Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxylamine/Pyridoxine Exeltis 10 mg/10 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 10 mg doxylamine hydrogen succinate and 10 mg pyridoxine hydrochloride.
Excipient(s) with known effect
Each tablet contains 0.008 mg of Allura Red AC aluminium lake (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

Doxylamine/Pyridoxine Exeltis is indicated for the symptomatic treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management.
Limitations of use: The combination doxylamine/pyridoxine has not been studied in case of hyperemesis gravidarum (see section 4.4).

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 must 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).

Doxylamine/Pyridoxine Exeltis should be taken as a daily prescription and not on an as needed basis. Continued need for Doxylamine/Pyridoxine Exeltis should be reassessed as the pregnancy progresses.

To prevent a sudden return of nausea and vomiting of pregnancy symptoms, a gradual tapering dose of Doxylamine/Pyridoxine Exeltis is recommended at the time of discontinuation.

Hepatic impairment
No pharmacokinetic studies have been conducted in hepatic impaired patients. Caution is however recommended due to potential for reduced metabolism, there is a possibility of dosage adjustment (see section 4.4).

Renal impairment
No pharmacokinetic studies have been conducted in renal impaired patients. Caution is however recommended due to potential for metabolite accumulation, there is a possibility of dosage adjustment (see section 4.4).

Paediatric population
Doxylamine/Pyridoxine Exeltis is not recommended for use in children under 18 years of age, due to lack of clinical data (see section 5.1).

Method of administration
Oral use.

Doxylamine/Pyridoxine Exeltis should be administered on an empty stomach with a glass of water (see section 4.5). The gastro-resistant tablets should be swallowed whole and should not be crushed, split or chewed.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. Concomitant use with monoamine oxidase inhibitors (MAOIs) (see section 4.5).

Concomitant use with potent inhibitors of CYP450 isoenzymes.

Porphyria.

4.4 Special warnings and precautions for use

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

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

This medicinal product has anticholinergic properties and, therefore, should be used with caution in patients with: increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction as the anticholinergic effects of this medicinal product may worsen these conditions.

This medicinal product should also be used with caution in patients with asthma or other breathing disorders, such as chronic bronchitis and pulmonary emphysema. It has been demonstrated that antihistamines reduce the volume of bronchial secretions and increase their viscosity, thereby making bronchial expectoration more difficult. This may result in respiratory obstruction, which may worsen these conditions. As such, care should be taken in these patients.

This medicinal product should be used with caution in patients with hepatic or renal impairment. No data are available. However, the metabolism of doxylamine and pyridoxine may theoretically be reduced in the presence of hepatic impairment. Also, there could be a theoretical metabolite accumulation in the presence of renal impairment.

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

There is limited evidence in cases of hyperemesis gravidarum for the combination doxylamine/pyridoxine. These patients should be treated by a specialist. Early treatment of symptoms related to morning sickness typically in pregnancy, is recommended to prevent progression to hyperemesis gravidarum. Caution should be taken with patients with hyperemesis gravidarum as this combination has not been studied in these cases (see section 4.1).

Photosensitivity reactions: Although not noted with doxylamine, an increased sensitivity of the skin to sunlight, with photodermatitis, has been observed with some antihistamines; thus, sunbathing should be avoided during treatment.

Ototoxic medications: Sedating antihistamines of the ethanolamine class, like doxylamine, could mask the warning signs of damage caused by ototoxic drugs such as antibacterial aminoglycosides, carboplatin, cisplatin, chloroquine and erythromycin, among others.

Care should be taken in epileptic patients as antihistamines have occasionally been associated with paradoxical hyperexcitability reactions, even at therapeutic doses.

Due to decreased sweating caused by anticholinergic effects, antihistamines may aggravate symptoms of dehydration and heat stroke.

Special precautions should be adopted in patients with long QT syndrome, as several antihistamines may prolong the mentioned QT interval, although this effect has not been observed specifically with doxylamine at therapeutic dose.

Hypokalemia or other electrolyte disturbances.

The risk of abuse and drug dependence of doxylamine is low. The occurrence of signs suggestive of abuse or dependence should be carefully monitored, especially in patients with a history of drug use disorders

Interference with allergy skin testing
Antihistamines may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing.
There have been reports of false positive urine screening tests for methadone, opiates, and phencyclidine phosphate (PCP) with doxylamine hydrogen succinate/pyridoxine hydrochloride use (see section 4.5).
This medicinal product contains Allura Red AC aluminium lake (E129) which may cause allergic reactions.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Known or theoretical interactions with antihistamines of the ethanolamine class:

- Anticholinergic agents (tricyclic antidepressants, MAOI, neuroleptics): may enhance toxicity due to the addition of their anticholinergic effects.

- Sedatives (barbiturates, benzodiazepines, antipsychotic agents, opioid analgesics): may enhance the hypnotic action.

- Antihypertensive drugs with sedative effect on the CNS (especially alpha-methyldopa) because they may enhance the sedative effect when administered with antihistamines.

- Alcohol: enhanced toxicity, with altered intellectual and psychomotor capacity, has been reported in some studies. The mechanism has not been established.

- Sodium oxybate as a not recommended combination with doxylamine due to its important central depressant effect.

- Ototoxic medications: Sedating antihistamines of the ethanolamine class, like doxylamine, could mask the warning signs of damage caused by ototoxic drugs such as antibacterial aminoglycosides.

- Photosensitizing medications: The concurrent use of antihistamines with other photosensitizing medications such as amiodarone, quinidine, imipramine, doxepin, amitriptyline, griseofulvin, chlorpheniramine, piroxicam, furosemide, captopril among others, may cause additive photosensitizing effects.

- Since several antihistaminic agents may prolong the QT interval, although this effect has not been observed with doxylamine at therapeutic dose, concomitant use of drugs that prolong the interval should be avoided (e.g. antiarrhythmic drugs, certain antibiotics, certain drugs for malaria, certain antihistaminic drugs, certain antilipidemic drugs or certain neuroleptic agents).
- Concomitant use of cytochrome P-450 inhibitors should be avoided (e.g. azole derivatives or macrolides).

- Concomitant use of drugs that cause electrolyte disturbances such as hypokalemia or hypomagnesemia (e.g. some diuretics) should be avoided.

The anticholinergic effects of doxylamine, a component of this medicinal product, could lead to false negatives in dermal hypersensitivity tests with antigen extracts. It is recommended to discontinue the treatment several days before starting the test.

Known or theoretical interactions with pyridoxine

- Reduce the effect of levodopa although it does not occur if co-administered with an inhibitor of dopa decarboxylase.
- It has been described a reduction in plasma levels of some antiepileptics such as phenobarbital and phenytoin.
- Some medications such as hydroxyzine, isoniazid or penicillamine may interfere with pyridoxine and may increase requirements for vitamin B6.

Food

A food-effect study has demonstrated that the delay in the onset of action of this medicinal product may be further delayed, and a reduction in absorption may occur when tablets are taken with food. Therefore, this medicinal product 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 hydrogen 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
This medicinal product is intended for use in pregnant women.
A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative nor feto/neonatal toxicity of doxylamine hydrogen succinate and pyridoxine hydrochloride.
Breast-feeding
The molecular weight of doxylamine hydrogen 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 hydrogen succinate through breast milk. Infants with apnoea or other respiratory syndromes may be particularly vulnerable to the sedative effects of this medicinal product resulting in worsening of their apnoea or respiratory conditions.
Pyridoxine hydrochloride/metabolites are excreted into human milk. There have been no reports of adverse reactions in infants presumably exposed to pyridoxine hydrochloride through human milk.
As newborn infants may be more sensitive to the effects of the antihistamines and to paradoxical irritability and excitation, a risk to newborns/infants cannot be excluded. This medicinal product is not recommended during lactation.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from this medicinal product therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Fertility
No human data available.

4.7 Effects on ability to drive and use machines

This medicinal product may cause somnolence and blurred vision, especially during the first few days of treatment. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using this medicinal product until cleared to do so by their healthcare provider.

4.8 Undesirable effects

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

There has been a vast clinical experience regarding the use of this medicinal product combination (doxylamine hydrogen 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 hydrogen 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, with this medicine and other similar medicine containing the same active ingredients.

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 reactions is qualified as "not known".

System Organ Class	Undesirable Effect	Frequency
Blood and lymphatic system disorders	**haemolytic anaemia**	**Rare**
Immune system disorders	**hypersensitivity**	**Not known**
Psychiatric disorders	**confusional state**	**Uncommon**
	agitation	**Rare**
	anxiety, disorientation, insomnia, irritability, nightmare	**Not known**
Nervous system disorders	**somnolence**	**Very common**
	dizziness	**Common**
	tremor, seizure	**Rare**
	headache, migraine, paraesthesia, psychomotor hyperactivity	**Not known**
Eye disorders	**diplopia, glaucoma**	**Uncommon**
	vision blurred, visual impairment	**Not known**
Ear and labyrinth disorders	**tinnitus**	**Uncommon**
	vertigo	**Not known**
Cardiac disorders	**palpitations, tachycardia**	**Not known**
Vascular disorders	**orthostatic hypotension**	**Uncommon**
Respiratory, thoracic and mediastinal disorders	**increased bronchial secretion**	**Common**
	dyspnoea	**Not known**
Gastrointestinal disorders	**dry mouth**	**Common**
	nausea, vomiting	**Uncommon**
	abdominal distension, abdominal pain, constipation, diarrhoea	**Not known**
Skin and subcutaneous tissue disorders	**photosensitivity reaction**	**Uncommon**
	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**
	asthenia, oedema peripheral	**Uncommon**
	chest discomfort, malaise	**Not known**

c. Description of selected adverse reactions

Severe drowsiness may occur if this medicinal product is taken along with CNS depressants including alcohol (see sections 4.4 and 4.5).

Anticholinergic effects of this medicinal product 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 at www.hpra.ie.

4.9 Overdose

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

Symptoms
Signs and symptoms of overdose 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, arrythmias, torsade de pointe 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 hydrogen 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: Antihistamines for systemic use, ATC code: R06AA59
Mechanism of action
This medicinal product provides the action of two unrelated compounds. Doxylamine hydrogen succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6) provide anti-nauseant and antiemetic activity.
Doxylamine hydrogen succinate is an ethanolamine derivative, an first generation antihistamine that is competitively, reversibly and non-specifically blocking H1-receptors. It is also a non-specific antagonist that blocks other receptors, such as central or peripheral muscarinic receptors. The antiemetic effect of doxylamine is also associated with the blocking of the central cholinergic and H1 receptors, although the mechanism of action is unknown.

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 hydrogen succinate and pyridoxine hydrochloride to treat nausea and vomiting of pregnancy has not been established.
Clinical efficacy and safety
The safety and efficacy of this medicinal product 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 this medicinal product 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 t medicine-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 treatment 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 this medicinal product 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 Hydrogen 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.

In the literature, the safety and effectiveness of Doxylamine/Pyridoxine Exeltis has been demonstrated in clinical trials, cohort studies and meta-analysis. The extensive post-marketing experience and numerous publications continue to support the positive benefit risk assessment of this medicinal product in the treatment of NVP in pregnant women.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with this medicinal product 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 this medicinal product 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 this medicinal product 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 Doxylamine/Pyridoxine Exeltis 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	1 280.9 ± 369.3	83.3 ± 20.6	7.2 ± 1.9	3 721.5 ± 1 318.5	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	1 587.2 ± 550.0	210.0 ± 54.4	6.8 ± 1.2
Pyridoxal 5'-Phosphate	1 536.4 ± 721.5	30.0 ± 10.0	11.7 ± 5.3	6 099.7 ± 1 383.7	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 Doxylamine/Pyridoxine Exeltis to healthy non-pregnant adult women

		$AUC_{0\text{-last}}$ (ng•h/mL)	**$AUC_{0\text{-inf}}$ (ng•h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**	**$t_{1/2el}$ (h)**
Doxylamine Mean±SD N=18	**Single**	911.4 ± 205.6	1 280.9 ± 369.3	83.3 ± 20.6	7.2 ± 1.9	10.1 ± 2.1
	Multiple	3 661.3 ± 1 279.2	3 721.5 ± 1 318.5	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 Doxylamine/Pyridoxine Exeltis under fed and fasted conditions in healthy non-pregnant adult women

		$AUC_{0\text{-t}}$ (ng•h/mL)	**$AUC_{0\text{-inf}}$ (ng•h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**	**$t_{1/2el}$ (h)**
Doxylamine Mean±SD N=42	**Fasted**	1 407.2 ± 336.9	1 447.9 ± 332.2	94.9 ± 18.4	5.1 ± 3.4	12.6 ± 3.4
	Fed	1 488.0 ± 463.2	1 579.0 ± 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 ± 14.5	24.2 ± 14.0[b]	13.7 ± 10.8	9.3 ± 4.0	0.5 ± 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 Doxylamine/Pyridoxine Exeltis 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 repeated dose toxicity, genotoxicity and carcinogenic potential.
Reproductive toxicity
In a reproductive toxicity study of a drug product containing equal concentrations of doxylamine hydrogen succinate and pyridoxine hydrochloride in rats, maternal toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Developmental toxicity (including reduced prenatal viability and reduced foetal body weight per litter, reduced foetal ossification in anterior distal limbs) only occurred in the presence of maternal toxicity (at doses from 60 times the maximum human recommended based on mg / m2). No teratogenic effects are reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Magnesium trisilicate
Croscarmellose sodium
Magnesium stearate
Silica, colloidal anhydrous
Coating
Hypromellose (E464)
Macrogol (400) (E1521)
Macrogol (8000) (E1521)
Methacrylic acid-ethyl acrylate copolymer (1:1)
Talc (E553b)
Silica, colloidal anhydrous
Sodium hydrogen carbonate (E500)
Sodium lauryl sulfate (E487)
Triethyl citrate
Simeticone emulsion
Titanium dioxide (E171)
Polysorbate 80 (E433)
Waxing
Wax Carnauba
Printing ink
Shellac (E904)
Allura Red AC aluminum lake (E129)
Propylene glycol (E1520)
Indigo carmine aluminum lake (E132)
Simeticone

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

OPA/Aluminium/PVC/Aluminium blisters.
Pack sizes of 10, 20, 30, 40, 50 and 60 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

Exeltis healthcare S.L.
Avenida Miralcampo 7
Azuqueca De Henares
Guadalajara
19200
Spain

8 MARKETING AUTHORISATION NUMBER

PA22998/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th December 2021

10 DATE OF REVISION OF THE TEXT

December 2021