FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

DICLECTIN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

pyridoxine (VIT B6) hydrochloride 10 mg
doxylamine succinate 10 mg

3. PHARMACEUTICAL FORM

Tablets delayed release

4. INDICATIONS AND USAGE

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

Limitations of Use

DICLECTIN has not been studied in women with hyperemesis gravidarum.

5. DOSAGE AND ADMINISTRATION

5.1 Dosage Information

Initially, take two DICLECTIN delayed-release tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking two tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, take the usual dose of two tablets at bedtime that night then take three tablets starting on Day 3 (one tablet in the morning and two tablets at bedtime). If these three tablets adequately control symptoms on Day 4, continue taking three tablets daily. Otherwise take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime).

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

Take on an empty stomach with a glass of water *[see Clinical Pharmacology (14.2)].* Swallow tablets whole. Do not crush, chew, or split DICLECTIN tablets.

Take as a daily prescription and not on an as needed basis. Reassess the woman for continued need for
DICLECTIN as her pregnancy progresses.

A gradual tapering dose of DICLECTIN® is recommended at the time of discontinuation to prevent a sudden onset of symptoms.

6. DOSAGE FORMS AND STRENGTHS

DICLECTIN delayed-release tablets are white, round, film coated tablets containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. The tablets are imprinted with the pink image of a pregnant woman on one side.

7. CONTRAINDICATIONS

DICLECTIN is contraindicated in women with any of the following conditions:

- Known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines,
  pyridoxine hydrochloride or any inactive ingredient in the formulation
- Monoamine oxidase (MAO) inhibitors intensify and prolong the adverse central nervous system effects of DICLECTIN *[see Drug Interactions (10.1)]*.

8. WARNINGS AND PRECAUTIONS

8.1 Activities Requiring Mental Alertness

DICLECTIN 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 DICLECTIN until cleared to do so by their healthcare provider.

DICLECTIN use 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 Drug Interactions (10.1)]*.

8.2 Concomitant Medical Conditions

DICLECTIN has anticholinergic properties and, therefore, should be used with caution in women with increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction.

8.3 Interference with Urine Screen for Methadone, Opiates and Phencyclidine Phosphate (PCP)

There have been reports of false positive urine screening tests for methadone, opiates, and PCP with doxylamine succinate/pyridoxine hydrochloride use *[see Drug Interactions (10.3)].*

9. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Somnolence *[see Warnings and Precautions (8.1)]*
- Falls or other accidents resulting from the effect of the combined use of DICLECTIN with CNS depressants including alcohol *[see Warnings and Precautions (8.1)]*

9.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety and efficacy of DICLECTIN were compared to placebo in a double-blind, randomized, multi-center trial in 261 women with nausea and vomiting of pregnancy. The mean gestational age at enrollment was 9.3 weeks, range 7 to 14 weeks gestation *[see Clinical Studies (16)]*. Adverse reactions for DICLECTIN that occurred at an incidence ≥5 percent and exceeded the incidence for placebo are summarized in Table 1.

Table 1: Number (Percent) of Subjects with ≥ 5 Percent Adverse Reactions in a 15-Day Placebo-
Controlled Study of DICLECTIN (Only Those Adverse Reactions Occurring at an Incidence ≥ 5 Percent and at a Higher Incidence with DICLECTIN than Placebo are Shown)

	DICLECTIN (N = 133)	Placebo (n = 128)
Somnolence	19 (14.3%)	15 (11.7%)

9.2 Postmarketing Experience

The following adverse events, listed alphabetically, have been identified during post-approval use of the combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: dyspnea, palpitation, tachycardia
Ear and labyrinth disorders: vertigo
Eye disorders: vision blurred, visual disturbances
Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhea
General disorders and administration site conditions: chest discomfort, fatigue, irritability, malaise
Immune system disorders: hypersensitivity
Nervous system disorders: dizziness, headache, migraines, paresthesia, psychomotor hyperactivity
Psychiatric disorders: anxiety, disorientation, insomnia, nightmares
Renal and urinary disorders: dysuria, urinary retention
Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, rash, rash maculo-papular

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

In addition, you may report by sending an e-mail message to: safety@tzamal-medical.co.il

10. DRUG INTERACTIONS

10.1 Drug Interactions

Use of DICLECTIN is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (drying) effects of antihistamines. Concurrent use of alcohol and other CNS depressants (such as hypnotic sedatives and tranquilizers) with DICLECTIN is not recommended.

10.2 Drug-Food Interactions

A food-effect study demonstrated that the delay in the onset of action of DICLECTIN may be further delayed, and a reduction in absorption may occur when tablets are taken with food *[see Dosage and Administration (5), Clinical Pharmacology (14.2)]*. Therefore, DICLECTIN should be taken on an empty stomach with a glass of water *[see Dosage and Administration (5)].*

10.3 False Positive Urine Tests for Methadone, Opiates and PCP

False positive 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.

11. USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

DICLECTIN is intended for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. Maternal risks are discussed throughout the labeling. No increased risk for congenital malformations has been reported in epidemiologic studies in pregnant women.

In the U.S. general population, the estimated background risks for major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Human Data
The combination of doxylamine succinate and pyridoxine hydrochloride has been the subject of many epidemiological studies (cohort, case control and meta-analyses) designed to detect possible teratogenicity. A meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991 reported no increased risk for malformations from first trimester exposures to doxylamine succinate and pyridoxine hydrochloride, with or without dicyclomine hydrochloride. A second meta-analysis of 12 cohort and 5 case-control studies published between 1963 and 1985 reported no statistically significant relationships between fetal abnormalities and the first trimester use of the combination doxylamine succinate and pyridoxine hydrochloride with or without dicyclomine hydrochloride.

11.2 Lactation

Women should not breastfeed while using DICLECTIN.

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 apnea or other respiratory syndromes may be particularly vulnerable to the sedative effects of DICLECTIN resulting in worsening of their apnea 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.

11.3 Pediatric Use

The safety and effectiveness of DICLECTIN in children under 18 years of age have not been established.

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.

12. OVERDOSAGE

12.1 Signs and Symptoms of Overdose

DICLECTIN is a delayed-release formulation, therefore, signs and symptoms of intoxication may not be apparent immediately.

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.

12.2 Management of Overdose

If treatment is needed, it consists of gastric lavage or activated charcoal, whole bowel irrigation and symptomatic treatment.

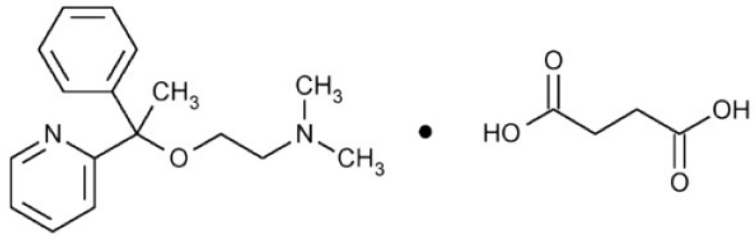
13. DESCRIPTION

DICLECTIN (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets are round, white, film-coated, delayed-release tablets containing 10 mg of doxylamine succinate and 10 mg of pyridoxine
hydrochloride. Tablets are imprinted on one side with the pink image of a pregnant woman.

Inactive ingredients are as follows:
Core: microcrystalline cellulose 102, magnesium trisilicate, magnesium stearate, croscarmellose sodium, colloidal silicon dioxide

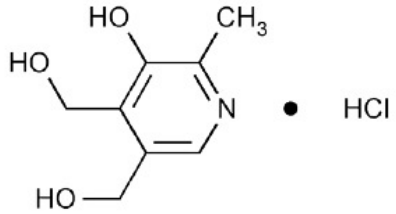
Enteric coating and printing: acryl-eze clear, opadry white YS-1-7003, opadry clear YS-1-7472, triethyl citrate, carnauba wax powder, simethicone emulsion 30%, opacode S-1-14022 pink DC

Doxylamine Succinate
Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1). The empirical formula is $C_{17}H_{22}N_2O \bullet C_4H_6O_4$ and the molecular mass is 388.46. The structural formula is:



Doxylamine succinate is a white to creamy white powder that is very soluble in water and alcohol, freely soluble in chloroform and very slightly soluble in ether and benzene.

Pyridoxine Hydrochloride
Pyridoxine hydrochloride is a vitamin B6 analog. The chemical name for pyridoxine hydrochloride is 3,4-pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride. The empirical formula is $C_8H_{11}NO_3 \bullet HCl$ and the
molecular mass is 205.64. The structural formula is:



Pyridoxine hydrochloride is a white or practically white crystalline powder that is freely soluble in water, slightly soluble in alcohol and insoluble in ether.

14. CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The mechanism of action of DICLECTIN is unknown.

14.2 Pharmacokinetics

The pharmacokinetics of DICLECTIN 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 DICLECTIN 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 Cmax 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 DICLECTIN in Healthy Non-Pregnant Adult Women

	Single Dose			Multiple Dose		
	AUC0-inf (ng•h/mL)	**Cmax (ng/mL)**	**Tmax (h)**	**AUC0-inf (ng•h/mL)**	**Cmax (ng/mL)**	**Tmax (h)**
Doxylamine	1280.9 ± 369.3	83.3 ± 20.6	7.2 ± 1.9	3721.5 ± 1318.5	168.6 ± 38.5	7.8 ± 1.6
Pyridoxine	43.4 ±	32.6 ±	5.7 ±	64.5 ±	46.1 ±	5.6 ±

	16.5	15.0	1.5	36.4	28.3	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 of DICLECTIN results in increased concentrations of doxylamine as well as increases in doxylamine Cmax and AUC0-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 of DICLECTIN. 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 DICLECTIN to Healthy Non-Pregnant Adult Women

		AUC0-last (ng•h/mL)	**AUC0-inf (ng•h/mL)**	**Cmax (ng/mL)**	**Tmax (h)**	**T1/2el (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

Food Effect

The administration of food delays the absorption of both doxylamine and pyridoxine. This delay is associated with a lower peak concentration of doxylamine, but the 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, lowering its Cmax and AUC by approximately 50% compared to fasting conditions. Similarly, food significantly reduces pyridoxal AUC and reduces its Cmax by 50% compared to fasting conditions. In contrast, food slightly increases pyridoxal 5'-phosphate Cmax 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 DICLECTIN Under Fed and Fasted Conditions in Healthy Non-Pregnant Adult Women

		AUC0-t (ng•h/mL)	AUC0-inf (ng•h/mL)	Cmax (ng/mL)	Tmax (h)	T1/2el (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 ± 10.8	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.

Metabolism

Doxylamine is biotransformed in the liver by N-dealkylation to its principal metabolites N-desmethyl-doxylamine and N, N-didesmethyldoxylamine.

Pyridoxine is a prodrug primarily metabolized in the liver.

Excretion

The principal 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 12.5 hours and 0.5 hours, respectively (see Table 5).

Table 5 – Terminal Elimination Half-Life (T1/2el) for DICLECTIN Administered as a Single Dose of Two Tablets under Fasting Conditions in Healthy Non-Pregnant Adult Women

	T1/2el (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

Use in Specific Populations
Race: No pharmacokinetic studies have been conducted related to race.

Hepatic Impairment: No pharmacokinetic studies have been conducted in hepatic impaired patients.

Renal Impairment: No pharmacokinetic studies have been conducted in renal impaired patients.

15. NONCLINICAL TOXICOLOGY

15.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenicity
Two-year carcinogenicity studies in rats and mice have been conducted with doxylamine succinate.
Doxylamine succinate is not likely to have human carcinogenic potential. The carcinogenic potential of pyridoxine hydrochloride has not been evaluated.

16. CLINICAL STUDIES

A double-blind, randomized, multi-center, placebo-controlled study was conducted to support the safety and efficacy of DICLECTIN in the treatment of nausea and vomiting of pregnancy. Adult women 18 years of age or older and 7 to 14 weeks gestation (median 9 weeks of gestation) with nausea and vomiting of pregnancy were randomized to 14 days of DICLECTIN or placebo. Two tablets of DICLECTIN 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 take 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 DICLECTIN-treated patients remained on 2 tablets daily, 21% received 3 tablets daily, and 60% received 4 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 DICLECTIN arm and 8.8 in the placebo arm. There was a 0.7 (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 DICLECTIN compared to placebo (see Table 6).

Table 6 – Change from Baseline in the Primary Endpoint, Pregnancy Unique-Quantification of Emesis (PUQE) Score at Day 15. (Intent-to-Treat Population with Last-Observation Carried Forward)

PUQE Score*	Doxylamine Succinate + Pyridoxine Hydrochloride	Placebo	Treatment Difference [95% Confidence Interval]
Baseline	9.0 ± 2.1	8.8 ± 2.1	
Change from baseline at Day 15	-4.8 ± 2.7	-3.9 ± 2.6	-0.7 [-1.2, -0.2]

*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 enrollment visit.

17. HOW SUPPLIED/STORAGE AND HANDLING

17.1 How supplied

DICLECTIN delayed-release tablets are supplied in a high-density polyethylene bottle with a polypropylene child-resistant cap and a silica gel desiccant canister. Each white, round, film-coated, delayed-release tablet contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and is imprinted on one side with the pink image of a pregnant woman. DICLECTIN tablets are provided in bottles of 100.

17.2 Storage and Handling

Store below 30°C. Keep bottle tightly closed and protect from moisture. Do not remove desiccant canister from bottle. Protect from light.

17.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

18. MANUFACTURER

Duchesnay Inc.
950 boul. Michèle-Bohec, Blainville, Québec
Canada J7C 5E2

19. REGISTRATION HOLDER

Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Petah-Tikva.

20. REGISTRATION NUMBER

153-11-34066
Revised in February 2024 according to the MOH guidelines.