PRODUCT MONOGRAPH

[Pr]pms-DOXYLAMINE-PYRIDOXINE

Doxylamine succinate/Pyridoxine hydrochloride Delayed-Release Tablets

10 mg/10 mg

Antinauseant against Nausea and Vomiting of Pregnancy

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[Pr]pms-DOXYLAMINE-PYRIDOXINE

Doxylamine succinate/Pyridoxine hydrochloride Delayed-Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet, 10 mg/10 mg	Colloidal Anhydrous Silica, Dibasic Calcium Phosphate, FD&C Blue #1 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, Glycerides, Hydroxypropyl Methylcellulose, Isopropyl Alcohol, Lecithin (Soya) FCC, Magnesium Stearate, Mannitol, Methacrylic Acid Copolymer, Methylated Silica, Methylcellulose, N-Butyl Alcohol, Polydimethylsiloxane, Polyethylene Glycol Sorbitan Tristearate, Propylene Glycol, Shellac Glaze, Simethicone, Sodium Bicarbonate, Sodium Lauryl Sulfate, Sorbic Acid, Sulfuric Acid, Talc, Titanium Dioxide, Triethyl Citrate

INDICATIONS AND CLINICAL USE

pms-DOXYLAMINE-PYRIDOXINE (doxylamine succinate/pyridoxine hydrochloride) is indicated for the management of nausea and vomiting of pregnancy.

CONTRAINDICATIONS

pms-DOXYLAMINE-PYRIDOXINE (doxylamine succinate/pyridoxine hydrochloride) is contraindicated in patients who:

- are hypersensitive to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any non medicinal ingredient in the formulation;
- are at risk for asthmatic attack;
- have narrow angle glaucoma;
- have stenosing peptic ulcer;
- have pyloroduodenal obstruction;
- have bladder-neck obstruction; or,
- receive monoamine oxidase inhibitors (MAOIs) [including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)].

WARNINGS AND PRECAUTIONS

General

Due to the anticholinergic properties of antihistamines, caution should be used when pms-DOXYLAMINE-PYRIDOXINE is taken concurrently with other medications or alcohol.

Carcinogenesis and Mutagenesis

See ACTION AND CLINICAL PHARMACOLOGY for human data and TOXICOLOGY for animal data.

Dependence/Tolerance

Like other antihistamines, doxylamine is prone to abuse. Knowledge of the clinical presentation of toxicity and the management of acute overdose is critical (see OVERDOSAGE).

Special Populations

Pregnant Women:
pms-DOXYLAMINE-PYRIDOXINE is intended for use in pregnant women. There has been a vast clinical experience (> 33 million pregnancies worldwide) regarding the use of a combination of doxylamine succinate, pyridoxine hydrochloride with or without dicyclomine hydrochloride in this population. Dicyclomine hydrochloride was a component of earlier formulations intended for nausea and vomiting of pregnancy (NVP) that has since been removed due to a lack of evidence of its contribution to efficacy.

Doxylamine succinate/pyridoxine hydrochloride delayed-release tablets have been the subject of many epidemiological studies (cohort, case control and meta- analyses) designed to detect possible teratogenicity. Two separate meta-analyses have been conducted to assess pregnancy outcome following the use of a combination of doxylamine succinate, pyridoxine hydrochloride with or without dicyclomine hydrochloride during the first trimester. McKeigue et al. conducted a meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991. No increased risk for malformations was found in first trimester exposures to doxylamine succinate and pyridoxine hydrochloride, with or without dicyclomine hydrochloride. A second meta-analysis, conducted by Einarson et al. incorporated 12 cohort and 5 case-control studies. No statistically significant relationships were found between first trimester use of the combination doxylamine succinate, pyridoxine hydrochloride with or without dicyclomine hydrochloride and fetal abnormalities.

In 1989, a report on the safety of Bendectin/doxylamine succinate/pyridoxine hydrochloride delayed-release tablets for use in the management of NVP was prepared by a panel of experts for the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch of Health Canada (currently called the Health Products and Food Branch). Bendectin is no longer available in Canada. pms-DOXYLAMINE-PYRIDOXINE contains two active ingredients: doxylamine succinate and pyridoxine hydrochloride. The panel report stated the following main conclusion: "Numerous studies in animals and in humans that have been reported in the scientific and medical literature demonstrate that Bendectin is not a teratogen. A compound that has no teratogenic effect

can be expected, solely on the basis of chance, to be associated with congenital malformations if it is used widely by pregnant women. The types of congenital malformations reported will vary considerably, not following a consistent pattern of birth defects. The safety of Bendectin/doxylamine succinate/pyridoxine hydrochloride delayed-release tablets in the management of nausea and vomiting of pregnancy has been established by its use in many thousands of pregnant women. The types and numbers of abnormal offspring born to these women were in no way different from those that would be expected, to occur in a similar group of women who did not take these drugs during pregnancy."

Baseline Risk: The background baseline risk of major malformations for all pregnancies is approximately 1-3%. This is the risk of having a child with a birth defect when no teratogenic exposure occurs in pregnancy. This underlying risk may be increased due to maternal age, medical or family history, or exposures to certain drugs, chemicals or levels of radiation known to cause birth defects. Published data show that doxylamine succinate/pyridoxine hydrochloride delayed-release tablets use in pregnancy does not increase a woman's baseline risk of having a child with a major malformation. No other prescription drug has been more extensively studied for safety in pregnancy.

Nursing Women:
The molecular weight of doxylamine succinate is low enough that passage into breast milk should be expected. Paradoxical effects on a nursing infant can be expected, such as unusual excitement, irritability or sedation. Caution is recommended particularly in infants with apnea or other respiratory syndrome. Pyridoxine hydrochloride is excreted into breast milk, but in the doses provided in doxylamine succinate/pyridoxine hydrochloride delayed-release tablets, presents no risk to a nursing infant. Nursing mothers treated with pms-DOXYLAMINE-PYRIDOXINE should not breastfeed or the use of pms-DOXYLAMINE-PYRIDOXINE during lactation should be avoided.

Occupational Hazards

pms-DOXYLAMINE-PYRIDOXINE may cause somnolence. Caution must be exercised in activities requiring mental alertness such as driving a car or operating heavy machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reaction associated with doxylamine succinate is somnolence. Other adverse drug reactions associated with doxylamine succinate may include: vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, irritability, convulsions, urinary retention or insomnia.

Pyridoxine is a vitamin that is generally recognized as having no adverse effects.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a randomized, double-blind, multi-center study in 2308 women with NVP, various combinations of doxylamine succinate, dicyclomine hydrochloride and pyridoxine hydrochloride (each at 10 mg) were compared with placebo in an 8-way study design. The incidence of adverse reactions was 8.7% in the doxylamine/pyridoxine group versus 11.2% in the placebo group. In the doxylamine/pyridoxine group, the most common adverse reactions were drowsiness (15/265, 5.7%), dizziness (3/265, 1.1%), fatigue or lethargy (2/265, 0.75%), gastric irritation, heartburn or indigestion (2/265, 0.75%) and headache (2/265, 0.75%). Corresponding values for the placebo group were drowsiness (8/269, 3%), dizziness (2/269, 0.75%), fatigue or lethargy (3/269, 1.1%), gastric irritation, heartburn or indigestion (0/269) and headache (4/269, 1.5%).

In a double-blind comparison study of placebo and combination drug product (doxylamine succinate, dicyclomine hydrochloride and pyridoxine hydrochloride) in 81 patients, 18 adverse events were reported (22.2%). In the active group, 12 side effects were reported (29.2%) versus 6 (15%) in the placebo group. Feelings of weakness were reported by 2/41 (5%) in the active group versus 0% in the placebo group, tiredness by 2/41 (5%) in the active versus 2/40 (5%) in the placebo group and drowsiness by 3/41 (7%) in the active versus 1/40 (2.5%) in the placebo group. Also reported were: lack of energy, constipation, furry sensation in mouth, wind and headache.

Safety of higher than standard doses of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets were evaluated in 225 pregnant women with NVP in an observational, prospective study. A total of 123 women received standard doses of up to 4 tablets a day and 102 women received a higher than standard dose ("supradose") of 5 to 12 tablets/day. Despite a twice larger mean maximal dose of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets, women receiving the supradose did not report more prevalent adverse effects of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets. In the supradose group, 32% (31/97) reported sleepiness, tiredness and/or drowsiness compared with 35% (42/122) among the standard dose recipients. There was no association between the dose per kg and rates of reported maternal adverse effects with doses ranging from 0.1 mg/kg to 2.0 mg/kg (1-12 tablets).

In a two-way crossover relative bioavailability study (02163) in 22 healthy, non-pregnant women, the rate and extent of absorption of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets were compared to a combination of doxylamine succinate and pyridoxine hydrochloride oral solutions. The number of adverse events experienced per treatment group is as follows: 46 adverse events following treatment A (doxylamine succinate/pyridoxine hydrochloride delayed-release tablets) and 25 adverse events following treatment B (oral solutions). The most commonly reported adverse events were “Headache” and “Nausea” (reported respectively on 17 and 12 occasions of 74 post-dose adverse events).

In a two-way crossover study (02191) in 22 healthy, non-pregnant female subjects, the effect of food on the bioavailability of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets administered under fasting and fed conditions was evaluated. The number of adverse events experienced per treatment group is as follows: 20 adverse events following treatment A (fed conditions) and 29 adverse events following treatment B (under fasting conditions). The most commonly reported adverse event was "Headache" (reported on 6 occasions out of 51 post-dose adverse events).

In a two-way crossover study (70294) in 44 healthy, non-pregnant female subjects, the effect of food on the bioavailability of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets administered under fasting and fed conditions was evaluated. A total of 52 treatment emergent adverse events were reported by 26 of the 44 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 30 adverse events reported by 18 of the 43 subjects who received treatment A and 22 adverse events reported by 15 of the 44 subjects who received treatment B. The most commonly reported adverse events were "Headache" and "Catheter site pain" (related to study design) reported equally by 6 and "Somnolence" reported by 5 of the subjects who constituted the safety population (n=44).

In a one-way crossover study (70381) in 18 healthy, non-pregnant female subjects, the safety and pharmacokinetic profile of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets, administered as a single dose or multiple (40 mg/day) doses, were evaluated. A total of 109 treatment-emergent adverse events were reported by 17 of the 18 subjects who received at least one dose of the study medication (safety population). None of these adverse events were serious. The most commonly reported adverse events were "Nausea" reported by 9 and "Headache" reported by 8 of the subjects who constituted the safety population (n=18).

Abnormal Hematologic and Clinical Chemistry Findings

None reported.

Post-Market Adverse Drug Reactions

The following adverse events, listed alphabetically, have been reported during post-marketing experience with doxylamine succinate/pyridoxine hydrochloride delayed-release tablets. Because these events 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: palpitation, tachycardia
Congenital, familial and genetic disorders: congenital anomalies*, tooth hypoplasia*
Ear and labyrinth disorders: ear discomfort, vertigo
Eye disorders: mydriasis, photophobia, vision blurred, visual acuity reduced, visual brightness
Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhoea, flatulence, hematemesis, nausea, tongue discolouration, vomiting
General disorders and administration site conditions: death, developmental delay*, discomfort, drug withdrawal syndrome, drug withdrawal syndrome neonatal*, fatigue, foaming at mouth, irritability†, malaise, oedema peripheral, pain
Immune system disorders: hypersensitivity
Injury, poisoning and procedural complications: overdose

Investigations: brachial pulse decreased, weight loss
Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia
Musculoskeletal and connective tissue disorders: musculoskeletal pain, pain in extremity
Nervous system disorders: convulsions*, dizziness, headache, hypoesthesia, hypersomnia*, loss of consciousness, somnolence
Pregnancy, puerperium and perinatal conditions: abortion spontaneous, foetal distress syndrome*, foetal hypokinesia*, intra-uterine death*, jaundice neonatal*, premature baby*, premature labour
Psychiatric disorders: anxiety, attention deficit/hyperactivity disorder*, depression, disorientation, impatience, insomnia, mood swings, nightmares
Renal and urinary disorders: dysuria, renal cyst*, urinary retention
Respiratory, thoracic and mediastinal disorders: hypoxia
Skin and subcutaneous tissue disorders: angioedema, erythema multiforme, hyperhydrosis, pruritus, rash, rash maculo-papular, skin decolouration
Social circumstances: mental disability*
Vascular disorders: hypotension, peripheral coldness

**with respect to fetus/child*
†with respect to woman and child

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

No formal drug-drug interaction studies have been performed with doxylamine succinate/pyridoxine hydrochloride delayed release tablets.

Table 1 - Theoretical Drug-Drug Interactions for Doxylamine Succinate

Drugs	Effect	Clinical comment
Monoamine oxidase inhibitors (MAOIs)	Enhance	MAOIs may prolong and intensify the effects of doxylamine succinate.
Antimuscarinic drugs	Additive	There is an increased risk of antimuscarinic side effects when doxylamine is given with other antimuscarinic drugs.
Alcohol and CNS depressants (barbiturates, hypnotics, narcotic analgesics, tranquilizers and sedatives)	Additive	Doxylamine succinate may increase the CNS depressant effects.

Table 2 - Theoretical Drug-Drug Interactions for Pyridoxine Hydrochloride

Drugs	Effect	Clinical comment
Levodopa	Reduces effectiveness	Pyridoxine enhances peripheral decarboxylation of levodopa reducing the effectiveness of levodopa.

Drug-Food Interactions
A food-effect study was conducted demonstrating that the delay in action of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets may be prolonged when tablets are taken with food (see DOSAGE AND ADMINISTRATION).

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Two (2) pms-DOXYLAMINE-PYRIDOXINE (doxylamine succinate/pyridoxine hydrochloride) delayed-release tablets at bedtime to control nausea and vomiting occurring in the morning; additionally one (1) delayed-release tablet in the morning and one (1) delayed-release tablet mid-afternoon to control symptoms throughout the day. The dosage schedule may be individualized according to timing, duration, severity and frequency of the symptoms experienced by the patient. pms-DOXYLAMINE-PYRIDOXINE can be prescribed in any trimester of pregnancy. pms-DOXYLAMINE-PYRIDOXINE is a delayed-release formulation that works optimally when given 4 to 6 hours prior to anticipated onset of symptoms. The delay in action may be prolonged when tablets are taken with food. However, based on the available data, the above recommended dosage schedule should be followed (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics).

pms-DOXYLAMINE-PYRIDOXINE tablets being of a delayed-release formulation should not be prescribed on an as needed basis (p.r.n.). It is important that pms-DOXYLAMINE-PYRIDOXINE is taken daily for optimal effect.

A gradual tapering dose of pms-DOXYLAMINE-PYRIDOXINE is recommended at the time of discontinuation to prevent a sudden onset of symptoms.

Missed Dose
In the event that a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped. The prescribed dosing schedule should be continued.

Administration
pms-DOXYLAMINE-PYRIDOXINE tablets are to be taken orally. pms-DOXYLAMINE-PYRIDOXINE tablets are a delayed-release formulation therefore they should not be crushed or split.

OVERDOSAGE

pms-DOXYLAMINE-PYRIDOXINE is delayed-release therefore signs and symptoms of intoxication may not be apparent immediately.

Signs and symptoms of intoxication may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia. If treatment is needed, it consists of gastric lavage or activated charcoal, whole bowel irrigation and a symptomatic treatment.

At toxic doses, doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis and death. Furthermore, false positives for methadone and phencyclidine may be present if tested using immunoassay-based urine drug screen kits. A prospective study on doxylamine overdosage identified that 16 of 27 patients developed rhabdomyolysis and 3 of these 16 patients developed acute renal failure.

Two fatal case reports involving toddlers who accidently ingested a combination of doxylamine, pyridoxine and dicyclomine have been documented.

Fatalities have been reported from doxylamine overdose. 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. There is no correlation between the amount of doxylamine ingested, the doxylamine plasma level and clinical symptomatology.

According to post-marketing overdose reports with products containing doxylamine, two fatal acute overdoses have been reported to the Canada Vigilance Program database. The dosage ingested and the blood concentration of doxylamine were not reported. In the medical literature, the lethal dosage of doxylamine in humans is reported as 25-250 mg/kg body weight.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Doxylamine succinate/pyridoxine hydrochloride delayed-release tablets provides the action of two unrelated compounds. Doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6) provide anti-nauseant and anti-emetic activity. The delayed action of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets permits the nighttime dose to be effective in the morning hours, when the patient needs it most.

Doxylamine can cross the blood-brain barrier and has a high affinity for H1 receptors in the brain.

The mechanism of action of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets is unknown.

Pharmacokinetics

The pharmacokinetics of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets have been characterized in healthy non-pregnant adult women. Pharmacokinetic results for doxylamine and pyridoxine, including its vitamin B6 metabolites, pyridoxal, pyridoxal 5'-phosphate, are summarized in Tables 3 to 6.

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 doxylamine succinate/pyridoxine hydrochloride delayed-release tablets administered in 18 healthy non-pregnant adult women. A single dose of doxylamine succinate/pyridoxine hydrochloride delayed-release tablet (two tablets at bedtime) was administered on Days 1 and 2. Multiple-doses of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets (one tablet in the morning, one tablet in the afternoon and two tablets at bedtime) were administered on Days 3-18. Single dose pharmacokinetics were determined from blood samples collected pre- and post-dose administration at bedtime on Day 1, with the last sample collected at 24 hours post dose administration. Multiple dose pharmacokinetics were determined from blood samples collected pre- and post-dose administration at bedtime on Day 18, with the last sample collected at 120 hours post-dose administration. Blood samples were also collected pre-dose administration at bedtime on Days 9, 10, 11, 16 and 17.

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 3).

Table 3 – Single-Dose and Multiple-Dose Pharmacokinetics of Doxylamine Succinate/Pyridoxine Hydrochloride Delayed-Release Tablets in Healthy Non-Pregnant Adult Women

	Single Dose			Multiple Dose		
	$AUC_{0\text{-last}}$ (ng•h/mL)	**C_{max} (ng/mL)**	**T_{max} (h)**	**$AUC_{0\text{-last}}$ (ng•h/mL)**	**C_{max} (ng/mL)**	**T_{max} (h)**
Doxylamine	911.4 ± 205.6	83.3 ± 20.6	7.2 ± 1.9	3661.3 ± 1279.2	168.6 ± 38.5	7.8 ± 1.6
Pyridoxine	39.3 ± 16.5	32.6 ± 15.0	5.7 ± 1.5	59.3 ± 33.9	46.1 ± 28.3	5.6 ± 1.3
Pyridoxal	187.5 ± 44.7	74.3 ± 21.8	6.5 ± 1.4	1296.7 ± 363.1	210.0 ± 54.4	6.8 ± 1.2
Pyridoxal 5`Phosphate	442.0 ± 155.6	30.0 ± 10.0	11.7 ± 5.3	4766.3 ± 1137.1	84.9 ± 16.9	6.3 ± 6.6

Multiple-dose administration of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets results in increased concentrations of doxylamine as well as increases in doxylamine C_{max} and $AUC_{0\text{-last}}$ 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 4).

Although no accumulation was observed for pyridoxine, the mean accumulation index for each metabolite (pyridoxal, pyridoxal 5'-phosphate) is more than 1.0 following multiple-dose

administration of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets. The time to reach the maximum concentration is not affected by multiple doses (see Table 3).

Table 4 – Pharmacokinetics of Doxylamine and Pyridoxine Following Single Dose and Multiple Dose Administration of Doxylamine Succinate/Pyridoxine Hydrochloride Delayed-Release Tablets to Healthy Non-Pregnant Adult Women

		$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•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

Food Effect:

The administration of food delays the absorption of doxylamine. This delay is associated with a lower peak concentration of doxylamine, but the extent of absorption is not affected (see Table 5).

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. Pyridoxal 5'-phosphate C_{max} and extent of absorption is comparable under fasting and fed conditions.

Table 5 – Pharmacokinetics of Doxylamine Following Administration of Doxylamine Succinate/Pyridoxine Hydrochloride Delayed-Release Tablets Under Fed and Fasted Conditions in Healthy Non-Pregnant Adult Women

		$AUC_{0\text{-t}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•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]

[a]N=37

Distribution:

Pyridoxine main active metabolite, pyridoxal 5'-phosphate, is released into the circulation (accounting for at least 60% of circulating vitamin B6) and is highly protein bound, primarily to albumin.

Metabolism:

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

Pyridoxine is a prodrug primarily metabolized in the liver. The metabolic scheme for pyridoxine is complex, with formation of primary and secondary metabolites along with interconversion back to pyridoxine.

Excretion:
The principle metabolites of doxylamine, N-desmethyl-doxylamine and N, N-didesmethyldoxylamine, are excreted by the kidney.

The major metabolite of pyridoxine, 4-pyridoxic acid, is inactive and is excreted in urine.

The terminal elimination half-life of doxylamine is 12.5 hours (see Table 6).

Table 6 – Terminal Elimination Half-Life ($T_{1/2el}$) for Doxylamine Succinate/Pyridoxine Hydrochloride Delayed-Release Tablets 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
Pyridoxal 5'-Phosphate	81.6 ± 42.2

Carcinogenesis and Mutagenesis

A case-control investigation was performed by the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) to analyze the incidence of childhood cancer in relation to the maternal consumption of doxylamine succinate, dicyclomine hydrochloride and pyridoxine hydrochloride.

Data were derived from interview reports and medical records of 555 mothers of children (under 15 years of age) with cancer and 1110 mothers of matched control children. Maternal ingestion of the antiemetic drug during the index pregnancy was not associated with increasing the risk of childhood malignant disease. No dose-response relationship was evident.

Special Populations and Conditions

Race: No data is available on differences in the pharmacokinetics of either doxylamine succinate or pyridoxine hydrochloride in different races.

Hepatic Insufficiency: No data is available on differences in the pharmacokinetics of either doxylamine succinate or pyridoxine hydrochloride in patients with hepatic insufficiency.

Renal Insufficiency: No data is available on differences in the pharmacokinetics of doxylamine succinate in renal insufficiency. For pyridoxine hydrochloride some metabolites are excreted renally. There are no data to suggest that this should alter the current dosage recommendation of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets.

Genetic Polymorphism: No data is available.

STORAGE AND STABILITY

Store between 15°C and 30°C. Protect from light. Keep out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Delayed-Release Tablets

10 mg/10 mg: Each white, round, biconvex, coated tablet ink-printed in black with "DP 10" on one side and nothing on the other side contains 10 mg of doxylamine succinate and 10 mg pyridoxine hydrochloride, and the following non medicinal ingredients: Colloidal Anhydrous Silica, Dibasic Calcium Phosphate, FD&C Blue #1 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, Glycerides, Hydroxypropyl Methylcellulose, Isopropyl Alcohol, Lecithin (Soya) FCC, Magnesium Stearate, Mannitol, Methacrylic Acid Copolymer, Methylated Silica, Methylcellulose, N-Butyl Alcohol, Polydimethylsiloxane, Polyethylene Glycol Sorbitan Tristearate, Propylene Glycol, Shellac Glaze, Simethicone, Sodium Bicarbonate, Sodium Lauryl Sulfate, Sorbic Acid, Sulfuric Acid, Talc, Titanium Dioxide, Triethyl Citrate. Available in HDPE bottles of 100 and 500 tablets

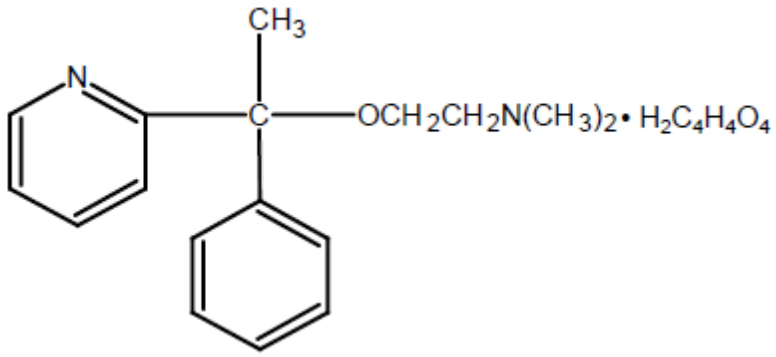
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Doxylamine succinate
Chemical names:	Ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1) 2-[α-[2-(dimethylamino)ethoxy]- α-methylbenzyl] pyridine succinate (1:1)
Molecular formula:	$C_{17}H_{22}N_2O \cdot C_4H_6O_4$
Molecular mass:	388.46 g/mol

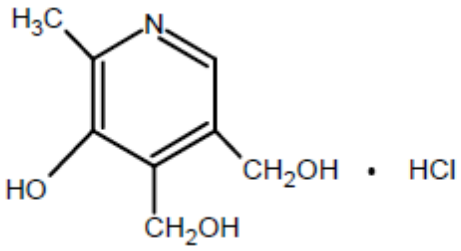
Structural formula:



Physicochemical properties:	Doxylamine succinate is very soluble in water and alcohol, readily soluble in chloroform and slightly soluble in ether and benzene.

Proper name:	Pyridoxine hydrochloride
Chemical name:	5-hydroxy-6-methyl-3,4-pyridine dimethanol hydrochloride
Molecular formula:	$C_8H_{11}NO_3 \bullet HCl$
Molecular mass:	205.4 g/mol

Structural formula:



Physicochemical properties:	Pyridoxine hydrochloride is readily soluble in water, slightly soluble in alcohol and insoluble in ether.

CLINICAL TRIALS

Study conducted under fasting conditions

A randomized, single dose, 2-period, 2-sequence, crossover design comparative bioavailability study of pms-DOXYLAMINE-PYRIDOXINE 10 mg/10 mg Delayed-Release Tablets (Pharmascience Inc.) was performed versus DICLECTIN 10 mg/10 mg Delayed-Release Tablets (Duchesnay Inc.) administered as 2 x 10 mg/10 mg dose to healthy adult male volunteers, between 20 and 55 years, under fasting conditions. Bioavailability data from 27 volunteers are summarized in the following tables:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Doxylamine **(2 x 10/10 mg)** From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng-h/mL)	1192.02 1236.97 (20.5)	1193.74 1232.78 (19.9)	99.86	96.63-103.19
AUC_I (ng-h/mL)	1244.99 1296.38 (21.9)	1248.72 1294.65 (21.6)	99.70	96.43-103.08
C_{max} (ng/mL)	74.38 76.14 (16.5)	74.74 76.22 (17.4)	99.51	95.62-103.57
T_{max}§ (h)	4.50 (3.00-6.00)	4.50 (2.00-8.00)		
$T_{½}$€ (h)	13.15 (17.5)	13.03 (18.1)		

* pms-DOXYLAMINE-PYRIDOXINE (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Pharmascience Inc., Montréal, Québec, Canada)
† DICLECTIN® (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Duchesnay Inc.) were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Pyridoxine **(2 x 10/10 mg)** From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng-h/mL)	40.69 43.52 (32.7)	41.99 44.73 (31.1)	96.91	90.02-104.33
AUC_I (ng-h/mL)	38.65 41.28 (34.7)	41.53 44.36-(33.5)	93.06	85.85-100.88
C_{max} (ng/mL)	39.62 46.19 (52.6)	42.96 47.55 (47.7)	92.23	77.01-110.46
T_{max}§ (h)	1.75 (0.67-4.5)	2.00 (1.00-6.00)		
$T_{½}$€ (h)	0.37 (168.4)	0.27 (37.9)		

* pms-DOXYLAMINE-PYRIDOXINE (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Pharmascience Inc., Montréal, Québec, Canada)

† DICLECTIN® (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Duchesnay Inc.) were purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV%) only

Study conducted under fed conditions

A randomized, single dose, 2-period, 2-sequence, crossover design comparative bioavailability study of pms-DOXYLAMINE-PYRIDOXINE 10 mg/10 mg Delayed-Release Tablets (Pharmascience Inc.) was performed versus DICLECTIN 10 mg/10 mg Delayed-Release Tablets (Duchesnay Inc.) administered as 2 x 10 mg/10 mg dose to healthy adult male volunteers, between 20 and 55 years under fed conditions. Bioavailability data from 27 volunteers are summarized in the following tables:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Doxylamine **(2 x 10/10 mg)** From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng-h/mL)	1363.37 1404.37 (23.7)	1329.03 1364.96 (22.9)	102.58	99.73-105.52
AUC_I (ng-h/mL)	1416.56 1460.33 (24.1)	1375.29 1414.53 (23.6)	103.00	100.31-105.77
C_{max} (ng/mL)	80.68 82.22 (19.5)	82.08 83.17 (17.7)	98.29	93.96-102.83
T_{max}§ (h)	8.00 (3.00-12.00)	8.50 (5.00-24.00)		
$T_{½}$€ (h)	13.66 (22.0)	13..30 (18.8)		

* pms-DOXYLAMINE-PYRIDOXINE (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Pharmascience Inc., Montréal, Québec, Canada)

† DICLECTIN® (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Duchesnay Inc.) were purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Pyridoxine (2 x 10/10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng-h/mL)	300.02 307.35 (22.9)	261.59 264.65 (17.0)	114.69	109.04-120.63
AUC_I (ng-h/mL)	304.14 310.51 (22.6)	276.57 278.08 (16.4)	109.97	102.89-117.54
C_{max} (ng/mL)	39.25 41.00 (30.4)	39.52 41.26 (32.80)	99.32	89.82-109.83
T_{max}§ (h)	6.00 (2.00-11.00)	7.50 (4.00-12.00)		
$T_{½}$€ (h)	18.49 (32.8)	20.70 (51.2)		

* pms-DOXYLAMINE-PYRIDOXINE (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Pharmascience Inc., Montréal, Québec, Canada)
† DICLECTIN® (doxylamine succinate/pyridoxine hydrochloride) 10 mg/10 mg delayed-release tablets (Duchesnay Inc.) were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

TOXICOLOGY

Reproductive Toxicology

Tyl *et al.* studied a drug product containing equal concentrations of doxylamine succinate and pyridoxine hydrochloride in rats at doses of 0, 200, 500 and 800 mg/kg/day. Both maternal and fetal toxicity were evident at the two highest doses. Developmental toxicity included reduced prenatal viability and reduced fetal body weight per litter (500 and 800 mg/kg/day). No teratogenic effects of this drug were found even at the maternally toxic dose of 800 mg/kg/day. The finding of minor skeletal variations, such as a shortened 13th rib, only at the toxic high doses is consistent with general toxicity.

Teratology studies in rabbits and reproduction studies in rats were conducted with doxylamine succinate alone, dicyclomine HCl alone, and a drug product containing a combination of doxylamine succinate, dicyclomine HCl and pyridoxine HCl. One of three groups of rats received 3-60 mg/kg/day of the combination, while the two other groups received 10-100 mg/kg/day of either dicyclomine or doxylamine. In the three rabbit groups, 3-30 mg/kg/day of the drug product containing the combination, and 10-100 mg/kg/day of either dicyclomine HCl or doxylamine succinate were given. No increase in congenital malformations or other adverse effects were noted in pregnancy when compared to nonexposed controls. None of these materials appeared to have any deleterious effects on reproductive parameters such as pregnancy maintenance, litter size, or fetal weight in the rabbit, except when toxic (100 mg/kg/day doxylamine succinate or dicyclomine HCl) levels were reached. In rats, these same drugs produced no alteration in breeding, conception, pregnancy maintenance, litter size, or fetal weight, although a mild dose-related decrease in neonatal

weight gains occurred in pups from doxylamine succinate and dicyclomine hydrochloride-treated dams.

In the first part of their investigation, Hendrickx et al. evaluated embryotoxicity of a combination of doxylamine succinate and pyridoxine hydrochloride in an uncontrolled small- scale study in preterm and term cynomolgus monkeys, rhesus monkeys and baboons. Some baboons received doxylamine succinate alone as opposed to the combination. Drugs were administered throughout the major period of organogenesis (gestation day 22 to 50). In these teratogenicity studies in the 3 species the treatment related effects of exposure to the combination of doxylamine succinate and pyridoxine hydrochloride *in utero* appear to be limited to a delay in closure of the ventricular septum that was evident at 100 days of gestation but not at term. Ventricular septal defects (VSD) were observed in 6 (40%) of the preterm cynomolgus monkeys, 2 (18%) of the preterm rhesus monkeys and 3 (23%) of the preterm baboons examined prenatally (day 100 of gestation). No dose response was evident and there were no other cardiac or extracardiac defects found except for one baboon fetus with multiple defects. No defects were observed in cynomolgus monkeys who were administered the combination of doxylamine succinate and pyridoxine hydrochloride for 4-day periods between 22 and 41 days of gestation. There was no association of this combination treatment with any noncardiac defect. In monkeys examined at term, there was no incidence of VSD, but one cynomolgous monkey had a mitral valve defect. This suggests an intrauterine delay in closure of the ventricular septum in monkeys, but that closure would occur before birth.

The second part of this investigation examined the embryotoxic and teratogenic potential of doxylamine succinate and pyridoxine hydrochloride in term cynomolgus monkeys. The combination of doxylamine succinate and pyridoxine hydrochloride pulverized tablets or placebo were administered double-blind by nasogastric intubation on days 22-50 of gestation at doses approximately 2, 5 and 20 times the MRHD. Fetuses were delivered by caesarean section near term and examined. No congenital malformations were noted, and no evidence of embryo, fetal or maternal toxicity was observed.

Carcinogenicity

Two-year carcinogenicity studies in rats and mice were conducted at the U.S. National Center for Toxicological Research (NCTR). The rodents were administered doxylamine succinate at dose levels of 0, 500, 1000 and 2000 parts per million (ppm) in rats and dose levels of 0, 190, 375 and 750 ppm in mice. There were no increases in neoplastic lesions in female rats. Liver neoplasms in male rats were found only in the high-dose group. A trend test was significant ($p = 0.05$) for increased incidence of hepatocellular adenoma and carcinoma with increasing doses of doxylamine succinate, but the increased incidence of either lesion alone in the high dose group was not significant compared with controls. The incidence of these lesions was within the range historically observed in this strain of rats, and the results are not considered to have clinical relevance in humans.

In the mouse bioassay, tumours that showed a statistically significant increase versus the control group in a trend test and in pairwise comparisons included hepatocellular adenomas and thyroid follicular cell adenomas. Doxylamine succinate produced a significant increase in hepatocellular adenomas in the mid to high dose group in male mice and the high dose group in female mice. There was no increase in the incidence of hepatocellular carcinomas in male mice and no hepatocellular carcinomas observed in any female mice. Thyroid follicular cell adenomas also were increased in

treated mice of both sexes. These observations are consistent with a hormonal imbalance caused by induction of cytochrome P450 by doxylamine succinate in mice. Since enzyme induction is not observed in humans, doxylamine succinate is not considered to pose a carcinogenic risk under clinical use.

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PART III: CONSUMER INFORMATION

[Pr]pms-DOXYLAMINE-PYRIDOXINE
Doxylamine succinate/Pyridoxine hydrochloride
Delayed-Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when pms-DOXYLAMINE-PYRIDOXINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-DOXYLAMINE-PYRIDOXINE. It does not take the place of talking to your doctor, pharmacist or healthcare professional. Contact your doctor, pharmacist or healthcare professional if you have any questions about the drug. Keep this leaflet with the medicine. You may need to read it again. As pms-DOXYLAMINE-PYRIDOXINE is a prescription medicine, it should only be used under medical supervision.

ABOUT THIS MEDICATION

What the medication is used for:
The management of nausea and vomiting of pregnancy. pms-DOXYLAMINE-PYRIDOXINE can be used during any trimester of pregnancy.

What it does:
pms-DOXYLAMINE-PYRIDOXINE provides the anti-nauseant and anti-vomiting action of two different ingredients: doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B_6).

When it should not be used:
You should not be given pms-DOXYLAMINE-PYRIDOXINE if you:

- are allergic to pms-DOXYLAMINE-PYRIDOXINE or to any of the non medicinal ingredients;
- have any of the following conditions: risk of asthmatic attack, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, bladder-neck obstruction;
- are receiving a monoamine oxidase inhibitor (MAOIs) [e.g., certain antidepressants, linezolid (an antibiotic), methylene blue (a diagnostic dye)].

What the medicinal ingredients are:
Doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B_6).

What the non medicinal ingredients are:
Colloidal Anhydrous Silica, Dibasic Calcium Phosphate, FD&C Blue #1 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, Glycerides, Hydroxypropyl Methylcellulose, Isopropyl Alcohol, Lecithin (Soya) FCC, Magnesium Stearate, Mannitol, Methacrylic Acid Copolymer, Methylated Silica, Methylcellulose, N-Butyl Alcohol, Polydimethylsiloxane, Polyethylene Glycol Sorbitan Tristearate, Propylene Glycol, Shellac Glaze, Simethicone, Sodium Bicarbonate, Sodium Lauryl Sulfate, Sorbic Acid, Sulfuric Acid, Talc, Titanium Dioxide, Triethyl Citrate.

What dosage forms it comes in:
Delayed-Release Tablets (Doxylamine succinate/Pyridoxine hydrochloride)**:** 10 mg/10 mg

WARNINGS AND PRECAUTIONS

pms-DOXYLAMINE-PYRIDOXINE may cause somnolence. Caution must be exercised in activities requiring mental alertness such as driving a car or operating heavy machinery. Until you know how you will react to this medication, do not drive or operate machinery.

pms-DOXYLAMINE-PYRIDOXINE may pass into breast milk and unusual excitement, irritability or sedation (sleepiness) may occur in the infant. Nursing mothers treated with pms-DOXYLAMINE-PYRIDOXINE should not breastfeed or the use of pms-DOXYLAMINE-PYRIDOXINE during lactation should be avoided.

INTERACTIONS WITH THIS MEDICATION

Deeper somnolence could be produced if pms-DOXYLAMINE-PYRIDOXINE is taken in combination with alcohol or other drugs such as drugs for cough or colds, pain killers or sleep aids.

You should tell your doctor if you are taking or have recently taken any medications (prescription or non-prescription) or natural/herbal products, especially:

- a monoamine oxidase inhibitor (MAOIs) [e.g., linezolid (an antibiotic), methylene blue (a diagnostic dye)]
- antimuscarinic drugs (used in treating a variety of conditions such as disorders of the bowel, bladder or respiratory systems, Parkinson's disease, certain heart conditions and insomnia).
- alcohol and other central nervous system depressants, such as drugs for anxiety, seizures, mental illness, and allergies, sleeping pills, anesthetics (used for surgery), certain pain medications.

PROPER USE OF THIS MEDICATION

pms-DOXYLAMINE-PYRIDOXINE is a delayed-release formulation that works best when taken 4 to 6 hours before needed and should be taken on a daily basis. If taken with food, it may take longer to feel a relief of symptoms.

Usual dose:
pms-DOXYLAMINE-PYRIDOXINE should be taken as prescribed by your doctor or healthcare professional.

1. Take two pms-DOXYLAMINE-PYRIDOXINE delayed-release tablets at bedtime to control nausea and vomiting occurring in the morning
2. Take 1 delayed-release tablet in the morning and,

3. Take 1 delayed-release tablet mid-afternoon to control symptoms throughout the day.

Your doctor or healthcare professional may adjust the dosing schedule according to your condition.

Do not stop taking pms-DOXYLAMINE-PYRIDOXINE on your own. Always consult your doctor or healthcare professional. They will gradually reduce your dose when stopping pms-DOXYLAMINE-PYRIDOXINE treatment to prevent a sudden return of nausea and vomiting.

This drug is specifically prescribed for you and your actual state of health. Do not give it to others, even if they have the same symptoms, and you yourself must not use it for any other condition than the one for which it was prescribed.

Tablets should not be crushed or split.

Missed Dose:
If you forget to take a dose of pms-DOXYLAMINE-PYRIDOXINE, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and continue with your regular dosing schedule. Do not try to make up for a missed dose by taking a double dose.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you suspect an accidental overdose, seek medical attention immediately. Do not wait for any signs or symptoms to appear before seeking medical attention, as they may not occur immediately.

Signs and symptoms of overdosage are restlessness, dryness of mouth, dilated pupils, sleepiness, dizziness, mental confusion and rapid heartbeat.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, pms-DOXYLAMINE-PYRIDOXINE can cause some side effects. You may not experience any of them. For most patients, these side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

If you experience an allergic reaction (including skin rash, hives, swelling, trouble breathing) or any severe or unusual side effects, seek immediate emergency medical assistance.

Side effects associated with pms-DOXYLAMINE-PYRIDOXINE are: somnolence, dizziness, nervousness, stomach pain, headache, diarrhea, irritability, or insomnia.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	None			
Very rare	Disorientation			✓
	Difficulty urinating		✓	
	Irregular heartbeat			✓
	Seizures			✓

This is not a complete list of side effects. For any unexpected effects while taking pms-DOXYLAMINE-PYRIDOXINE, contact your doctor, pharmacist or healthcare professional.

HOW TO STORE IT

Store between 15°C and 30°C.

Protect from light.

Keep out of reach and sight of children.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical

advice.

MORE INFORMATION

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by
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