Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xonvea 10 mg/10 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

Excipient(s) with known effect
Each tablet contains trace amounts of azo colouring agent E129

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet (tablet)

White, round, film-coated tablet with a pink image of a pregnant woman on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Xonvea is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

4.2 Posology and method of administration

Posology
The recommended starting dose is two tablets at bedtime (Day 1). If this dose adequately controls symptoms the next day, the patient can continue taking two tablets at bedtime. However, if symptoms persist into the afternoon of Day 2, the patient should continue the usual dose of two tablets at bedtime (Day 2) and on Day 3 take three tablets (one tablet in the morning and two tablets at bedtime). If these three tablets do not adequately control symptoms on Day 3, the patient can take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime).
The maximum recommended daily dose is four tablets (one in the morning, one in the mid-afternoon and two at bedtime).
Xonvea should be taken as a daily prescription and not on an as needed basis. Continued need for Xonvea should be reassessed as the pregnancy progresses.
To prevent a sudden return of nausea and vomiting of pregnancy symptoms, a gradual tapering dose of Xonvea is recommended at the time of discontinuation.

Paediatric population
Xonvea is not indicated for use in children under 18 years of age. The safety and efficacy of Xonvea has not been established in that population (see section 5.1). No data are available.

Method of administration
Xonvea should be administered on an empty stomach with a glass of water (see section 4.5). The tablets should be swallowed whole and should not be crushed, split or chewed.

4.3 Contraindications

Hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any of the excipients listed in section 6.1.

Concomitant use with monoamine oxidase inhibitors (MAOIs) (see section 4.5).

4.4 Special warnings and precautions for use

Xonvea may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine (see section 4.8).

Use of Xonvea is not recommended if a woman is concurrently using central nervous system (CNS) depressants including alcohol (see section 4.5).

Xonvea has anticholinergic properties and, therefore, should be used with caution in patients with: asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction.

Xonvea contains pyridoxine hydrochloride, a vitamin B6 analog, therefore additional levels from diet and vitamin B6 supplements should be assessed.

Xonvea contains traces of the azo colouring agent Allura Red AC Aluminum Lake (E129) which may cause allergic reactions.

There is limited evidence in cases of hyperemesis gravidarum for the combination doxylamine/pyridoxine. These patients should be treated by a specialist.

There have been reports of false positive urine screening tests for methadone, opiates and phencyclidine phosphate (PCP) with doxylamine succinate/pyridoxine hydrochloride use (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interactions

Monoamine oxidase inhibitors
Monoamine oxidase inhibitors (MAOIs) prolong and intensify the anticholinergic effects of antihistamines.

Central nervous system depressants
Concurrent use with central nervous system (CNS) depressants including alcohol, hypnotic sedatives and tranquilizers is not recommended. The combination may result in severe drowsiness.

Food
A food-effect study has demonstrated that the delay in the onset of action of Xonvea may be further delayed, and a reduction in absorption may occur when tablets are taken with food. Therefore, Xonvea should be taken on an empty stomach with a glass of water (see section 4.2).

Interference with Urine Screen for Methadone, Opiates and PCP
False positive urine drug screens for methadone, opiates, and PCP can occur with doxylamine succinate/pyridoxine hydrochloride use. Confirmatory tests, such as Gas Chromatography Mass Spectrometry (GC-MS), should be used to confirm the identity of the substance in the event of a positive immunoassay result.

4.6 Fertility, pregnancy and lactation

Pregnancy
Xonvea is intended for use in pregnant women.
A large amount of data on pregnant women indicates no malformative nor feto/neonatal toxicity of doxylamine succinate and pyridoxine hydrochloride.

Breast-feeding
The molecular weight of doxylamine succinate is low enough that passage into breast milk can be expected. Excitement, irritability and sedation have been reported in nursing infants presumably exposed to doxylamine succinate through breast milk. Infants with apnoea or other respiratory syndromes may be particularly vulnerable to the sedative effects of Xonvea resulting in worsening of their apnoea or respiratory conditions.

Pyridoxine hydrochloride is excreted into breast milk. There have been no reports of adverse events in infants presumably exposed to pyridoxine hydrochloride through breast milk.
A risk to breastfed infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Xonvea therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Xonvea caused no impairment of fertility or reproductive performance in rats (see section 5.3). No human data available.

4.7 Effects on ability to drive and use machines

Xonvea has a moderate to major influence on the ability to drive and use machines. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using Xonvea until cleared to do so by their healthcare provider.

4.8 Undesirable effects

a. Summary of the safety profile
Adverse event information is derived from clinical trials and worldwide post-marketing experience.

There has been a vast clinical experience regarding the use of the Xonvea combination (doxylamine succinate and pyridoxine hydrochloride). In a double-blind, randomised, placebo-controlled trial of 15 days duration, 261 women with nausea and vomiting of pregnancy were included of which 128 were treated with placebo and 133 with doxylamine succinate/pyridoxine hydrochloride. The mean gestational age at enrolment was 9.3 weeks; gestation range was from 7 to 14 weeks. The incidence of treatment-emergent adverse events was similar for both treatment and placebo groups. The most frequently reported adverse reaction (≥5% and exceeding the rate in placebo) was somnolence.

b. Tabulated list of adverse reactions
The following listing of adverse reactions is based on clinical trial experience and/or post-marketing use.

Undesirable effects are displayed by MedDRA System Organ Classes and use the following conventions for frequency: 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); not known (cannot be estimated from the available data).

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

System Organ Class	**Undesirable Effect**	**Frequency**
Immune system disorders	**hypersensitivity**	**Not known**
Psychiatric disorders	**anxiety, disorientation, insomnia, nightmares**	**Not known**
Nervous system disorders	**somnolence**	**Very common**
	dizziness	**Common**
	headache, migraines, paresthesia, psychomotor hyperactivity	**Not known**
Eye disorders	**vision blurred, visual disturbances**	**Not known**
Ear and labyrinth disorders	**vertigo**	**Not known**
Cardiac disorders	**dyspnea, palpitation, tachycardia**	**Not known**
Gastrointestinal disorders	**dry mouth**	**Common**
	abdominal distention, abdominal pain, constipation, diarrhoea	**Not known**
Skin and subcutaneous tissue disorders	**hyperhidrosis, pruritus, rash, rash maculo-papular**	**Not known**
Renal and urinary disorders	**dysuria, urinary retention**	**Not known**
General disorders and administration site conditions	**fatigue**	**Common**
	chest discomfort, irritability, malaise	**Not known**

c. Description of selected adverse reactions
Severe drowsiness may occur if Xonvea is taken along with CNS depressants including alcohol (see sections 4.4 and 4.5).

Anticholinergic effects of Xonvea may be prolonged and intensified by monoamine oxidase inhibitors (MAOIs) (see sections 4.3 and 4.5).

Possible adverse anticholinergic effects associated with the use of antihistamines as a class in general include: dryness of mouth, nose and throat; dysuria; urinary retention; vertigo, visual disturbances, blurred vision, diplopia, tinnitus; acute labyrinthitis; insomnia; tremors, nervousness; irritability; and facial dyskinesia. Tightness of chest, thickening of bronchial secretions, wheezing, nasal stuffiness, sweating, chills, early menses, toxic psychosis, headache, faintness and paresthesia have occurred.

Rarely, agranulocytosis, haemolytic anaemia, leukopenia, thrombocytopenia, and pancytopenia have been reported in a few patients receiving some antihistamines. Increased appetite and/or weight gain also occurred in patients receiving antihistamines.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie Email: medsafety@hpra.ie.

4.9 Overdose

Xonvea is a delayed-release formulation; therefore, signs and symptoms may not be apparent immediately.

Symptoms
Signs and symptoms of overdosage may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia.
At toxic doses, doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis, acute renal failure and death.

Management
In the event of an overdose, treatment consists of gastric lavage or activated charcoal, whole bowel irrigation and symptomatic treatment. Management should be in accordance with established treatment guidelines.

Paediatric population
Fatalities have been reported from doxylamine overdose in children. The overdose cases have been characterized by coma, grand mal seizures and cardiorespiratory arrest. Children appear to be at a high risk for cardiorespiratory arrest. A toxic dose for children of more than 1.8 mg/kg has been reported. A 3 year old child died 18 hours after ingesting 1,000 mg doxylamine succinate. However, there is no correlation between the amount of doxylamine ingested, the doxylamine plasma level and clinical symptomatology.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: aminoalkyl ethers, ATC code: R06AA59
Mechanism of action
Xonvea provides the action of two unrelated compounds. Doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6) provide anti-nauseant and antiemetic activity.

Doxylamine succinate, an ethanolamine, first-generation antihistamine crosses the blood-brain barrier and exerts an antiemetic action by selectively binding to H1 receptors in the brain.

Pyridoxine hydrochloride, a water-soluble vitamin, is converted to pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate. Although pyridoxal 5'-phosphate is the main active antiemetic metabolite, the other metabolites also contribute to the biological activity.

The mechanism of action of the combination of doxylamine succinate and pyridoxine hydrochloride to treat nausea and vomiting of pregnancy has not been established.

Clinical efficacy and safety

The safety and efficacy of Xonvea were compared to placebo in a double-blind, randomised, multi-centre trial in 261 adult women 18 years of age or older. The mean gestational age at enrolment was 9.3 weeks, range 7 to 14 weeks gestation. Two tablets of Xonvea were administered at bedtime on Day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of Day 2, the woman was directed to her usual dose of two tablets at bedtime that night and, beginning on Day 3, to take one tablet in the morning and two tablets at bedtime. Based upon assessment of remaining symptoms at her clinic visit on Day 4 (± 1 day), the woman may have been directed to take an additional tablet mid-afternoon. A maximum of four tablets (one in the morning, one in the mid-afternoon and two at bedtime) were taken daily.

Over the treatment period, 19% of Xonvea-treated patients remained on two tablets daily, 21% three tablets daily, and 60% received four tablets daily.

The primary efficacy endpoint was the change from baseline at Day 15 in the Pregnancy Unique-Quantification of Emesis (PUQE) score. The PUQE score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe).

At baseline, the mean PUQE score was 9.0 in the Xonvea arm and 8.8 in the placebo arm. There was a 0.9 (95% confidence interval 0.2 to 1.2 with p-value 0.006) mean decrease (improvement in nausea and vomiting symptoms) from baseline in PUQE score at Day 15 with Xonvea compared to placebo (see Table 1).

Table 1 - Change from Baseline in the Primary Endpoint, Pregnancy Unique-Quantification of Emesis (PUQE) Score at Day 15*

PUQE Score**	**Doxylamine Succinate +Pyridoxine Hydrochloride**	**Placebo**	**Treatment Difference [95% Confidence Interval]**
Baseline Change from baseline at Day 15	9.0 ± 2.1 -4.8 ± 2.7	8.8 ± 2.1 -3.9 ± 2.6	-0.9 [-1.2, -0.2]

* Intent-to-Treat Population with Last-Observation Carried Forward
** The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score incorporated the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated form 3 (no symptoms) to 15 (most severe). Baseline was defined as the PUQE score completed at the enrolment visit.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Xonvea in all subsets of the paediatric population in treatment of nausea and vomiting of pregnancy (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of Xonvea has been characterised in healthy non-pregnant adult women. Pharmacokinetic results for doxylamine and pyridoxine, including its vitamin B_6 metabolites, pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate, are summarised in Tables 2 to 5.

Absorption
A single-dose (two tablets) and multiple-dose (four tablets daily), open-label study was conducted to assess the safety and pharmacokinetic profile of Xonvea administered in healthy non-pregnant adult women. Single-doses (two tablets at bedtime) were administered on Days 1 and 2. Multiple-doses (one tablet in the morning, one tablet in the afternoon and two tablets at bedtime) were administered on Days 3-18.

Blood samples for pharmacokinetic analysis were collected pre-and post-dose on Days 2 and 18 as well as pre-dose prior to bedtime dose only (trough) on Days 9, 10, 11, 16, 17 and 18.

Doxylamine and pyridoxine are absorbed in the gastrointestinal tract, mainly in the jejunum.

The C_{max} of doxylamine and pyridoxine are achieved within 7.5 and 5.5 hours, respectively (see Table 2).

Table 2 - Single-Dose and Multiple-Dose Pharmacokinetics of Xonvea in Healthy Non-Pregnant Adult Women

	Single Dose			Multiple Dose		
	AUC_{0-inf}	C_{max}	T_{max}	AUC_{0-inf}	C_{max}	T_{max}
	(ng•h/mL)	(ng/mL)	(h)	(ng•h/mL)	(ng/mL)	(h)
Doxylamine	1280.9 ± 369.3	83.3 ± 20.6	7.2 ± 1.9	3721.5 ± 1318.5	168.6 ± 38.5	7.8 ± 1.6
Pyridoxine	43.4 ± 16.5	32.6 ± 15.0	5.7 ± 1.5	64.5 ± 36.4	46.1 ± 28.3	5.6 ± 1.3
Pyridoxal	211.6 ± 46.1	74.3 ± 21.8	6.5 ± 1.4	1587.2 ± 550.0	210.0 ± 54.4	6.8 ± 1.2
Pyridoxal 5'-Phosphate	1536.4 ± 721.5	30.0 ± 10.0	11.7 ± 5.3	6099.7 ± 1383.7	84.9 ± 16.9	6.3 ± 6.6
Pyridoxamine	4.1 ± 2.7	0.5 ± 0.7	5.9 ± 2.1	2.6 ± 0.8	0.5 ± 0.2	6.6 ± 1.4
Pyridoxamine 5'-phosphate	5.2 ± 3.8	0.7 ± 0.5	14.8 ± 6.6	94.5 ± 58.0	2.3 ± 1.7	12.4 ± 11.2

Multiple-dose administration resulted in increased concentrations of doxylamine as well as increases in doxylamine C_{max} and AUC_{0-last} of absorption. The time to reach the maximum concentration is not affected by multiple doses. The mean accumulation index is more than 1.0 suggesting that doxylamine accumulates following multiple dosing (see Table 3).

Although no accumulation was observed for pyridoxine, the mean accumulation index for each metabolite (pyridoxal, pyridoxal 5'-phosphate, and pyridoxamine 5'-phosphate, and pyridoxamine 5'-phosphate) is more than 1.0 following multiple-dose administration. The time to reach the maximum concentration is not affected by multiple doses (see Table 2).

Table 3 - Pharmacokinetics of Doxylamine and Pyridoxine Following Single Dose and Multiple Dose Administration of Xonvea to Healthy Non-Pregnant Adult Women

		AUC_{0-last} (ng•h/mL)	AUC_{0-inf} (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2el}$ (h)
Doxylamine Mean±SD N=18	**Single**	911.4 ± 205.6	1280.9 ± 369.3	83.3 ± 20.6	7.2 ± 1.9	10.1 ± 2.1
	Multiple	3661.3 ± 1279.2	3721.5 ± 1318.5	168.6 ± 38.5	7.8 ± 1.6	11.9 ± 3.3
Pyridoxine Mean±SD N=18	**Single**	39.3 ± 16.5	43.4 ± 16.5	32.6 ± 15.0	5.7 ± 1.5	0.5 ± 0.2
	Multiple	59.3 ± 33.9	64.5 ± 36.4	46.1 ± 28.3	5.6 ± 1.3	0.5 ± 0.1

The administration of food delays the absorption of both doxylamine and pyridoxine. This delay is associated with a lower peak concentration of doxylamine, but extent of absorption is not affected (see Table 4).

The effect of food on the peak concentration and the extent of absorption of the pyridoxine component is more complex because the pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate metabolites also contribute to the biological activity. Food significantly reduces the bioavailability of pyridoxine and pyridoxal lowering their C_{max} and AUC by approximately 50% compared to fasting conditions. In contrast, food slightly increases pyridoxal 5'-phosphate C_{max} and extent of absorption. As for pyridoxamine and pyridoxamine 5-phosphate, the rate and extent of absorption seem to decrease under fed conditions.

Table 4 - Pharmacokinetics of Doxylamine and Pyridoxine Following Administration of Xonvea Under Fed and Fasted Conditions in Healthy Non-Pregnant Adult Women

		AUC_{0-t} (ng•h/mL)	AUC_{0-inf} (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2el}$ (h)
Doxylamine Mean±SD N=42	**Fasted**	1407.2 ± 336.9	1447.9 ± 332.2	94.9 ± 18.4	5.1 ± 3.4	12.6 ± 3.4
	Fed	1488.0 ± 463.2	1579.0 ± 422.7[a]	75.7 ± 16.6	14.9 ± 7.4	12.5 ± 2.9[a]
Pyridoxine Mean±SD N=42	**Fasted**	33.8 ± 13.7	39.5 ± 12.9[c]	35.5 ± 21.4	2.5 ± 0.9	0.4 ± 0.2[c]
	Fed	18.3 ±	24.2 ±	13.7 ±	9.3 ±	0.5 ±

		14.5	14.0 [b]	10.8	4.0	0.2 [b]

[a] N=37; [b] N=18; [c] N=31

Distribution
Pyridoxine is highly protein bound, primarily to albumin. Its main active metabolite pyridoxal 5'-phosphate (PLP) accounts for at least 60% of circulating vitamin B_6 concentrations.

Biotransformation
Doxylamine is biotransformed in the liver by N-dealkylation to its principle metabolites N-desmethyl-doxylamine and N,N-didesmethyldoxylamine.
Pyridoxine is a prodrug primarily metabolised in the liver.

Elimination
The principle metabolites of doxylamine, N-desmethyl-doxylamine and N,N-didesmethyldoxylamine, are excreted by the kidney.
The terminal elimination half-life of doxylamine and pyridoxine are 12.6 hours and 0.4 hours, respectively (see Table 5).

Table 5 - Terminal Elimination Half-Life ($T_{1/2el}$) for Xonvea Administered as a Single Dose of Two Tablets under Fasting Conditions in Healthy Non-Pregnant Adult Women

	$T_{1/2el}$ (h)
Doxylamine	12.6 ± 3.4
Pyridoxine	0.4 ± 0.2
Pyridoxal	2.1 ± 2.2
Pyridoxal 5'-Phosphate	81.6 ± 42.2
Pyridoxamine	3.1 ± 2.5
Pyridoxamine 5'-Phosphate	66.5 ± 51.3

Hepatic Impairment: No pharmacokinetic studies have been conducted in hepatic impaired patients.
Renal Impairment: No pharmacokinetic studies have been conducted in renal impaired patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on available data of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Magnesium trisilicate
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica

Coating
Hypromellose (E464)
Macrogol (400) (E1521)
Macrogol (8000) (E1521)
Methacrylic acid-ethyl acrylate copolymer (1:1)
Talc (E553b)
Colloidal anhydrous silica
Sodium bicarbonate (E500)
Sodium lauryl sulfate (E487)
Triethyl citrate
Simeticone emulsion

Titanium dioxide (E171)
Polysorbate 80 (E433)

Waxing
Carnauba wax

Printing ink
Shellac
Allura Red AC aluminum lake (E129)
Propylene glycol (E1520)
Indigo carmine aluminum lake (E132)
Simeticone emulsion

6.2 Incompatibilities

Not applicable

6.3 Shelf life

42 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium unit dose blisters.

Pack sizes of 20, 30 and 40 gastro-resistant tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharma (Ireland) Limited
United Drug Distributors, United Drug House
Magna Business Park, Magna Drive
Citywest
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2325/016/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th April 2019

10 DATE OF REVISION OF THE TEXT

February 2020