1. NAME OF THE MEDICINAL PRODUCT

Cariban 10 mg/10 mg modified-release capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Doxylamine succinate …….. 10 mg
Pyridoxine hydrochlorid) ……. 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 capsule, hard.

Green capsule, size 3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cariban is indicated for the symptomatic treatment of nausea and vomiting during pregnancy (NVP) 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.

4.2 Posology and method of administration

Posology

The recommended dose is:
If nauseas are in the morning take 2 capsules at bedtime. If this dose controls symptoms the next day, continue taking two capsules daily at bedtime. If nauseas persist during day, take 1 capsule in the morning and another one in the afternoon.

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

Doxylamine is metabolised by the liver and for that reason, the dose should be adjusted depending on the degree on hepatic impairment.

No data is available on differences in the pharmacokinetics of the combination of doxylamine succinate and pyridoxine hydrochloride in patients with hepatic impairment.

Renal impairment

The reduction dose of this medicinal product in patients with renal imparment is recommended because it could be a metabolite accumulation.
No data is available on differences in the pharmacokinetics of the combination of doxylamine succinate and pyridoxine hydrochloride in patients with 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.
- Asthmatic attacks (see section 4.4).
- Narrow-angle glaucoma.
- Stenosing peptic ulcer.
- Pyloroduodenal obstruction.
- Bladder-neck obstruction.
- 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, urinary obstruction, thyroid dysfunction, cardiovascular alterations and hypertension as the anticholinergic effects of this medicinal product may get 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.

- Hepatic and/or renal impairment: No data is available in patients with hepatic and/or renal impairment for doxylamine/pyridoxine combination, but take in to account that doxylamine is metabolised by the liver, the dose should be adjusted depending on the degree on hepatic impairment. Furthermore, a reduction dose of this medicinal product in patients with renal imparment is recommended because it could be a metabolite accumulation

- 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.

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.
- 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 B6.

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

Numerous epidemiological studies which indicate that the fixed combination of doxylamine succinate 10 mg/pyridoxine hydrochloride 10 mg does not exert adverse effects on gestational development or on the health of the foetus or newborn have been performed. Epidemiological evidence concerning its possible association with congenital malformations has been summarised in two meta-analyses. The first of these gave an OR for any congenital defect of

1.01 (95% CI: 0.66-1.55) and the second an OR of 0.95 (95% CI: 0.88-1.04). As such, both conclude that the fixed combination doxylamine succinate 10 mg / pyridoxine hydrochloride 10 mg is not associated with an increased malformation rate. Consequently, Cariban may be used safely during pregnancy when indicated.

Animals treated with high doses of pyridoxine, doxylamine, as well as their combination, have not shown relevant effects on reproductive function and embryonic and fetal development (see section 5.3).

Reproductive toxicity effects has been observed for the combination doxylamine/pyridoxine at similar doses to the maximum human dose recommended, based in mg/m^2 (see section 5.3)

Consequently, Cariban may be used during pregnancy when indicated.

Breast-feeding

Nursing mothers should not breastfeed whilst receiving Cariban or during lactation Cariban should be avoided.

No data is available describing the use of the fixed combination of doxylamine 10 mg/pyridoxine 10 mg during lactation. However, it's known that some antihistaminics agents are excreted into breast milk and that will provide adverse effects to a breastfeeding nursing infant. there are data for both components of the fixed combination and data are also available for both components as single agents. Breastfeeding should be stopped before starting Cariban treatment.

Fertility

A study performed orally administering high doses of doxylamine in rats showed that this compound does not produce adverse effects on fertility at doses up to 24 times the maximum recommended human dose (see section 5.3).

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.

List of adverse reactions

Adverse reactions reported in post-marketing experience are listed in descending order within each 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)

Common:
Nervous system disorders: somnolence.
Gastrointestinal disorders: dry mouth, constipation.
Eye disorders: vision blurred.
Renal and urinary disorders: urinary retention.
Respiratory, thoracic and mediastinal disorders: increased bronchial secretion.

Uncommon:
General disorders and administration site conditions: asthenia, oedema peripheral.
Vascular disorders: orthostatic hypotension.
Gastrointestinal disorders: nausea, vomiting, diarrhoea.
Nervous system disorders: confusional state.
Ear and labyrinth disorders: tinnitus.
Eye disorders: diplopia, glaucoma.
Skin and subcutaneous tissue disorders: rash, photosensitivity reactions.

Rare:
Blood disorders: haemolytic anaemia.
Nervous system disorders: tremor, convulsion, agitation.

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 Spanish Pharmacovigilance System for Medicinal Products for Human Use (www.notificaRAM.es).

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 PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

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

Antiemetic, histamine (H1) antagonist, muscarinic cholinergic antagonist.

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, although it is less potent than other ethanolamines.

The antiemetic action of doxylamine is also associated with blocking of the central cholinergic and H1 receptors.

Pyridoxine is a water-soluble vitamin factor (vitamin B6) 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-desmetildoxylamine and N,N-didesmetildoxylamine, 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 B6 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 hydrochlorure) 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

a) Repeated dose toxicity:
There have been no studies of toxicity with the combination of doxylamine and pyridoxine.

Regarding pyridoxine, the registered effects in oral, subcutaneous and intravenous administration on rats and dogs at doses from 40 times than the maximum human recommended doses based on mg/m^2) were mainly neurological effects such as ataxia, muscle weakness, lack of coordination, hypotonia, forelimbs flexed and propioceptive abnormalities. These effects were accompanied by injuries in the nervous system.

Regarding doxylamine, the observed effects at doses considered higher than the maximum human recommended doses (from 8 times based on mg/m^2) in toxicity studies conducted in rats, dogs and monkeys show non significant importance in clinical use, like eating less, decreased body weight and growth, mydriasis, apprehensiveness and death. Also, show moderate hepatic impariment in rats and mice fed diets which 1500 ppm of doxylamine.

b) Mutagenicity and Carcinogenicity:
No genotoxicity or carcinogenicity studies have been performed with pyridoxine, or with the combination of pyridoxine and doxylamine.
Doxylamine succinate did not show genotoxic potential in vitro in various strains of *Salmonella typhimurium* and in human lymphocytes, or in vivo in hamsters' bone marrow and mouse embryos' blood when administered to these animals. However, at doses of 500 and 750 µM it slightly induces unscheduled DNA synthesis in primay rat hepatocytes in the absence of an exogenous metabolic system. Furthermore, studies of doxylamine succinate carcinogenicity in rats and mice for two years have concluded that it is unlikely that this compound has carcinogenic potential in humans.

c*) Reproductive toxicity:*
Coadministration doxylamine and pyridoxine orally to rats during organogenesis caused maternal toxicity including mortality and toxicity in the development of offspring (weight

reduction, viability and ossification, shortening rib) only at doses from 60 times the maximum human recommended based on mg / m2 indicating little relevance to clinical use. However in monkeys produced delayed closure of the ventricular septum in offspring prenatally at similar doses the maximum recommended based on mg / m2 human dose and defect of the mitral valve in the offspring of postnatal way only at doses of 40 times the maximum recommended human based on mg / m2 indicating little relevance to clinical use doses.

The oral administration of pyridoxine at doses up to 200 times the maximum recommended human dose based on mg / m2 rats has not demonstrated alterations on embryo-fetal development.
Regarding doxylamine, it caused no effects on fertility and embryonic early, pre and postnatal development of the offspring of rats treated orally at doses up to 24 times the maximum recommended human dose based on mg / m2 (no effects on appearance, behavior, food consumption, body weight, conception rates in treated animals, nor the litter size, survival, and anatomical and functional abnormalities of the offspring). However, administration of doxylamine during organogenesis caused the following effects but only at doses considered above the maximum recommended human indicating little relevance to clinical use dose: dose of from 9 times the maximum recommended human dose based on mg / m2 administered orally, intravenously or intramuscularly caused alterations in fetuses on the normal development of vertebral skeleton, costal and extremities, connective tissue and normal articular and urogenital and ocular apparatus in rats, rabbits and marmosets . These doses resulted in lethality while rabbit mothers intramuscular doses of 27 times the maximum recommended human dose based on mg / m2 caused abortions in mothers marmosets.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, corn starch, shellac, povidone, talc, methacrylic acid – methyl methacrylate copolymer and silica colloidal anhydrous.
Hard gelatine capsule: gelatine, indigo carmine, quinoline yellow and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Cartons containing 24 hard capsules in 2 PVC/PVdC-Aluminium blisters, with 12capsules in each blister

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Registration number: 44.139

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1967/06/16

10. DATE OF REVISION OF THE TEXT

March 2016