Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cariban 10 mg/10 mg modified-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Doxylamine succinate ..... 10 mg
Pyridoxine hydrochloride ..... 10 mg

Excipient with known effect: Sucrose (79.5 mg per capsule).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release hard capsule.

Green capsule, size 3, containing two types of modified-release pellets one for each active ingredient, one containing Pyridoxine hydrochloride and the other containing Doxylamine succinate.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cariban is indicated for the symptomatic treatment of nausea and vomiting during pregnancy in adults 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 dose is:
If nauseas are in the morning take 2 capsules at bedtime (Day 1). If this dose controls symptoms the next day, continue taking two capsules daily at bedtime. However, if symptoms persist into the afternoon of Day 2, the patient should continue the usual dose of two capsules at bedtime (Day 2) and on Day 3 take three capsules (one capsule in the morning and two capsules at bedtime). If these three capsules do not adequately control symptoms on Day 3, the patient can take four capsules starting on Day 4 (one capsule in the morning, one capsule mid-afternoon and two capsules at bedtime).

The maximum recommended dose is four capsules (one in the morning, one in the mid-afternoon and two at bedtime) daily.

Special populations

Hepatic impairment

No pharmacokinetic studies have been conducted in hepatic impaired patients.
No data is available on differences in the pharmacokinetics of the combination of doxylamine succinate and pyridoxine hydrochloride in patients with hepatic impairment, but take in to account that doxylamine is metabolised by the liver, the dose should be adjusted depending on the degree on hepatic impairment.

Renal impairment

No pharmacokinetic studies have been conducted in renal impaired patients.
No data is available on differences in the pharmacokinetics of the combination of doxylamine succinate and pyridoxine hydrochloride in patients with renal impairment; but take in to account that it could be a metabolite accumulation, the dose should be reduced depending on the degree on renal impairment.

Paediatric population

The safety and efficacy of doxylamine/pyridoxine in children under the age of 18, has not yet been established.

Method of administration

Oral use.

Capsules must be taken on an empty stomach.

Capsules should be swallowed whole with water, without chewing.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity reactions to any other ethanolamine derivative antihistamines.
- Concomitant use with monoamine oxidase (MAO) inhibitors, since the adverse central nervous system effects of Cariban are intensified and prolonged.
- Concomitant use with potent inhibitors of CYP450 isoenzymes.
- Porphyria.

4.4 Special warnings and precautions for use

The suitability of treating patients with the following must be evaluated:

- Increased intraocular pressure, narrow angle glaucoma, urinary obstruction, thyroid dysfunction, cardiovascular alterations, hypertension, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction, as the anticholinergic effects of this medicinal product may worsen these conditions.
- 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 could worsen these conditions. As such, care should be taken in these patients.
- 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.
- Hypokalemia or other electrolyte disturbances.
- 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).
- Doxylamine succinate and pyridoxine hydrochloride delayed-release capsules may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine. Women should avoid engaging in activities

requiring complete mental alertness, such as driving or operating heavy machinery, while using doxylamine succinate and pyridoxine hydrochloride delayed-release capsules until cleared to do so by their healthcare provider.

- Cariban is not recommended if a woman is concurrently using central nervous system (CNS) depressants including alcohol. The combination may result in severe drowsiness leading to falls or accidents (see section 4.5).
- 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.
- The suitability of treating patients with the following must be evaluated: 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).
- Cariban contains pyridoxine hydrochloride, a vitamin B_6 analog, therefore additional levels from diet and vitamin B_6 supplements should be assessed.

Interference with allergy skin testing

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

Warnings on excipients

This medicinal product contains sucrose. Patients with hereditary intolerance to fructose, glucose or galactose malabsorption, or sucrase – isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Cariban.

For antihistamines of the ethanolamine class interactions are known with the following medicinal products:

- 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, 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.

Pyridoxine interactions are known with the following medicinal products:

- 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 B_6.

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.

The effect of food on the bioavailability of doxylamine and pyridoxine has been studied. AUC and Cmax parameters from doxylamine demonstrates the absence of food effect on their bioavailability; only a delay in Tmax is evidenced. The delay in action may be prolonged when capsules are taken with food.

4.6 Fertility, pregnancy and lactation

Pregnancy

Cariban is intended for use in pregnant women. Epidemiological studies and meta-analyses indicates no malformative toxicity of doxylamine succinate and pyridoxine hydrochloride.
Due to the anticholinergic and sedative properties of doxylamine succinate (see section 5.1), caution should be taken with the newborn in case of mother's treatment until delivery.

Breast-feeding

Physico-chemical data suggest excretion of doxylamine succinate in human breast milk. As newborn infants may be more sensitive to the effects of the antihistamines and to paradoxical irritability and excitation, a risk to the suckling child cannot be excluded. Cariban is not recommended during lactation.

Fertility

A study of doxylamine in rats does not produce adverse effects on fertility (see section 5.3). No human data available.

4.7 Effects on ability to drive and use machines

Cariban has major influence on the ability to drive and use machines.

This medicinal product may cause somnolence and blurred vision, especially during the first few days of treatment. Therefore patients should avoid engaging in activities requiring complete mental alertness, such as driving or using heavy machinery.

4.8 Undesirable effects

Summary of safety profile

Adverse reactions associated with the use of the combination of doxylamine / pyridoxine are comparable to those occurring with the sedating antihistamines as the sole active ingredient.

Like all medicines, this medicine can cause side effects.

The most frequent adverse reactions include somnolence and anticholinergic effects (1%-9%) such as dry mouth, constipation, urinary retention, increased bronchial secretion and blurred vision.

Tabulated list of adverse reactions

The following listing of adverse reactions is based in post-marketing experience.

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, including isolated reports)
Not known (frequency cannot be estimated from the available data)

System Organ Class	Undesirable Effect	Frequency
Nervous system disorders	somnolence	Common
	confusional state	Uncommon
	tremor, convulsion, agitation	Rare
Gastrointestinal disorders	dry mouth, constipation	Common
	nausea, vomiting, diarrhoea	Uncommon
Eye disorders	vision blurred	Common
	diplopia, glaucoma	Uncommon
Renal and urinary disorders	urinary retention	Common
Respiratory, thoracic and mediastinal disorders	increased bronchial secretion	Common
General disorders and administration site conditions	asthenia, oedema peripheral	Uncommon
Vascular disorders	orthostatic hypotension	Uncommon
Ear and labyrinth disorders	tinnitus	Uncommon
	vertigo	Not known
Skin and subcutaneous tissue disorders	rash, photosensitivity reactions	Uncommon
Blood disorders	haemolytic anaemia	Rare
Cardiac disorders	tachycardia	Not known
Respiratory effects	dyspnea	Not known

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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Overdose phenomena have been described at dose ranges of 250 – 1000 mg/day for doxylamine.
The symptoms of overdose with antihistamines include excitation with agitation, hallucinations, ataxia, loss of coordination and seizures. The latter occur intermittently. Prodromal symptoms may include tremors and athetotic movements. Fixed and dilated pupils, integumentary reddening (face) and hyperaemia are the signs that most commonly resemble atropine intoxication. The terminal phase is accompanied by coma, which is aggravated by cardiocirculatory collapse. Death may occur in a period of 2 to 98 hours. On occasions, depression and coma may precede a phase of excitation and seizures.

Rhabdomyolysis has also been reported in cases of doxylamine overdoses.

Taking into account that Cariban is a delayed-release formulation, signs and symptoms of intoxication may not be apparent immediately.

Pyridoxine is associated with adverse effects only after long-term use of large doses. Severe neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for period of 2 to 40 months.

Treatment involves gastric lavage, emetics, universal antidote, respiratory stimulants, parenteral cholinergic agents, such as bethanechol, if applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use, ATC code: R06AA59

Mechanism of action and pharmacodynamic effects

Doxylamine is an ethanolamine derivative, a first-generation antihistamine that competitively, reversibly and non-specifically blocks H1 receptors. It is also a non-specific antagonist that can block other receptors, such as central or peripheral muscarinic receptors.
The antiemetic action of doxylamine is also associated with blocking of the central cholinergic and H1 receptors, although the mechanism of action is unknown

Pyridoxine is a water-soluble vitamin factor (vitamin B_6) whose active form is pyridoxal 5'-phosphate. It acts as an enzyme co-factor in numerous biochemical reactions involved in the digestive breakdown of proteins and amino acids and, to a lesser extent, lipids and carbohydrates. Pyridoxine is also involved in the metabolism of unsaturated fatty acids (conversion of linoleic acid into arachidonic acid). It is a coenzyme for transaminases and decarboxylases and allows the conversion of tryptophan into nicotinic acid.

Clinical efficacy and safety

Clinical experience with the combination of doxylamine and pyridoxine has been reported extensively in the literature. Several double-blind, placebo-controlled studies as well as open-label studies demonstrate the efficacy and safety of the combination for the symptomatic treatment of nausea and vomiting of pregnancy.

5.2 Pharmacokinetic properties

Active substances are incorporated into coated microgranules with a dialysing membrane that releases the active substances after a certain period of time. Therefore, the onset of pharmacological effects is delayed and Cmax is reached at 6-7 hours approx. after ingestion in fasted conditions for doxylamine and at 4 hours approx for pyridoxine.

Absorbtion
Doxylamine is absorbed throughout the gastrointestinal tract. Peak concentrations are reached at 6-7 hours after oral administration in fasted conditions, and its therapeutic activity is extended for a period of 4-6 hours.
Pyridoxine is rapidly absorbed in the gastrointestinal tract, mainly in the jejunum. Absorption does not vary with age but is affected in alcoholic patients.

A study performed concerning the effect of food showed that the onset of action of Cariban may be delayed and its absorbtion may also be reduced when capsules are administered with meals.

Distribution
The general distribution of doxylamine occurs quickly. Its binding to plasma proteins is low compared with other antihistamines, with values of human albumin binding of 24%. Doxylamine is able to cross the blood brain barrier.

The main active metabolite of pyridoxine (pyridoxal 5-phosphate) is released into the blood, where it binds strongly to plasma proteins.

Metabolism or Biotransformation
Doxylamine is biotransformed in the liver through a N-dealkylation to it's main metabolites, N-desmethyldoxylamine and N,N-didesmethyldoxylamine, that are excreted by the kidneys.

Pyridoxine is mainly metabolised in the liver by phosphorylation.

Elimination
The elimination half-life for doxylamine is about 10 hours. Its main metabolites (N-desmethyldoxylamine and N,N-didesmethyldoxylamine) are excreted in the urine.

The elimination half-life for pyridoxine, administered in a dose of 20 mg in fast conditions, is 1.90 hours, while for it's main metabolites is 454.71 hours for pyridoxal-5-phosphate and 118.56 hours for pyridoxal. In terms of relative serum concentrations, a steady state is not reached during the 6-8 weeks that nausea and vomiting generally last during pregnancy unless loading doses of vitamin B_6 are administered. The main metabolite of pyridoxine, 4-pyridoxic acid, is inactive and is excreted in the urine.

Pharmacokinetic/pharmacodynamic relationships

One study examined the pharmacokinetic effects of doxylamine in 12 healthy women volunteers receiving an oral dose of 2 capsules (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) in fasted and fed state. The mean pharmacokinetics parameters (±SD) were:

	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
R-doxylamina	47.30 ± 6.25	6.58 ± 1.52	10.84 ± 2.65
S-doxylamina	43.78 ± 5.64	6.50 ± 1.37	12.33 ± 2.02
Pyridoxal-5-phosphate	64.99 ± 45.17	50.42 ± 99.46	454.71 ± 663.56
Pyridoxal	35.85 ± 9.51	4.94 ± 1.04	118.56 ± 51.88
Pyridoxina	15.80 ± 2.96	3.89 ± 0.98	1.90 ± 1.38
Main pharmacokinetics parameters of Cariban in fasted conditions			
	C_{max} (ng/ml)	**T_{max} (h)**	**$t_{1/2}$ (h)**
R-doxylamina	44.89 ± 5.90	11.28 ± 2.50	10 .98 ± 2.44
S-doxylamina	42.07 ± 3.54	11.28 ± 2.50	12.19 ± 2.09
Pyridoxal-5-phosphate	61.81 ± 25.97	83.13 ± 134.93	191.75 ± 199.72
Pyridoxal	31.72 ± 9.71	5.83 ± 1.44	106.00 ± 69.27
Pyridoxina	11.87 ± 5.34	4.79 ± 2.48	3.34 ± 1.50
Main pharmacokinetics parameters of Cariban in fed conditions			

5.3 Preclinical safety data

No repeat dose toxicity studies with the combination of doxylamine and pyridoxine are available.

Regarding pyridoxine, the registered effects after repeated oral, subcutaneous and intravenous administration on rats and dogs at ≥40 fold the maximum recommended humans doses ((MRHD) based on mg/m^2) were mainly neurological effects such as ataxia, muscle weakness, lack of coordination, hypotonia, forelimbs flexed and propioceptive abnormalities. In dogs, these effects were accompanied by injuries in the nervous system (loss of myelin and axons at the dorsal funiculi and posterior dorsal roots and degenerative lesions in the dorsal funiculus, the trigeminal nerve fiber and the spinal tracts of the trigeminal nerves).

Doxylamine induced hepatic damage in rodents at doses ≥10 fold the MRHD.

No genotoxicity or carcinogenicity studies have been performed with pyridoxine, or with the combination of pyridoxine and doxylamine.
Genotoxicity studies with doxylamine do not indicate a genotoxic risk for humans.

In the carcinogenicity studies doxylamine induced liver tumours in mice and rats, and thyroid tumours in mice. The induction of CYP450 enzyme and thyroxine glucuronidation, with the subsequent decrease in serum thyroxine levels and increase in thyroid stimulating hormones, are the most probable mechanisms underlying the induction of these tumours in animals. These mechanisms are not considered relevant for humans.

Fertility studies in animals with pyridoxine have not been performed. Pyridoxine does not show signs of reproductive toxicity in embryofetal development studies in rats at oral doses up to 200-fold the MHRD.

Doxylamine had no effect on the fertility of male and female rats at doses 24-fold the MHRD. Studies in mice show that doxylamine crosses the placental barrier, and the drug is detected in the embryos at concentrations above the pregnant female plasma levels. Doxylamine administered separately or in combination with pyridoxine to rats, rabbits and monkeys during the period of organogenesis caused adverse effects on fetuses (reduced prenatal viability, fetal body weight and skeletal malformations). Signs of teratogenicity were observed at doses from 9 to 120 fold the MHRD indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, corn starch, shellac, povidone, talc, methacrylic acid – methyl methacrylate copolymer (1:1) and silica colloidal anhydrous.

Hard gelatine capsule: gelatine, indigo carmine (E132), quinoline yellow (E104) and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Cartons containing:

- 12 hard capsules in 1 PVC/PVdC-Aluminium blisters, with 12 capsules in each blister
- 24 hard capsules in 2 PVC/PVdC-Aluminium blisters, with 12 capsules in each blister
- 48 hard capsules in 4 PVC/PVdC-Aluminium blisters, with 12 capsules in each blister
- Multipack: 48 hard capsules (two packs of 24 capsules) in 4 PVC/PVdC-Aluminium blisters, with 12 capsules in each blister

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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Viale Fulvio Testi
330 - 20126 Milano
Italy

8 MARKETING AUTHORISATION NUMBER

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