1. **NAME OF THE MEDICINAL PRODUCT**

Cariban 10 mg/10 mg modified-release hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each modified-release hard capsule contains:

- Doxylamine (INN) succinate .................................. 10 mg
- Pyridoxine (INN) hydrochloride ............................ 10 mg

Excipients: sucrose

For the full list of excipients, see Section 6.1.

3. **PHARMACEUTICAL FORM**

Modified-release hard capsules

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

4.2. Symptomatic treatment of nausea and vomiting.

4.2. **Posology and method of administration** Cariban is administered orally.

The posology of Cariban is as follows:

*Adults and children over 12 years of age*: 1 capsule/8 h, up to a maximum of 70 mg per day (equivalent to 7 capsules).

*Pregnant women*: if the nausea occurs in the morning, take two capsules upon going to bed. If the nausea occurs during the day, take one capsule in the morning and another in the afternoon.

4.3. **Contraindications**

- Hypersensitivity to the active substances or to any of the excipients
- Hypersensitivity reactions to any other H1 antihistamine
- Asthma attacks
- Porphyria

4.4. **Special warnings and precautions for use**

The suitability of treating patients with the following must be evaluated:
- Glaucoma, pyloroduodenal obstruction, intestinal obstruction, stenosing peptic ulcer, urinary bladder obstruction, symptomatic prostate hypertrophy, urinary retention, hyperthyroidism, cardiovascular alterations and hypertension as the anticholinergic effects of this medicinal product may worsen these conditions.

- Lower respiratory tract disease, such as asthma, pulmonary emphysema or chronic obstructive pulmonary disease. 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.

- Moderate or severe renal impairment

- Hepatic impairment, dose adjustment may be necessary

- Photosensitivity reactions: As an increased sensitivity of the skin to sunlight, with photodermatitis, has been observed with some antihistamines, sunbathing should be avoided during treatment.

- The antiemetic effect of Cariban may interfere in the diagnosis of appendicitis.

- As it may mask symptoms of ototoxicity (such as tinnitus and dizziness), Cariban must be administered with care in patients treated concomitantly with potentially ototoxic medications.

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

**Warnings on excipients**

This medicinal product contains sucrose. Patients with hereditary intolerance to fructose, glucose or galactose absorption problems, or saccharase – isomaltase deficiency should not use this medication.

**4.5. Interaction with other medicinal products and other forms of interaction**

Cariban presents the following interactions:

- 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

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

The anticholinergic effects of this medicinal product could lead to false negatives in dermal hypersensitivity tests with antigen extracts. Suspending treatment at least 72 hours before the event is recommended.
4.6. Fertility, pregnancy and lactation

Numerous epidemiological studies which indicate that Cariban 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 Cariban is not associated with an increased malformation rate. Consequently, Cariban may be used safely during pregnancy when indicated.

Although pyridoxine is not toxic at the recommended dose, chronic administration at high doses may cause neurotoxicity. Pyridoxal (the active form of pyridoxine) crosses the placental barrier, reaching foetal plasma concentrations 5 times higher than those in the mother.

4.7. Effects on ability to drive and use machines

The influence of Cariban on the ability to drive and operate machinery is significant. This medicinal product may cause drowsiness, especially during the first few days of treatment, therefore situations that require a special level of alertness, such as driving vehicles or using hazardous machinery, must be avoided during treatment.

4.8. Undesirable effects

The following definitions are applicable to the incidence of adverse reactions:

- Very common (≥1/10);
- Common (≥1/100, <1/10);
- Uncommon (≥1/1000, <1/100);
- Rare (≥1/10,000, <1/1000);
- Very rare (<1/10,000).

The undesirable events are listed in descending order of severity within each degree of frequency.

The following adverse reactions have been reported after the administration of Cariban:

**General disorders:**
- Uncommon: asthenia

**Cardiovascular disorders:**
- Uncommon: orthostatic hypotension, peripheral oedema

**Blood disorders:**
- Rare: haemolytic anaemia

**Gastrointestinal disorders:**
- Common: dry mouth, constipation
- Uncommon: nausea, vomiting, diarrhoea.

**Nervous system disorders:**
- Common: drowsiness, especially upon commencing treatment, which usually decreases after 2-3 days.
- Uncommon: confusion
- Rare: tremor, seizures, paradoxical excitation, especially in children and the elderly
Ear and labyrinth disorders:
Uncommon: tinnitus

Renal and urinary disorders:
Common: urinary retention

Respiratory, thoracic and mediastinal disorders:
Common: bronchial hypersecretion

Eye disorders:
Common: blurred vision
Uncommon: diplopia, glaucoma

Skin and subcutaneous tissue disorders:
Uncommon: exanthematous rash, photosensitivity reactions

The adverse reactions mentioned above arise due to the action of doxylamine succinate as pyridoxine hydrochloride does not present side-effects, although chronic administration at high doses has been associated with neurotoxicity (see section 4.6).

4.9. Overdose

Overdose phenomena have been described at doses in the range 0.1–2.0 mg/kg body weight.

The symptoms of overdose include excitation with agitation, hallucinations, ataxia, loss of coordination, athetosis 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. 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: R06AA09.

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

Doxylamine succinate is an ethanolamine derivative, in other words a first-generation antihistamines that competitively, reversibly and non-specifically blocks H1 receptors and is also a non-specific antagonist that can block other receptors, such as
central or peripheral muscarinic receptors, with marked anticholinergic activity, although it is less potent than other ethanolamines.

Its anti-allergic action results from blocking of the H1 receptors, thereby decreasing the systemic effects of histamine, in other words decreasing the associated vascular permeability, reddening and oedema.

Its antiemetic action is also associated with blocking of the central cholinergic and H1 receptors, although has yet to be fully proven.

Its sedative action is related to its ability to cross the blood-brain barrier and its high affinity for central H1 receptors. Doxylamine induces a stronger sedative effect than other ethanolamines. If taken at high doses, and as is the case with other H1 blockers, it exhibits anticholinergic effects.

Pyridoxine hydrochloride (vitamin B6) is a water-soluble vitamin factor whose active form is pyridoxal 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. It 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.

5.2. Pharmacokinetic properties

The active substances are incorporated into microgranules coated with a dialysing membrane that releases the active substances after a certain period of time such that their effect begins to be noted five hours after ingestion.

**Doxylamine succinate**

This substance is well absorbed gastrointestinally. Peak concentrations are reached 2-3 hours after oral administration, and its therapeutic activity lasts for a period of 4-6 hours. Doxylamine is biotransformed to its main metabolites (N-demethyl- and N,N-didemethyldoxylamine) in the liver by N-dealkylation. These metabolites are excreted via the kidneys.

Some studies have examined the pharmacokinetic effects of doxylamine in women, with the 12 healthy women volunteers who acted as the control group receiving an oral dose of 25 mg. The mean peak plasma concentration of 103 ± 8 ng/ml was reached 2.4 ± 0.4 hours post-administration. The half-life was 10.1 ± 1.1 hours, with an apparent clearance of 3 ± 0.4 ml/min/kg.

**Pyridoxine hydrochloride**

Pyridoxine is rapidly absorbed in the gastrointestinal tract, mainly in the jejunum. Absorption does not vary with age but is affected in alcoholic patients. It is mainly metabolised in the liver by phosphorylation. The main active metabolite (pyridoxal 5-phosphate) is released into the blood, where it binds strongly to proteins. The main metabolite 4-pyridoxic acid is inactive and is excreted in the urine. The elimination half-life for pyridoxine has been estimated to vary in the range 20 to 46 hours. As regards 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.
5.3. Preclinical safety data

Preclinical safety studies in animals showed an eventual mutagenesis and teratogenicity profile at doses much higher than those used in the therapeutic range in humans.

Studies in mice using doxylamine succinate doses 125-times higher than the maximum dose in humans showed no observable evidence of congenital abnormalities. However, doses 125- to 375-times higher than the maximum human dose produced abnormalities in rats.

Primates that received doses 10- to 20-times the maximum human dose of doxylamine succinate and pyridoxine hydrochloride presented intraventricular septal defects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microgranules: sucrose, corn starch, shellac, povidone, talc, methacrylate polymer (Eudragit L).

Ingredients of the capsule: gelatine, indigo carmine, quinoline yellow, titanium dioxide and water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

No special storage conditions are required.

6.5. Nature and contents of container

Cartons containing 24 capsules in 3 blisters, with 8 capsules/blister.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORITY HOLDER

Laboratorios INIBSA, S.A.

Carretera de Sabadell a Granollers Km. 14,5

08185 LLIÇA DE VALL - Barcelona

SPAIN
8. MARKETING AUTHORISATION NUMBER

Registration no. 44.139

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

16/03/1967

10. DATE OF REVISION OF THE TEXT

January 2008