Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxylamine/Pyridoxine Exeltis Healthcare 20mg/ 20mg modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 20 mg doxylamine hydrogen succinate and 20 mg pyridoxine hydrochloride. Doxylamine/Pyridoxine Exeltis Healthcare is comprised of an enteric-coated core containing 10 mg doxylamine hydrogen succinate and 10 mg pyridoxine hydrochloride and an immediate-release multilayer coating containing 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), an azo colouring agent.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet
Pink, round, film-coated tablet with a pink image of a pregnant woman on one side and the letter "D" on the other side. The tablet size is approximately 9mm in diameter and 4mm thick.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxylamine/Pyridoxine Exeltis Healthcareis indicated for the symptomatic treatment of nausea and vomiting of pregnancy (NVP) in pregnant women ≥18 years who do not respond to conservative management (i.e., lifestyle and diet change).
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 of Doxylamine/Pyridoxine Exeltis Healthcare is one tablet (20mg/20mg) at bedtime on Day 1 and on Day 2. If symptoms are not adequately controlled on Day 2, the dose can be increased on Day 3 to one additional tablet (20mg/20mg) in the morning and one tablet (20mg/20mg) at bedtime (for a total of two tablets per day). The maximum recommended dose is two tablets daily, one in the morning and one at bedtime (for a maximum daily dose of 40mg/40mg). Doxylamine/Pyridoxine Exeltis Healthcareshould be taken as a daily prescription and not on an as needed basis. Continued need for Doxylamine/Pyridoxine Exeltis Healthcare should be reassessed as the pregnancy progresses.
Some women may achieve symptom control at intermediatory doses of 30mg/30mg. This dose is not achievable with Doxylamine/Pyridoxine Exeltis Healthcare 20mg/20mg. Other formulations of doxylamine hydrogen succinate/pyridoxine hydrochloride are available which provide for greater flexibility to dose adjust according to severity of symptoms. With Doxylamine/Pyridoxine Exeltis Healthcare20mg/20mg modified-release tablet formulation, the maximum daily recommended dosing of 40mg/40mg consists of only two tablets daily.
To prevent a sudden return of nausea and vomiting of pregnancy symptoms, a gradual tapering dose of Doxylamine/Pyridoxine Exeltis Healthcare 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 Healthcare 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 Healthcare should be administered on an empty stomach with a glass of water (see section 4.5). The modified-release tablets should be swallowed whole and should not be crushed, split or chewed to preserve the enteric-coated core properties.

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) or use of Doxylamine/Pyridoxine Exeltis Healthcare up to 14 days after cessation of MAOIs (see section 4.5).
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.

Doxylamine/Pyridoxine Exeltis Healthcare contains pyridoxine hydrochloride, a vitamin B6 analog, therefore additional levels from diet and vitamin B6 supplements should be assessed.

The combination doxylamine/pyridoxine has not been studied in cases of hyperemesis gravidarum; therefore, caution should be taken. 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 (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.

The suitability of treating patients with hypokalemia or other electrolyte disturbances must be evaluated.

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

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).

Interference with allergy skin testing

Antihistamines may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing.

This medicinal product contains Allura Red AC aluminium lake (E129), an azo colouring agent, 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 interaction

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. Monoamine oxidase inhibitors (MAOIs) prolong and intensify the anticholinergic effects of antihistamines and concomitant treatment with MAOIs or use of Doxylamine/Pyridoxine Exeltis Healthcare up to 14 days after cessation of MAOIs is contraindicated (see section 4.3).
- Sedatives (barbiturates, benzodiazepines, antipsychotic agents, opioid analgesics): may enhance the hypnotic action.
- Concurrent use with central nervous system (CNS) depressants including alcohol, hypnotic sedatives and tranquilizers is not recommended. The combination may result in severe drowsiness (see section 4.8).
- 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).
- Due to the known metabolism pathway of doxylamine and lack of data on interactions, concomitant use with potent inhibitors of CYP2D6 (e.g. fluoxetine, terbinafine), CYP1A2 (e.g. fluvoxamine, cimetidine) and CYP2C9 (e.g. gemfibrozil, amiodarone) should be avoided as a precautionary measure.
- 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 (see section 5.2). 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, including two meta-analyses with over 168,000 patients and 18,000 exposures to the doxylamine/pyridoxine combination during first trimester, 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

Doxylamine/Pyridoxine Exeltis Healthcare has a moderate to major influence on the ability to drive and use machines.

Doxylamine/Pyridoxine Exeltis Healthcare may cause somnolence and blurred vision, especially during the first few days of treatment (see section 4.8). Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using Doxylamine/Pyridoxine Exeltis Healthcare 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 Doxylamine/Pyridoxine Exeltis Healthcare combination (doxylamine hydrogen succinate and pyridoxine hydrochloride). The most frequently reported adverse reaction (≥5% and

exceeding the rate in placebo) was somnolence in a double-blind, randomised, placebo-controlled trial of 15 days duration, including 261 women with nausea and vomiting of pregnancy (128 treated with placebo and 133 with doxylamine hydrogen succinate/pyridoxine hydrochloride)

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 events 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, nightmares	Not known
Nervous system disorders	somnolence	Very common
	dizziness	Common
	tremor, seizure	Rare
	headache, migraines, paresthesia, 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	palpitation, 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 distention, 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 Doxylamine/Pyridoxine Exeltis Healthcare is taken along with CNS depressants including alcohol (see sections 4.4 and 4.5).
Anticholinergic effects of Doxylamine/Pyridoxine Exeltis Healthcare may be modified 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 Website: www.hpra.ie

4.9 Overdose

Doxylamine/Pyridoxine Exeltis Healthcareis a modified-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, arrythmias, torsade de pointe and death.

Management
In the event of an overdose, treatment consists of 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
Doxylamine/Pyridoxine Exeltis Healthcare 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, a 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 the combination of doxylamine hydrogen succinate and pyridoxine hydrochloride 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.

The efficacy study has been conducted with a 10mg/ 10mg gastro-resistant tablet formulation of doxylamine and pyridoxine. Even though the release pattern of the 20mg/ 20 mg modified-release (with an immediate release and a gastro-resistant component) tablet formulation (Doxylamine/Pyridoxine Exeltis Healthcare) is different from the release pattern of the 10mg/ 10mg gastro-resistant tablet formulation of doxylamine and pyridoxine, comparable exposures (90% CI within 80-125%) for AUC, C_{max} and C_{min} were shown for doxylamine and pyridoxal 5'-phosphate following administration of the same daily dose and therefore the results of the efficacy study with the 10mg/ 10mg gastro-resistant tablet formulation are also supportive for the 20mg/ 20mg tablet formulation Doxylamine/Pyridoxine Exeltis Healthcare.

Two 10mg/ 10mg gastro-resistant tablet 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 for a maximum daily dose of 40mg of doxylamine and 40mg of pyridoxine.

Over the treatment period, 60% of product-treated patients received the maximum daily dose of 40mg of doxylamine and 40mg of pyridoxine.

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 product 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 the 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.
§ Calculated Cohen's d coefficient = 0.34. The difference in mean PUQE score reduction is considered a "medium-size effect" as per Cohen's d coefficient (of 0.34) where >0.20 = medium effect.

In the literature, the safety and effectiveness of the combination of doxylamine hydrogen succinate and pyridoxine hydrochloride has been demonstrated in the treatment of NVP in pregnant women.

Paediatric population
The safety and efficacy of Doxylamine/Pyridoxine Exeltis Healthcare has not been established in the paediatric population. No data are available. (see section 4.2 for information on paediatric use)

5.2 Pharmacokinetic properties

The pharmacokinetics of Doxylamine/Pyridoxine Exeltis Healthcare has been characterised in healthy non-pregnant adult women in a single-dose study (one tablet) and a multiple-dose study (two tablets daily from Day 1 to 11).

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

When formulated as a modified-release tablet, after single dose administration, the median peak plasma concentration of doxylamine and pyridoxine was achieved within 4.5 and 0.5 hours, respectively.

Multiple-dose administration resulted in:

- Increased concentrations of doxylamine as well as increased C_{max} by 1.8 and AUC of absorption by 2.0. The time to reach the maximum concentration was reduced by multiple doses, from a mean of 20.0 hours (range of 2.00-23.0) to 3.50 hours (range of 1.00-20.0). The mean accumulation index was 1.99 suggesting that doxylamine accumulates following multiple dosing.
- Although no accumulation was observed for pyridoxine, the mean accumulation index for the main active metabolite pyridoxal 5'-phosphate was 2.61 following multiple-dose administration. The time to reach the maximum concentration was slightly affected by multiple doses, from a mean of 21.0 hours (range of 15.0-23.9) to 15.0 hours (range of 2.00-24.0).

In a food-effect, single-dose, crossover clinical trial conducted in 23 healthy, premenopausal women:

- The administration of a high fat, high calorie meal delayed the absorption of doxylamine, pyridoxine, and pyridoxine metabolites. This delay was associated with lower peak concentrations of doxylamine, pyridoxine, and pyridoxal.
- The extent of absorption for pyridoxine was decreased. The effect of food on the peak concentration and the extent of absorption of the pyridoxine component is more complex because pyridoxine metabolites such as pyridoxal, pyridoxamine, pyridoxal 5′-phosphate, and pyridoxamine 5′-phosphate also contribute to biological activity.
- Food significantly reduced the bioavailability of pyridoxine, lowering its C_{max} and AUC by approximately 67% and 37%, respectively, compared to fasting conditions. In contrast, food did not affect the C_{max} and AUC of the main active metabolite pyridoxal 5′-phosphate.

Distribution

Doxylamine is low protein binding (unbound fraction of 28.7% in rat), highly permeable, and is not a substrate of P-glycoprotein, leading to a wide distribution into tissues. Doxylamine crosses the blood-brain barrier and has a high affinity for H1 receptors.

Pyridoxine is highly protein bound, primarily to albumin. Its metabolites, pyridoxal and pyridoxal 5'-phosphate are partially and almost completely bound to albumin in plasma, respectively. 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 primarily by the cytochrome P450 enzymes CYP2D6, CYP1A2, and CYP2C9, to its principle metabolites N-desmethyl-doxylamine and N,N-didesmethyldoxylamine. Pyridoxine is a prodrug primarily metabolised in the liver, with a high first pass effect. The metabolic scheme for pyridoxine is complex, with formation of primary and secondary metabolites along with interconversion back to pyridoxine. Pyridoxine and its metabolites, pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate contribute to biologic activity.

Elimination

The principle metabolites of doxylamine, N-desmethyl-doxylamine and N,N-didesmethyldoxylamine, are excreted by the kidney.

Renal elimination is also the main pathway of excretion for the derivatives of pyridoxine metabolism (reported to be 74% of a 100 mg intravenous dose of pyridoxine), mainly as the inactive form 4-pyridoxic acid.

When formulated as a modified-release tablet, after single dose administration, the terminal elimination half-life of doxylamine and pyridoxine are 12.43 and 0.27 hours, respectively.

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)
Methacrylic acid-ethyl acrylate copolymer (1:1)
Talc (E553b)
Silica, colloidal anhydrous
Sodium hydrogen carbonate (E500)
Sodium lauryl sulfate (E487)
Triethyl citrate
Polyvinyl Alcohol-part. hydrolyzed
Titanium dioxide (E171)
Macrogol (E1521)
Iron Oxide Red
Simeticone emulsion

Waxing
Carnauba wax

Printing ink
Shellac (E904)
Allura Red AC aluminum lake (E129)
Propylene glycol (E1520)
Indigo carmine aluminum lake (E132)
Simeticone
Ammonium Hydroxide 28% (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

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, 60 and 100 modified-release 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 De Miralcampo 7
Poligono Industrial Miralcampo
Azuqueca De Henares
Guadalajara
19200
Spain

8 MARKETING AUTHORISATION NUMBER

PA22998/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th June 2023

10 DATE OF REVISION OF THE TEXT

February 2025