ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Xolremdi 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of mavorixafor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Size 1 opaque hard gelatine capsules (length approx. 19.4 mm) with white body and light blue cap. The white capsule body is imprinted with “100 mg” in black ink, and the light blue capsule cap is imprinted with “MX4” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment should only be initiated by specialist physicians with experience in the diagnosis or management of immune deficiencies.

Posology

The recommended dose is:
- Weight more than 50 kg: 400 mg (four 100 mg capsules) orally once daily on an empty stomach after an overnight fast, and at least 30 minutes before food.
- Weight less than or equal to 50 kg: 300 mg (three 100 mg capsules) orally once daily on an empty stomach after an overnight fast, and at least 30 minutes before food.

Missed dose
If a dose is missed, the next dose should be taken as scheduled. The patient should not take a double dose to make up for a missed dose.

Dose modifications

Concomitant use of Xolremdi with strong or moderate CYP3A4 inhibitors
When used concomitantly with a strong CYP3A4 inhibitor, daily dose should be reduced to 200 mg.

When used concomitantly with a moderate CYP3A4 inhibitor, Xolremdi adverse reactions that may be associated with an increase in mavorixafor exposure should be monitored more frequently (see section 4.5), and the Xolremdi daily dose should be reduced by steps of 100 mg, as clinically necessary, but not to a dose less than 200 mg.

Concomitant use of Xolremdi with P-gp inhibitors
When used concomitantly with a P-gp inhibitor, Xolremdi adverse reactions that may be associated with an increase in mavorixafor exposure should be monitored more frequently (see section 4.5), and the Xolremdi daily dose should be reduced by steps of 100 mg, as clinically necessary, but not to a dose less than 200 mg.

Special populations

Risk of QTc prolongation
In patients with risk factors for QTc prolongation and/or when used concomitantly with medicinal product with a known potential to prolong the QTc interval, QTc assessment and monitoring is required (see section 4.4). If dose reduction is required, the daily dose should be reduced by steps of 100 mg, but not to a dose less than 200 mg. Discontinuation of Xolremdi may be required (see section 4.4).

Elderly
There are limited data on patients aged 65 years and older.

Renal impairment
The safety and efficacy of Xolremdi have not been established in patients with severe renal impairment (creatinine clearance 15 to less than 30 mL/min) or end-stage renal disease (creatinine clearance less than 15 mL/min). It is not recommended to administer Xolremdi to patients with severe renal impairment or end-stage renal disease. No dose adjustment is recommended in patients with creatinine clearance ≥ 30 mL/min, including in patients with mild to moderate renal impairment.

Hepatic impairment
The safety and efficacy of Xolremdi have not been established in patients with moderate to severe hepatic impairment (ChildPugh score ≥ 7). Xolremdi is not recommended for use in patients with moderate to severe hepatic impairment. No dose adjustment is recommended in patients with mild hepatic impairment.

Paediatric population

The safety and efficacy of Xolremdi in children from 2 to 11 years of age have not yet been established. No data are available.

Xolremdi should not be used in children < 2 years of age because exposure to mavorixafor may cause developmental defects (see section 5.3).

Method of administration

Xolremdi is for oral use.

The capsule should be taken on an empty stomach after an overnight fast, and at least 30 minutes before food (see section 5.2).

The capsules should be swallowed whole and should not be opened, broken or chewed to ensure product efficacy and stability.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use with medicinal products highly dependent on CYP2D6 for clearance (e.g. dextromethorphan, codeine, tramadol) (see section 4.5).

During pregnancy (see sections 4.4, 4.6 and 5.3).

4.4 Special warnings and precautions for use

Reproductive toxicity

Based on its mechanism of action, mavorixafor may cause foetal harm when administered to a pregnant woman (see sections 4.3, 4.6 and 5.3).

The pregnancy status of female patients of childbearing potential who are engaging in activities of reproductive potential should be verified prior to starting Xolremdi. Female patients of childbearing potential must avoid becoming pregnant by using an effective method of contraception (e.g. double-barrier contraception) during treatment with Xolremdi and for three weeks after the final dose (see sections 4.6 and 5.3).

Male patients with female partners of childbearing potential should use condoms during sexual intercourse while taking Xolremdi and for at least three weeks after stopping treatment.

If exposure to mavorixafor during pregnancy has occurred, the female patient should contact their doctor promptly and treatment with mavorixafor discontinued.

In order to assist healthcare professionals (HCPs) and patients to minimise the potential risk of embryo-foetal toxicity, a HCP guide will be distributed to the HCPs who are experienced in the treatment of WHIM syndrome and a patient card will be provided in the product package.

QTc prolongation

Mavorixafor causes concentration-dependent QTc prolongation (see section 5.1). Concomitant use of Xolremdi with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de Pointes, other serious arrythmias, and sudden death.

Any modifiable risk factors for QTc prolongation should be corrected, and QTc should be assessed at baseline and monitored during treatment as clinically indicated in patients with risk factors for QTc prolongation (e.g. congestive heart failure, Long QT Syndrome, hypokalaemia) or receiving concomitant medicinal products that increase mavorixafor exposure and/or active substances with a known potential to prolong the QTc interval. Dose reduction (see section 4.2) or discontinuation of Xolremdi may be required.

Patients without confirmed CXCR4 gene variants

The efficacy and safety of Xolremdi have not been established in patients with WHIM-syndrome who do not carry pathogenic CXCR4 variants.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially ‘sodium- free’.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interaction information for Xolremdi with potential concomitant medicinal products is summarized in Table 1, Table 2 and Table 3.

Interaction studies have only been performed in adults.

Table 1: Effect of Xolremdi on other medicinal products (examples include, but are not limited to)

Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}[a]**	**Recommendation concerning co-administration with Xolremdi**
CYP2D6 substrates		
e.g. dextromethorphan, codeine, tramadol	*Dextromethorphan*[b] ↑ C_{max} by 6.5-fold (5.1 to 8.3) ↑ AUC by 9-fold (6.5 to 12.3).	Mavorixafor is a CYP2D6 inhibitor. Concomitant use of Xolremdi with medicinal products highly dependent on CYP2D6 for clearance is contraindicated (see section 4.3). Following discontinuation of mavorixafor, the inhibitory effect on CYP2D6 may persist; a washout period of approximately 30 days (corresponding to 9 half-lives) should be considered prior to initiating treatment with medicinal products highly dependent on CYP2D6 for clearance.
CYP3A4 substrates		
e.g. midazolam, alprazolam, everolimus, telithromycin, telaprevir, ceritinib, ribociclib, atazanavir.	*Midazolam*[b] ↑ C_{max} by 1.1-fold (1.0 to 1.3) ↑ AUC by 1.7-fold (1.4 to 2.1).	Mavorixafor is a CYP3A4 inhibitor. When used concomitantly with CYP3A4 substrates, where minimal substrate concentration changes may lead to serious adverse reactions, CYP3A4 substrate related adverse reactions should be monitored more frequently.
P-gp substrates		
digoxin	*Digoxin*[c] ↑ C_{max} by 1.5-fold (1.3 to 1.8) ↑ AUC by 1.6-fold (1.4 to 1.9)	When Xolremdi is used concomitantly with digoxin, the serum concentrations of digoxin should be measured before initiating concomitant use of Xolremdi, and monitoring of serum digoxin concentrations should be continued as recommended in the digoxin SmPC.
<u>*Other P-gp substrates*</u> e.g. dabigatran etexilate, edoxaban, fexofenadine	Interaction not studied.	When Xolremdi is used concomitantly with other P-gp substrates where minimal substrate concentration changes may lead to serious adverse reactions, P-gp substrate related adverse reactions should be monitored more frequently.

OCT2/MATE1 substrates		
metformin	*Metformin* [d] ↓ C_{max} by 35% (17 to 49%) ↓ AUC by 35% (20 to 47%)	Monitor for glycemic control and adjust the dose of metformin as necessary. Mavorixafor may decrease the mean C_{max} and AUC of metformin, which may reduce metformin's effectiveness. The mechanism of this interaction is unknown.

[a] All interactions studies conducted in healthy subjects.
[b] Concomitant use with Xolremdi 400 mg
[c] Concomitant use of a single oral dose of a transporter cocktail containing 0.25 mg of digoxin with Xolremdi dosed to steady state (400 mg/day).
[d] Concomitant use of a single oral dose of a transporter cocktail containing 10 mg of metformin with Xolremdi dosed to steady state (400 mg/day)

Table 2: Effect of other medicinal products on Xolremdi (examples include, but are not limited to)

Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a]**	**Recommendation concerning co-administration with Xolremdi**
CYP3A4 inducers		
e.g. apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin, phenobarbital, St. John's wort	Interaction not studied. *Expected:* ↓ Mavorixafor C_{max} ↓ Mavorixafor AUC	Mavorixafor is a CYP3A4 substrate. Concomitant use with a strong CYP3A4 inducer is expected to decrease the concentration of mavorixafor, which may reduce the therapeutic effect of Xolremdi. Concomitant use is not recommended.
Strong or moderate CYP3A4 inhibitors		
e.g. itraconazole, amiodarone, diltiazem, fluconazole, ketoconazole, clarithromycin, erythromycin, nefazodone.	*Itraconazole* [b] ↑Mavorixafor exposure by approximately 2-fold *Expected:* ↑ Mavorixafor C_{max} ↑ Mavorixafor AUC	Mavorixafor is a CYP3A4 substrate. Concomitant use with a strong or moderate CYP3A4 inhibitors is expected to increase the exposure of mavorixafor and may increase the risk of adverse reactions. When used with a strong CYP3A4 inhibitor, the daily dose should be reduced to 200 mg (see section 4.2). When used with a moderate CYP3A4 inhibitor, adverse reactions should be monitored more frequently and the daily dose should be reduced by steps of 100 mg, *as clinically necessary*, but not to a dose less than 200 mg (see section 4.2).
P-gp inhibitors		
itraconazole (200 mg), verapamil	*Itraconazole* [b] ↑Mavorixafor exposure by approximately 2-fold *Expected:* ↑ Mavorixafor C_{max} ↑ Mavorixafor AUC	Mavorixafor is a substrate of P-gp. When Xolremdi is used concomitantly with P-gp inhibitors, Xolremdi adverse reactions that may be associated with an increase in mavorixafor exposure should be monitored more frequently, and the Xolremdi daily dose should be reduced by steps of 100 mg, *as clinically necessary*, but not to a dose less than 200 mg (see section 4.2).

[a] All interactions studies conducted in healthy subjects.
[b] Concomitant use of Xolremdi 200 mg with 200 mg itraconazole.

Table 3: Interaction of anti-arrhythmic medicinal products and other medicinal products that may prolong the QT interval

Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Xolremdi**
Anti-arrhythmic medicinal products (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol) Other medicinal products that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron)	Interaction not studied. Expected to prolong QTc interval	Xolremdi causes concentration-dependent QTc prolongation. Concomitant use of Xolremdi with other products that are associated with QTc prolongation may lead to an increase in the QTc interval (see sections 4.4 and 5.1). When used concomitantly with medicinal product with a known potential to prolong the QTc interval, QTc assessment and monitoring is required (see sections 4.2 and 4.4). If dose reduction is required, the daily dose should be reduced by steps of 100 mg, but not to a dose less than 200 mg. Discontinuation of Xolremdi may be required (see sections 4.2 and 4.4).

Food

Patients should be advised to avoid eating or drinking products with grapefruit, as grapefruit is a strong CYP3A4 inhibitor and may increase the risk of adverse reactions from Xolremdi.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

The pregnancy status of female patients of childbearing potential who are engaging in activities of reproductive potential should be verified prior to starting Xolremdi. Female patients of childbearing potential must avoid becoming pregnant by using an effective method of contraception (e.g., double-barrier contraception) during treatment with Xolremdi and for three weeks after the final dose (see section 4.4).

Male patients with female partners of childbearing potential should use condoms during sexual intercourse while taking Xolremdi and for at least three weeks after stopping treatment.

Pregnancy

There are no or a limited amount of data from the use of mavorixafor in pregnant women.

Based on its mechanism of action, mavorixafor may cause foetal harm when administered to a pregnant woman (see section 5.3).

Xolremdi is contraindicated during pregnancy (see section 4.3).

If exposure to mavorixafor during pregnancy has occurred, the female patient should contact their doctor promptly and treatment with mavorixafor discontinued.

Breast-feeding

Mavorixafor has not been studied in breast-feeding women. It is unknown whether mavorixafor/metabolites are excreted in human and animal milk.

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding during treatment and for three weeks after the final dose or to discontinue Xolremdi therapy, considering the benefit of breast-feeding for the child and the benefit of Xolremdi therapy for the woman.

Fertility

The effect of mavorixafor on human fertility is unknown. The effect of mavorixafor on male or female fertility was not studied in designated reproductive toxicology studies. In chronic duration repeat-dose toxicity studies, testicular changes were observed in one study in which treatment was initiated in young prepubertal dogs. The relevance of these findings for male patients is not known (see section 5.3).

4.7 Effects on ability to drive and use machines

Xolremdi may have influence on the ability to drive and use machines. Patients should be advised not to drive or use machines if they are experiencing nervous system adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

The safety data described below reflect exposure in 38 patients with WHIM syndrome treated with mavorixafor, with a treatment duration range from less than 6 months (7 patients) to 4 years (7 patients), with median duration of exposure of 2 years. The most common adverse reactions observed, of any grade reported, were gastrointestinal effects [nausea (21.1%), diarrhoea (18.4%), vomiting (13.2%), dyspepsia (10.5%), abdominal pain (10.5%)], rash (13.2%), and headache (10.5%).

Gastrointestinal effects may occur after starting Xolremdi; these reactions usually resolve within the first 3 months even if Xolremdi is continued.

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials with mavorixafor are listed below in Table 4. These included two clinical trials in which 38 patients with WHIM syndrome were treated with mavorixafor.

The adverse reactions are listed in Table 4 according to MedDRA system organ class and frequency. The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data).

Table 4: Adverse reactions

System organ class	Adverse reaction	Frequency
Nervous system disorders	Headache	Very common
	Dizziness	Common
	Syncope	Common
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common

System organ class	Adverse reaction	Frequency
Gastrointestinal disorders	Nausea	Very common
	Diarrhoea	Very common
	Dyspepsia	Very common
	Abdominal pain	Very common
	Vomiting	Very common
Skin and subcutaneous tissue disorders	Rash*	Very common
	Dry skin	Common
	Psoriasiform dermatitis	Common

*the following grouping contain the following MedDRA preferred terms:
Rash: rash macular, rash pruritic, rash papular

Paediatric population

In the pivotal Phase 3 study X4P-001-103, 7 of 14 patients treated with mavorixafor were aged between 12 to < 18 years. No patients in the Phase 2 study X4P-001-MKKA were younger than 18 years.

The safety profile in patients 12 to < 18 years of age was similar to that observed in the overall population, including adults and adolescent patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote or therapeutic intervention to enhance elimination of mavorixafor. In the event of overdose, it is recommended to stop treatment, and symptomatic supportive treatment be initiated as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Other immunostimulants, ATC code: L03AX24

Mechanism of action

Mavorixafor is a CXC Chemokine Receptor 4 (CXCR4) antagonist that blocks the binding of the CXCR4 ligand, stromal-derived factor-1α (SDF-1α)/CXC Chemokine Ligand 12 (CXCL12). SDF-1/CXCR4 plays a role in trafficking and homing of leukocytes to and from the bone marrow compartment. Gain of function mutations in the CXCR4 receptor gene that occur in patients with WHIM syndrome lead to increased responsiveness to CXCL12 and retention of leukocytes in the bone marrow. Mavorixafor inhibits the response to CXCL12 in both wild-type and mutated CXCR4 variants associated with WHIM syndrome. Treatment with mavorixafor results in increased mobilisation of neutrophils and lymphocytes and monocytes from the bone marrow into peripheral circulation.

Pharmacodynamic effects

Absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) peaked at 4 hours after Xolremdi dosing and returned towards baseline within 24 h after dosing. Over mavorixafor doses of 50 mg (0.125 times the maximum recommended dose) to 400 mg once daily, higher mavorixafor exposure at steady state was associated with longer mean time (hours) above ANC threshold (TAT_{ANC}) of 500 cells/μL and longer mean time (hours) above ALC threshold (TAT_{ALC}) of 1 000 cells/μL over a 24-hour period.

Cardiac electrophysiology

In a QT study, the maximum mean increase in the QTc interval was 15.6 ms (upper bound of the 90% confidence interval = 19.8 ms) after administration of Xolremdi 800 mg (2 times the maximum recommended dose) in healthy volunteers. See section 4.4.

Clinical efficacy and safety

Xolremdi was assessed in two clinical studies. Study X4P-001-103 (hereafter, study 1) was a pivotal Phase 3 randomised, double-blind, placebo-controlled, multicentre clinical study in adult and adolescent (aged 12 years and older) patients with WHIM syndrome. Study X4P-001-MKKA (hereafter, study 2) was a supportive open-label Phase 2 study in adult patients with WHIM syndrome.

Phase 3 study (pivotal)
The efficacy of Xolremdi in adult and adolescent patients aged 12 to < 18 years with WHIM syndrome was evaluated in the 52-week, randomised, double-blind, placebo-controlled period of study 1. All enrolled patients had a genotype-confirmed variant of CXCR4 consistent with WHIM syndrome, and a confirmed ANC ≤ 400 cells/μL. Mavorixafor 400 mg was administered orally once daily to adults and adolescents weighing > 50 kg and 200 mg once daily to adolescents weighing ≤ 50 kg. Patients were permitted to continue (but not initiate) immunoglobulin therapy at the same dose. Use of other CXCR4 antagonists or granulocyte-colony stimulating factor (G-CSF) was not permitted.

Thirty-one patients were randomised 1:1 to receive either placebo (n=17) or mavorixafor (n=14) once daily for 52 weeks. Baseline patient demographics and disease characteristics are shown in Table 5.

Table 5: Baseline demographic and baseline characteristics in patients with WHIM syndrome (study 1)

Demographics and disease characteristics	Xolremdi (N = 14)	Placebo (N = 17)
Demographics		
Age (years) mean (SD)	22.1 (12.20)	30.9 (21.25)
Age group, n (%)	-	-
12 to < 18 years	7 (50.0)	8 (47.1)
≥ 18 years	7 (50.0)	9 (52.9)
Sex, n (%)	-	-
Male	5 (35.7)	8 (47.1)
Female	9 (64.3)	9 (52.9)
Race, n (%)	-	-
White	13 (93)	16 (94)
Asian	0	1 (6)
Other	1 (7)	0

Demographics and disease characteristics	Xolremdi (N = 14)	Placebo (N = 17)
Disease characteristics		
Baseline Ig use, n (%)	-	-
Yes	6 (42.9)	8 (47.1)
Baseline mean absolute neutrophil count (ANC) (cells/µL) mean (SD)	155 (93.8)	281 (232.7)
Baseline mean absolute lymphocyte count (ALC) (cells/µL) mean (SD)	501 (204.8)	563 (199.1)

Abbreviations: SD = standard deviation; Ig = immunoglobulin.
Note: Percentages are calculated based on the number of patients within each characteristic as denominator.

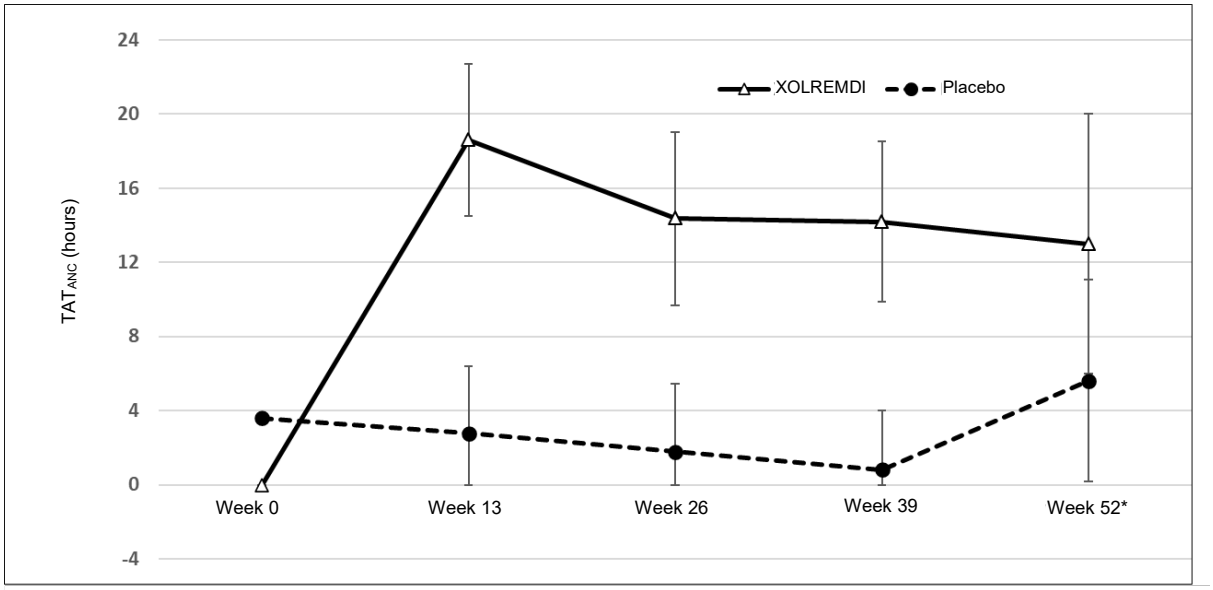
The primary efficacy endpoint was improvement in ANC as measured by the mean time (hours) above ANC threshold (TAT_{ANC}) of 500 cells/µL which was assessed over a 24-hour period 4 times throughout the study (every 3 months for 12 months). Over the 52-week period, TAT_{ANC} was statistically significantly greater in patients treated with mavorixafor compared with placebo. See Table 6 and Figure 1.

Table 6: Mean time (hours) above ANC threshold (TAT_{ANC}) in study 1

		Xolremdi (n = 14)	Placebo (n = 17)
TAT_{ANC} (hours)			
Baseline	Mean (SD)	0.0 (0.0)	3.6 (5.7)
Overall MMRM results	LS mean (SE)	15.0 (1.89)	2.8 (1.52)
	LS mean 95% CI	(11.2, 18.9)	(0.0, 5.9)
	Difference from placebo:		
	LS mean difference (SE)	12.30 (2.5)	-
	LS mean difference 95% CI	(7.2, 17.4)	-
	P-value[1]	< 0.0001	-

Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; LS = least squares; MMRM = mixed-model repeated measures; SD = standard deviation; SE = standard error; TAT = time above threshold of 500 cells/µL.
[1] The results are based on an MMRM analysis with time above threshold as a dependent variable; treatment, visit (weeks 13, 26, 39 and 52), treatment × visit, Ig use (randomisation strata), and baseline time above threshold as covariates; and patient as the repeated random effect.

Figure 1: TAT_{ANC} over time (hours) (LS Mean ± 95% CI) by treatment Group (study 1)



Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; LS = least squares; TAT = total time (hours) above threshold (500 cells/µL) in 24 hours.
*At week 52, 3 of 17 placebo patients were given mavorixafor in advance of their TAT measurement as they entered the open-label period of the study; one mavorixafor patient did not take mavorixafor. All data were included in the ITT analysis.

The key secondary efficacy endpoint was improvement in ALC as measured by the mean time (hours) above ALC threshold (TAT_{ALC}) of 1 000 cells/µL over a 24-hour period. Over the 52-week period, TAT_{ALC} was statistically significantly greater in patients treated with mavorixafor compared with placebo. See Table 7.

Table 7: Mean time (hours) above ALC threshold (TAT_{ALC}) in study 1

		Xolremdi (n = 14)	**Placebo (n = 17)**
TAT_{ALC} (hours)			
Baseline	Mean (SD)	2.2 (5.07)	2.8 (5.86)
Overall MMRM results	LS mean (SE)	15.8 (1.39)	4.6 (1.15)
	LS mean 95% CI	(13.0, 18.7)	(2.2, 6.9)
	Difference from placebo:		
	LS mean difference (SE)	11.3 (1.80)	-
	LS mean difference 95% CI	(7.5, 15.0)	-
	P-value[1]	< 0.0001	-

Abbreviations: ALC = absolute lymphocyte count; CI = confidence interval; LS = least squares; MMRM = mixed-model repeated measures; SD = standard deviation; SE = standard error; TAT = time above threshold of 1 000 cells/µL.
[1] The results are based on an MMRM analysis with time above threshold as a dependent variable; treatment, visit (weeks 13, 26, 39 and 52), treatment × visit, Ig use (randomisation strata), and baseline time above threshold as covariates; and patient as the repeated random effect.

The efficacy of mavorixafor was further assessed on total infection score and total wart change score. Across the 52-week treatment period, the severity-weighted total infection score was numerically lower in mavorixafor-treated patients [LS mean (SE) 7.41 (2.805)] compared with placebo-treated patients [LS mean (SE) 12.27 (2.443)] with a mean difference of -4.85 [95% CI (-12.57, 2.86)]. Similarly, the annualised infection rate was numerically lower in mavorixafor-treated patients [LS mean (SE) 1.7 (0.5)] compared with placebo-treated patients [LS mean (SE) 4.2 (0.7)] with a rate ratio

of 0.417 [95% CI (0.220, 0.789)]. There was no difference in total wart change scores between the mavorixafor and placebo treatment arms over the 52-week period.

Phase 2 study (supportive)
In an open-label Phase 2 (study 2) in 8 adult patients with WHIM syndrome, the pharmacodynamics of mavorixafor over the dose range 50 to 400 mg administered orally once daily, were evaluated. Doses of 300 to 400 mg achieved sustained increases in ANC ≥ 600 cells/µL and ALC ≥ 1 000 cells/µL.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xolremdi in one or more subsets of the paediatric population for the treatment of WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome (see section 4.2 for information on paediatric use).

Other information

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Mavorixafor pharmacokinetic parameters are presented as geometric mean (CV%) in adults with WHIM syndrome unless otherwise specified. Mavorixafor steady state C_{max} is 3 304 (58.6%) ng/mL and the AUC from 0 to 24 hours (AUC_{0-24h}) is 13 970 (58.4%) ng×h/mL following 400 mg once daily.

Absorption

Mavorixafor median (range) time to C_{max} (t_{max}) is 2.8 hours (1.9 to 4 hours) at the highest approved recommended dose.

Effect of food
High fat meal: Mavorixafor C_{max} decreased by 66% and AUC decreased by 55% following single-dose administration of Xolremdi 400 mg with a high-fat meal (1 000 calories, 50% fat) to healthy subjects.

Low fat meal: Mavorixafor C_{max} decreased by 55% and AUC decreased by 51% following single-dose administration of Xolremdi 400 mg with a low-fat meal (500 calories, 25% fat) to healthy subjects. In addition, a 14% higher mavorixafor C_{max} and 18% lower AUC was observed following single-dose administration of Xolremdi 400 mg with a low-fat meal to healthy subjects after an overnight fast compared to fasting for an additional 4 hours after the Xolremdi dose (see section 4.2).

Distribution

Mavorixafor volume of distribution is 120 L/kg. Mavorixafor is > 93% bound to human plasma proteins *in vitro*.

Biotransformation

CYP3A4 and, to a lesser extent, CYP2D6 are primarily responsible for mavorixafor metabolism.

Elimination

Mavorixafor's terminal half-life was 82 h with an apparent clearance of 62 L/h following single-dose administration of Xolremdi 400 mg in healthy subjects. Mavorixafor exhibits at least partial nonlinear apparent clearance; however, this is not clinically significant at the approved recommended dose.

After a single oral dose of radiolabelled mavorixafor, 74.2% of the administered dose was recovered out of which 61.0% of administered radioactivity was recovered in faeces and 13.2% (3% unchanged) was recovered in the urine over the 240-hour collection period in healthy subjects.

Linearity/non-linearity

Mavorixafor demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in C_{max} and AUC_{0-24h} over a dose range of 50 mg (0.125 times the recommended dose) to 400 mg. Mavorixafor steady state is reached after approximately 9 to 12 days in healthy subjects at the highest approved recommended dose.

Pharmacokinetic/pharmacodynamic relationship(s)

In study 2, mean ANC levels for doses 50 to 200 mg generally remained below the clinical benefit threshold of 500 cells/μL during the 24-hour dosing interval. For 300 mg and 400 mg, mean ANC levels rose above the threshold by approximately 1 hour post-dose and remained above or at the threshold over the entire dosing interval. A mavorixafor dose of 300/400 mg QD was required to achieve $AUC_{ANC} \geq 600$/μL and $AUC_{ALC} \geq 1\ 000$/μL.

Drug interaction studies

For information regarding drug interactions with other medicinal products please refer to section 4.5.

Other medicinal products: No clinically significant differences in the pharmacokinetics of caffeine (CYP1A2 substrate), losartan (CYP2C9 substrate), omeprazole (CYP2C19 substrate), furosemide (OAT1 and OAT3 substrate) and oral contraceptives were observed following concomitant use with mavorixafor.

Special populations

Hepatic impairment
Mavorixafor is metabolised by the liver. The effect of moderate to severe hepatic impairment on the pharmacokinetics of mavorixafor has not been studied (see section 4.2).

Renal impairment
Renal clearance is a minor excretion pathway for mavorixafor.
No clinically significant differences in the pharmacokinetics of mavorixafor were observed in mild to moderate renal impairment (CLcr 30 to less than 90 mL/min). The pharmacokinetics of mavorixafor have not been studied in subjects with severe renal impairment or end-stage renal disease (see section 4.2).

Elderly
In clinical studies of Xolremdi in patients with WHIM syndrome, 2 (5%) patients were aged 65 years and older, and no patients were aged 75 years and older. Clinical studies did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

Race/Ethnicity
The effect of race/ethnicity on mavorixafor systemic exposure is unknown.

Gender
The effect of gender on mavorixafor systemic exposure is unknown.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels comparable to clinical exposure levels and with possible relevance to clinical use were as follows: testicular toxicity, hepatotoxicity, retinal degeneration and atrophy.

Genotoxicity

Mavorixafor was not genotoxic in an *in vitro* bacterial reverse mutation assay (Ames test), in an *in vitro* human lymphocyte culture chromosome aberration assay, or in an *in vivo* rat bone marrow micronucleus assay.

Reproductive toxicity

Animal reproduction studies have not been conducted with mavorixafor to evaluate effects on reproduction and embryo-foetal development. CXCR4/SDF-1 signalling plays an important role in mammalian embryo-foetal and placental development. In mice, CXCR4-/- knockout is embryo lethal and causes multiple developmental toxicities, most notably in the hematopoietic, cardiovascular and nervous systems. CXCR4/SDF-1 levels also have a key role in stimulating trophoblast proliferation and differentiation necessary for appropriate placental growth and function in humans. Based on its mechanism of action, Xolremdi may cause foetal harm when administered to a pregnant woman.

The effect of mavorixafor on male or female fertility was not studied in designated reproductive toxicology studies.

In a 39-week study with initiation of treatment in young prepubertal dogs, testicular changes of seminiferous tubule degeneration/atrophy including spermatogonial stem cell depletion were observed at exposure levels equivalent to the human exposure at MRHD; similar changes were not observed in a 13-week dog study in sexually mature male dogs and in a 26-week dog study in juvenile dogs covering the period of puberty. The mechanism by which mavorixafor may exert this effect is unknown, but a relation to pharmacological action of mavorixafor cannot be excluded.
There are no data on the recovery of this effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Silica, colloidal anhydrous (E551)
Croscarmellose sodium (E468)
Calcium hydrogen phosphate dihydrate (E3431(ii))
Cellulose, microcrystalline (E460(i))
Sodium laurilsulfate
Sodium stearyl fumarate

Capsule shell

Indigotine (E132)
Gelatine (E441)
Titanium dioxide (E171)

Printing ink

Ammonia solution, concentrated (E527)
Black iron oxide (E172)
Isopropyl alcohol
n-butyl alcohol,
Propylene glycol (E1520)
Shellac glaze in ethanol (E904)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening the bottle: 45 days.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene round white bottle with 38 mm child-resistant screw cap with label. Each bottle contains one desiccant positioned between the rayon coil and cap.

Pack sizes of 60, 90 or 120 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

X4 Pharmaceuticals (Austria) GmbH
Hohenstaufengasse 9/DG
1010 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2017/001
EU/1/26/2017/002
EU/1/26/2017/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Catalent Germany Schorndorf GmbH
Steinbeisstrasse 1 - 2
73614 Schorndorf
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Xolremdi in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reducing the potential risk of embryo-foetal toxicity associated with Xolremdi.

The MAH shall ensure that in each member state where Xolremdi is marketed, all healthcare professionals who are expected to prescribe Xolremdi have access to/are provided with the following educational package:
- Physician educational materials

The MAH shall ensure that in each Member State where Xolremdi is marketed, all patients/carers who are expected to use Xolremdi are provided with the following educational package:

- Patient card

Physician educational material:

- Summary of Product Characteristics
- Guide for healthcare professionals

- **Guide for Healthcare Professionals**
  - Xolremdi may cause embryo-foetal harm when administered to a pregnant woman.
  - Xolremdi is contraindicated in pregnant women.
  - The pregnancy status of female patients of childbearing potential who are engaging in activities of reproductive potential should be verified prior to starting Xolremdi.
  - Female patients of childbearing potential must avoid becoming pregnant by using an effective method of contraception (e.g. double-barrier contraception) during treatment with Xolremdi and for three weeks after the final dose.
  - Male patients with female partners of childbearing potential should use condoms during sexual intercourse while taking Xolremdi and for at least three weeks after stopping treatment.
  - Treatment with Xolremdi should be discontinued if a patient is planning to become pregnant or has become pregnant.
  - A patient card is included in the product package and the healthcare professional should inform each female patient of childbearing potential, and each male patient with female partners of childbearing potential, prior to initiation of treatment, about the purpose and importance of the card.
  - Appropriate actions should be taken if a pregnancy is detected and the patient should receive appropriate counselling on possible actions by a specialist.

The patient information pack:

- Package leaflet
- Patient card

- **Patient card**:
  - Warning not to take Xolremdi if pregnant. Xolremdi poses a potential risk to your unborn child.
  - Instruction to use highly effective contraception methods (e.g. double-barrier contraception) for women of childbearing potential during treatment with Xolremdi and for three weeks after the last dose.
  - Instruction for male patients to use effective contraception when having sexual intercourse with a female partner of childbearing potential during treatment with Xolremdi and for three weeks after the last dose.
  - Instruction to contact relevant healthcare professional immediately if pregnancy is suspected.
  - Instruction to read the package leaflet for further information and guidance.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to investigate the long-term safety and efficacy of mavorixafor in the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes in patients 12 years of age and older, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.	Annually (within annual reassessment)
In order to ensure adequate monitoring of safety and efficacy of mavorixafor 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, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of mavorixafor.	Annually (within annual reassessment)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xolremdi 100 mg hard capsules
mavorixafor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg mavorixafor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

60 hard capsules
90 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, use within 45 days.
Open date:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

X4 Pharmaceuticals (Austria) GmbH
Hohenstaufengasse 9/DG
1010 Vienna, Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2017/001 60 hard capsules
EU/1/26/2017/002 90 hard capsules
EU/1/26/2017/003 120 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolremdi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Xolremdi 100 mg hard capsules
mavorixafor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg of mavorixafor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

60 hard capsules
90 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, use within 45 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

X4 Pharmaceuticals (Austria) GmbH

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2017/001 60 hard capsules
EU/1/26/2017/002 90 hard capsules
EU/1/26/2017/003 120 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON PATIENT CARD

Patient card for Xolremdi (mavorixafor)

PREGNANCY AND CONTRACEPTION

This card has important information about Xolremdi.

- Do not take Xolremdi if you are pregnant or think you might be pregnant, as it could harm your unborn baby.
- If you can become pregnant, you must use a highly effective contraception (e.g. double barrier) while taking Xolremdi and for three weeks after your last dose.
- If you are a male patient and your partner can become pregnant, you must use a condom while taking Xolremdi and for three weeks after your last dose.
- If you or your partner think there may be a pregnancy, contact your doctor immediately.

Please also read the package leaflet carefully as it contains important information.
If you have any questions about Xolremdi, talk to your doctor.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xolremdi 100 mg hard capsules
mavorixafor

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- Inside the pack you will find a patient card which you should read carefully.

What is in this leaflet

1. What Xolremdi is and what it is used for

Xolremdi contains the active substance mavorixafor. Mavorixafor belongs to a group of medicines known as other immunostimulants.

Xolremdi is used to treat WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) in patients aged 12 years and older.
Hypogammaglobulinemia is a condition in which the level of antibodies is low. Myelokathexis is a condition in which the body fails to release mature blood cells from the bone marrow.

WHIM syndrome is an inherited disorder caused by mutations (changes) in a person's genes that affect the immune system, making it harder for the body to fight infections. Xolremdi is used in patients with WHIM syndrome caused by a change in the *CXCR4* gene.

The active substance in Xolremdi, mavorixafor, works by increasing the movement of immune cells from the bone marrow to the blood. The increased number of immune cells in the blood decreases the risk of infection in patients with WHIM syndrome.

2. What you need to know before you take Xolremdi

Do not take Xolremdi
- if you are allergic to mavorixafor or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant.

- if you are taking any medicines which are broken down in the body by a liver enzyme (protein) known as CYP2D6, such as medicines to:
    - relieve cough (such as codeine, dextromethorphan);
    - treat pain (such as codeine, tramadol).

Warnings and precautions
Talk to your doctor or pharmacist before taking Xolremdi, if
- you are pregnant, think you may be pregnant or are planning to have a baby.
- you have risk factors for QTc prolongation (abnormal electrical activity of the heart that affects its rhythm) such as:
    - hypokalaemia (low blood potassium levels),
    - congestive heart failure (when the heart does not pump blood as well as it should)
    - long QT syndrome (a heart rhythm that causes fast, chaotic heartbeats), or take medicines that can cause QTc prolongation or that increase the levels of Xolremdi in the blood (see "Other medicines and Xolremdi").

This can increase the risk of serious side effects affecting the electrical activity of the heart such as Torsades de Pointes (abnormal electrical activity in the heart with life-threatening rhythm disturbance), serious arrhythmias (abnormal or irregular heartbeat) and sudden death. In this case, your doctor will correct any modifiable risk factor for QTc prolongation and will check the electrical activity of your heart before and during treatment with Xolremdi and may decide to give you a lower dose or advise that you should not take Xolremdi.

Children and adolescents
Do not give this medicine to children below the age of 12 years. It has not been studied in these patients.

Do not give this medicine to children between the ages of 2 and 11 years, because it is not known if it is safe. Do not give this medicine to children under 2 years of age as it may cause developmental defects.

Other medicines and Xolremdi
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines and supplements **should not be taken together with Xolremdi** as they may reduce the effectiveness of Xolremdi by decreasing the amount of Xolremdi in the blood. Tell your doctor or pharmacist before you take Xolremdi if you are taking any of the following medicines to:
- treat anxiety and depression (**St. John's wort**);
- treat cancer (such as **apalutamine, enzalutamide, mitotane**);
- treat seizures and other conditions (such as **carbamazepine, phenytoin, phenobarbital**);
- treat infections (**rifampicin**, only when used for ≥ 5 days).

The following medicines may increase the risk of side effects with Xolremdi by increasing the amount of Xolremdi in the blood:
- medicines used to treat fungal infections (such as **fluconazole, itraconazole, ketoconazole**);
- antibiotics used to treat bacterial infections (such as **clarithromycin, erythromycin**);
- medicines used to treat depression (such as **nefazodone**);
- medicines used to treat heart conditions (such as **amiodarone, diltiazem, verapamil**).

Xolremdi may increase the side effects of the following medicines by increasing the amount of these medicines in the blood:
- medicines used to relieve allergies (such as **fexofenadine**);
- medicines used to treat blood conditions (such as **dabigatran etexilate**, **edoxaban**);
- medicines to treat viral infections (such as **telaprevir**);
- medicines used to treat HIV infection and AIDS (such as **atazanavir**);
- medicines to treat cancer (such as **ribociclib, ceritinib, everolimus**);

- antibiotics used to treat bacterial infections (such as **telithromycin**);
- medicines to treat anxiety or sleep disorders (such as **midazolam, alprazolam**);
- a medicine used to treat a heart condition (**digoxin**).

Xolremdi may reduce the effectiveness of the following medicine by decreasing the amount of this in the blood:
- **metformin**, a medicine used to treat diabetes.

The following medicines can increase the risk of serious side effects affecting the electrical activity of the heart when taken with Xolremdi:
- medicines used to treat irregular heartbeat (such as **amiodarone, disopyramide, procainamide**).
- other medicines that affect the electrical activity of the heart (such as **chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron**).

If you are taking any of the medicines listed above, inform your doctor or pharmacist before taking Xolremdi.

Xolremdi with food and drink
You should avoid eating or drinking products with grapefruit, as grapefruit may increase the risk of side effects from Xolremdi.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Do not take this medicine if you are pregnant as it is expected to be harmful to an unborn baby. You should have a negative pregnancy test before starting treatment.

There is little or no data on its use during pregnancy. Based on how it works, this medicine could harm your unborn baby.

Female and male contraception

Inside your pack of Xolremdi you will find a patient card which you should read carefully.

If you are a woman who can become pregnant, you must use highly effective birth control (e.g., double-barrier contraception (birth control) such as condom and diaphragm) during treatment with Xolremdi and for three weeks after the last dose. Your doctor can advise you on suitable methods of contraception. If you do become pregnant during treatment, tell your doctor right away.

If you are a man, you must use a condom when having sexual intercourse with a female partner who is able to become pregnant while you are taking Xolremdi and for three weeks after the last dose. You must tell your doctor if your female partner becomes pregnant.

Breast-feeding

Xolremdi has not been studied in breast-feeding women. It is not known whether Xolremdi passes into breast milk. A risk to the baby cannot be excluded.

If you are breast-feeding or planning to breast-feed, ask your doctor for advice before taking this medicine. Your doctor will discuss the potential risk(s) of treatment with Xolremdi whilst you are breast-feeding.

Fertility

There is no human data on the effect of Xolremdi on male or female fertility. Based on animal studies, Xolremdi may reduce fertility in men. You should discuss with your doctor before starting treatment.

Driving and using machines
Xolremdi could have an effect on your ability to drive and use machines. If you experience dizziness or fainting, do not drive or use machines until you feel better.

Xolremdi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

3. How to take Xolremdi

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Xolremdi is:
- For patients weighing **more than 50 kg**: 400 mg (four 100 mg capsules) taken by mouth, at least 30 minutes before breakfast on an empty stomach after an overnight fast.
- For patients weighing **less than or equal to 50 kg**: 300 mg (three 100 mg capsules) taken by mouth, at least 30 minutes before breakfast on an empty stomach after an overnight fast.

Your doctor may tell you to take a lower dose if you are taking other medicines which may cause serious side effects when taken together with Xolremdi.

Xolremdi capsules should be swallowed whole and not opened, broken or chewed.

Use in children and adolescents
Xolremdi is intended for use in patients aged 12 years and older.

Do not give this medicine to children between the ages of 2 and 11 years, because it is not known if it is safe.

Do not give this medicine to children under 2 years of age as it may cause developmental defects.

If you take more Xolremdi than you should
If you have accidentally taken more Xolremdi than you should, stop taking this medicine and tell your doctor straight away.

If you forget to take Xolremdi
If you forget to take this medicine in the morning, skip the dose for the day and take your next dose the following morning as scheduled. Do not take a double dose to make up for a forgotten dose.

If you stop taking Xolremdi
Your doctor should determine how long you should take Xolremdi, and when treatment may be stopped. Do not stop taking your medicine until your doctor advises you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people)
- Feeling sick (nausea)
- Belly (abdominal) pain
- Indigestion (dyspepsia)
- Diarrhoea
- Vomiting
- Headache
- Rash, including a rash with small, flat, discolored patches (rash macular), itchy rash (rash pruritic) and a rash with small, raised bumps (rash papular)

Common (may affect up to 1 in 10 people)
- Dizziness
- Fainting (syncope)
- Nose bleeding (epistaxis)
- Dry skin
- Red, scaly patches on the skin, accompanied by itching and discomfort (psoriasiform dermatitis)

Reporting of side effects
If you get any side effects, talk to your doctor or, pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Xolremdi

Keep this medicine out of the sight and reach of children.

Store in a refrigerator (2 °C – 8 °C).
Keep the bottle tightly closed in order to protect from moisture.

Do not use this medicine after the expiry date which is stated on the bottle and carton after EXP. The expiry date refers to the last day of that month.

After the first opening of the bottle, the medicine should be used within 45 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xolremdi contains
- The active substance is mavorixafor. Each hard capsule contains 100 mg of mavorixafor.
- The other ingredients are:
  Capsule content: silica, colloidal anhydrous (E551), croscarmellose sodium (E468), calcium hydrogen phosphate dihydrate (E3431 (ii)), cellulose, microcrystalline (E460(i)), sodium lauril sulfate, and sodium stearyl fumarate. See section 2 “Xolremdi contains sodium”.
  Capsule shell: indigotine (E132), gelatine (E441) and titanium dioxide (E171).
  Printing ink: ammonia solution, concentrated (E527), black iron oxide (E172), isopropyl alcohol, n-butyl alcohol, propylene glycol (E1520) and shellac glaze in ethanol (E904).

What Xolremdi looks like and contents of the pack
Xolremdi 100 mg is supplied as an opaque white, hard capsule (capsule) with a light blue cap. The white capsule body is printed with “100 mg” in black ink, and the light blue capsule cap is printed with “MX4” in black ink.

Xolremdi is packaged in a high-density polyethylene round white bottle with child-resistant screw cap with integrated desiccant and label. The bottle contains 60, 90 or 120 hard capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
X4 Pharmaceuticals (Austria) GmbH
Hohenstaufengasse 9/DG
1010 Vienna
Austria

Manufacturer
Catalent Germany Schorndorf GmbH
Steinbeisstrasse 1 - 2
73614 Schorndorf
Germany

This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.