorders, inflammatory diseases and specific types of cancer. Further investigation and effective clinical trials will be essential in establishing its future influence on healthcare. There exists a good scope for further pharmaceutical research (new dosage forms and drug combinations) and clinical research (new indications) on mavorixafor for the scientific fraternity involved in developing treatments for CXCR4-related disorders.

Author Contributions

Mohd Imran, Abida and Basheeruddin Asdaq conceptualized, supervised and reviewed the article. All other members performed the literature search and provided valuable input on the manuscript writing.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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