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A Review on-Mavorixafor Capsule: "WHIM Syndromes"

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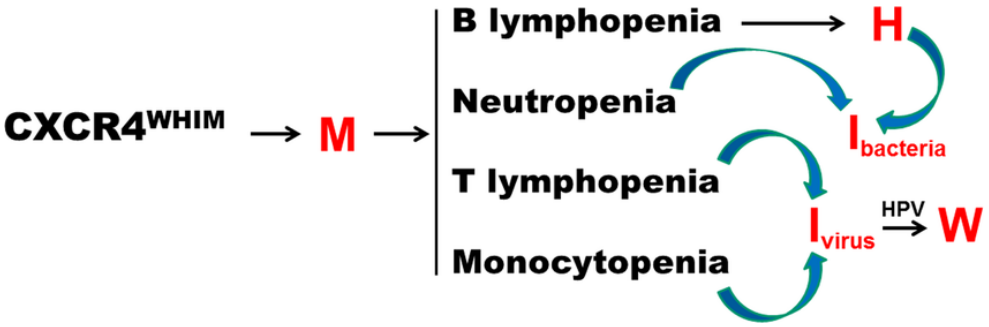
Abstract:-
An uncommon primary immunodeficiency that is autosomal dominant is called WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome.Increasing the mobilisation and trafficking of white blood cells from the bone marrow is Mavorixafor, an oral small molecule selective antagonist of the CXCR4 receptor.The CXCR4 Receptor gene ,which is involved in blood cell migration into and out of the bone marrow , has mutation (changes) in patient with WHIM syndrome .The oral medication Mavorixafor is intended to lower CXCR4 receptor activation and facilitate the release of neutrophils from the bone marrow in to the blood stream , which will aid the body in fighting infections .In patients 12 years of age and older , whose care is now restricted to treating the many symptoms of WHIM syndrome , Mavorixafor , if licensed , would offer the first targeted treatment option for WHIM syndrome.

Keywords :
- Mavorixafor
- CXCR4 Antagonist
- WHIM Syndroms
- Lympocytes Count

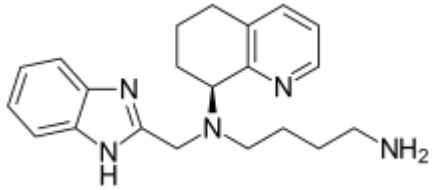
I. Introduction

Mostly caused by gain-of-function variants in the CXCR4 gene, warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is an uncommon autosomal-dominant immunodeficiency that impairs leukocyte trafficking between bone marrow and blood by truncating the carboxyl terminus of C-X-C chemokine receptor type 4 (CXCR4).



In both healthy and pathological conditions, chemokine receptors engage with appropriate ligands to mediate a variety of cell migratory pathways . The chemokine receptor CXCR4, which is highly characterised, has crucial roles in immunological response, neuronal migration of haematopoietic stem cells (HSCs), inflammation, and HIV infection.

Table :

Structure	

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Trade name	Xolremdi
Other names	X4P-001; AMD-070
Routes of administration	Oral Route
Drug class	CXCR4 antagonist
IUPAC name	*N′*-(1*H*-Benzimidazol-2-ylmethyl)-*N′*-[(8*S*)-5,6,7,8-tetrahydroquinolin-8-yl]butane-1,4-diamine
Formula	$C_{21}H_{27}N_5$
Molar mass	349.482 g·mol^{-1}

Mechanism of action :

CXCR4 gene mutations that result in an overactivation of CXCR4 signalling pathways are the cause of WHIM syndrome. CXCR4.4 activation is inhibited by xolremdi.

Pharmacokinetic :

In individuals with WHIM syndrome, Mavorixafor pharmacokinetic characteristics are expressed as geometric mean (CV%) unless otherwise noted. Mavorixa for a steady state Cmax of 3304 (58.6%) ng/mL and an AUC of 13970 (58.4%) ng*h/mL after a 400 mg dose once a day are the values obtained.

Absorption :

The maximum recommended dosage for Mavorixa is 2.8 hours (1.9 to 4 hours) at the median (range) time to Cmax (Tmax).

Distribution :

The distribution volume for Mavorixafor is 768 litres. In vitro, Mavorixafor binds to human plasma proteins to a greater than 93% degree.

Metabolism :

Mavorixafor metabolism is mostly caused by CYP3A4 and, to a lesser extent, CYP2D6.

Elimination :

The apparent clearance of Mavorixafor was 62 L/h (40%), while its terminal half-life was 82 h (34%).

Excretion :

During the 240-hour collection period in healthy participants, 13.2% (3% unaltered) of the administered radioactivity was recovered in the urine and 61.0% of the supplied dose was recovered in faeces following a single oral dose of radiolabeled mavorixafor.

Pharmacodynamic :

Absolute Neutrophil Count (ANC) and Absolute Lymphocyte Count (ALC) :

Following the administration of XOLREMDI, ANC and ALC reached their peak four hours later and returned to baseline 24 hours later. For mavorixa, higher exposure at steady state to doses ranging from 50 mg (0.125 times the maximum recommended dosage) to 400 mg once daily was linked to longer mean time (hours) above the ANC threshold (TATANC) of 500 cells/µL and longer mean time (hours) above the ALC threshold (TATALC) of 1,000 cells/µL over a 24-hour period.

UV Spectroscopy Method :

UV Spectroscopy is a valuable tool for analyzing Mavorixafor , paticularly for determining its concentration and purity the following method was used :

1. Sample preparation :

Preparing standard solutions with different concentrations required dissolving Mavorixafor in an appropriate solvent.

2.Spectrophotometric Analysis :

UV Spectra were recorded using a UV - visible spectrophotometer (eg, PerkinElmer Lambda 25) within the range of 200 - 400 nm . The absorbance maxima specific to Mavorixafor were identified.

3. Calibration curve :

A calibration curve was generated by plotting absorbance against concentration.the linear range and regression parameters were established to quantify Mavorixafor in formulations and biological samples.

4. Validation :

The UV spectroscopy method was validated for accuracy, precision, specificity and reproducibility according to ICH guidelines .

Sample Preparation:

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Solvent selection :
According to the USP solubility requirements, Mavorixafor is sparingly soluble in DMSO and acetonitrile, readily soluble in methanol, 95% ethanol and n-octanol, soluble in toluene, and very faintly soluble in HPLC grade water.
The USP solubility criteria state that,Mavorixafor is soluble in pH 1.2 to 5.5 aqueous buffers and in pH 6.0 aqueous buffer, sparingly soluble in pH 6.8 aqueous buffer, and little soluble in pH 7.5 aqueous buffer.
Concentration :
A series of standarsd solutions are prepared at known concentrations to established a calibration curve.
Instrument Calibration:
Wavelength Selection:
The maximum absorbance wavelength (λmax) for, Mavorixafor determined using a UV spectrophotometer.Typically, this involves scanning a range of wavelengths to identify the peak.
Baseline Correction:
A blank solution is measured to account for any interference from the solvent.
Data Acquisition:
Measurement: The absorbance of the Mavorixafor solutions is measured at λmax. This data is used to create a calibration curve plotting absorbance against concentration.
Analysis of Samples: Test samples of Mavorixafor formulations are analyzed in the same manner to determine their concentration.

Results Interpretation:
Calibration Curve:
A linear relationship between absorbance and concentration indicates the method's reliability. The slope and intercept of the curve are calculated to quantify unknown samples.
Limit of Detection :
(LOD) and Limit of Quantification (LOQ): These parameters are determined to assess the method sensitivity.
Indication :
To treat warts,hypogammaglobulinemia,infection,andmyelokathexis (WHIM) syndrome in adults and adolescents over the age of twelve, in order to boost the quantity of mature neutrophils and lymphocytes in the blood vessels.
Side Effects *:*
i.rash.
ii.itching.
iii.runny or stuffy nose.
iv.dizziness.
v.vomiting.

Adverse Effects *:*
i.Thrombocytopenia (21%)
ii.Pityriasis (14%)
iii.Rash (14%)
iv.Rhinitis (14%)
v.Epistaxis (14%)
vi.Vomiting (14%)
vii.Dizziness (14%)

Uses :
Treating -
i.Warts
ii.Hypogammaglobulinemia
iii.Immunodeficiency
iv.Myelokathexis syndrome
v.Used to increase the number of circulating mature neutrophils and lymphocytes.

II. Conclusion

Low numbers of T and B cells are among the immune system abnormalities associated with WHIM syndrome. Following Mavorixafor treatment, T- and B-cell levels returned to normal. This may have helped participants with WHIM syndrome receiving mavorixafor reduce their infection rate, severity, and duration during RCP, especially when combined with previously noted increased ANC.

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