

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclegis[®] gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

Excipient(s) with known effect

Each tablet contains trace amounts of azo colouring agent 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

Diclegis is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

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 should 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).

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

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

Paediatric population

Diclegis is not indicated for use in children under 18 years of age. The safety and efficacy of Diclegis has not been established in that population (see section 5.1). No data are available.

Method of administration

Diclegis should be administered on an empty stomach with a glass of water (see section 4.5). The tablets should be swallowed whole and should not be crushed, split or chewed.

4.3 Contraindications

Hypersensitivity to doxylamine succinate, other ethanalamine derivative antihistamines, pyridoxine hydrochloride or any of the excipients listed in section 6.1.

Concomitant use with monoamine oxidase inhibitors (MAOIs) (see section 4.5).

4.4 Special warnings and precautions for use

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

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

Diclegis has anticholinergic properties and, therefore, should be used with caution in patients with: asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction.

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

Diclegis contains traces of the azo colouring agent Allura Red AC Aluminium Lake (E129) which may cause allergic reactions.

There is limited evidence in cases of hyperemesis gravidarum for the combination doxylamine/pyridoxine. These patients should be treated by a specialist.

There have been reports of false positive urine screening tests for methadone, opiates, and phencyclidine phosphate (PCP) with doxylamine succinate/pyridoxine hydrochloride use (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) prolong and intensify the anticholinergic effects of antihistamines.

Central nervous system depressants

Concurrent use with central nervous system (CNS) depressants including alcohol, hypnotic sedatives and tranquilizers is not recommended. The combination may result in severe drowsiness.

Food

A food-effect study has demonstrated that the delay in the onset of action of Diclegis may be further delayed, and a reduction in absorption may occur when tablets are taken with food. Therefore, Diclegis 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 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

Diclegis is intended for use in pregnant women.

A large amount of data on pregnant women indicates no malformative nor fetoneonatal toxicity of doxylamine succinate and pyridoxine hydrochloride.

Breast-feeding

The molecular weight of doxylamine 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 succinate through breast milk. Infants with apnoea or other respiratory syndromes may be particularly vulnerable to the sedative effects of Diclegis resulting in worsening of their apnoea or respiratory conditions.

Pyridoxine hydrochloride is excreted into breast milk. There have been no reports of adverse events in infants presumably exposed to pyridoxine hydrochloride through breast milk.

A risk to breastfed infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Diclegis therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Diclegis caused no impairment of fertility or reproductive performance in rats (see section 5.3). No human data available.

4.7 Effects on ability to drive and use machines

Diclegis has a moderate to major influence on the ability to drive and use machines.

Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using Diclegis 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 Diclegis combination (doxylamine succinate and pyridoxine hydrochloride). In a double-blind, randomized, 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 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 ($\geq 5\%$ 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.

Undesirable effects are displayed by MedDRA System Organ Classes and use the following conventions for frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
Immune system disorders	hypersensitivity	Not known
Psychiatric disorders	anxiety, disorientation, insomnia, nightmare	Not known
Nervous system disorders	somnolence	Very common
	dizziness	Common
	headache, migraine, paraesthesia, psychomotor hyperactivity	Not known
Eye disorders	vision blurred, visual disturbances	Not known
Ear and labyrinth disorders	vertigo	Not known
Cardiac disorders	dyspnea, palpitations, tachycardia	Not known
Gastrointestinal disorders	dry mouth	Common
	abdominal distension, abdominal pain, constipation, diarrhoea	Not known
Skin and subcutaneous tissue disorders	hyperhidrosis, pruritus, rash, rash maculopapular	Not known
Renal and urinary disorders	dysuria, urinary retention	Not known
General disorders and administration site conditions	fatigue	Common
	chest discomfort, irritability, malaise	Not known

c. Description of selected adverse reactions

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

Anticholinergic effects of Diclegis 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.

4.9 Overdose

Diclegis 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 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 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: aminoalkyl ethers, ATC code: R06AA59

Mechanism of action

Diclegis provides the action of two unrelated compounds. Doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6) provide anti-nauseant and antiemetic activity.

Doxylamine succinate, an ethanolamine, first-generation antihistamine crosses the blood-brain barrier and exerts an antiemetic action by selectively binding to H1 receptors in the brain.

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 succinate and pyridoxine hydrochloride to treat nausea and vomiting of pregnancy has not been established.

Clinical efficacy and safety

The safety and efficacy of Diclegis were compared to placebo in a double-blind, randomized, multi-center 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 Diclegis 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 Diclegis-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 Diclegis 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 Succinate +Pyridoxine Hydrochloride	Placebo	Treatment Difference [95% Confidence Interval]
Baseline	9.0 \pm 2.1	8.8 \pm 2.1	
Change from baseline at Day 15	-4.8 \pm 2.7	-3.9 \pm 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 from 3 (no symptoms) to 15 (most severe). Baseline was defined as the PUQE score completed at the enrolment visit.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Diclegis 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 Diclegis has been characterized in healthy non-pregnant adult women. Pharmacokinetic results for doxylamine and pyridoxine, including its vitamin B₆ metabolites, pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate, are summarized 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 Diclegis 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 Diclegis in healthy non-pregnant adult women

	Single Dose			Multiple Dose		
	AUC _{0-inf} (ng•h/mL)	C _{max} (ng/mL)	t _{max} (h)	AUC _{0-inf} (ng•h/mL)	C _{max} (ng/mL)	t _{max} (h)
Doxylamine	1280.9 \pm 369.3	83.3 \pm 20.6	7.2 \pm 1.9	3721.5 \pm 1318.5	168.6 \pm 38.5	7.8 \pm 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	1587.2 ± 550.0	210.0 ± 54.4	6.8 ± 1.2
Pyridoxal 5'-Phosphate	1536.4 ± 721.5	30.0 ± 10.0	11.7 ± 5.3	6099.7 ± 1383.7	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) 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 Diclegis to healthy non-pregnant adult women

		$AUC_{0-last}(ng\cdot h/mL)$	$AUC_{0-inf}(ng\cdot h/mL)$	$C_{max}(ng/mL)$	$t_{max}(h)$	$t_{1/2el}(h)$
Doxylamine Mean±SD N=18	Single	911.4 ± 205.6	1280.9 ± 369.3	83.3 ± 20.6	7.2 ± 1.9	10.1 ± 2.1
	Multiple	3661.3 ± 1279.2	3721.5 ± 1318.5	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 Diclegis under fed and fasted conditions in healthy non-pregnant adult women

		$AUC_{0-t}(ng\cdot h/mL)$	$AUC_{0-inf}(ng\cdot h/mL)$	$C_{max}(ng/mL)$	$t_{max}(h)$	$t_{1/2el}(h)$
Doxylamine Mean±SD N=42	Fasted	1407.2 ± 336.9	1447.9 ± 332.2	94.9 ± 18.4	5.1 ± 3.4	12.6 ± 3.4
	Fed	1488.0 ± 463.2	1579.0 ± 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 ± 0.8	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 B₆ 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 Diclegis 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 safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

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), Methacrylic acid-ethyl acrylate copolymer (1:1), Talc, Silica, colloidal anhydrous, Sodium hydrogen carbonate, Sodium lauryl sulfate, Triethyl citrate, Polydimethylsiloxane, Polyethylene glycol sorbitan tristearate, Silica gel, Methylcellulose, Dimethyl siloxane hydroxyl-terminated, Glycerides C14-18 mono and di, Sulfuric acid, sorbic acid, benzoic acid, 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), n-Butyl alcohol, Ammonium hydroxide, Isopropyl alcohol, Simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.

Keep out of sight and reach of children.

6.5 Nature and contents of container

OPA/Aluminium/PVC/Aluminium blisters.

Pack sizes of 2x10, 3x10, 4x10, 6x10 gastro-resistant tablets. Not all pack sizes may be marketed.

7. MARKETING AUTHORISATION HOLDER

Exeltis (Thailand) Co.,Ltd., Bangkok, Thailand
Manufactured by Duchesnay Inc., Blainville, QC, Canada

8. MARKETING AUTHORISATION NUMBER(S)

On process

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

On process

10. DATE OF REVISION OF THE TEXT

Dec 2022