HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BONJESTA safely and effectively. See full prescribing information for BONJESTA.

BONJESTA (doxylamine succinate and pyridoxine hydrochloride), extended-release tablets, for oral use.
Initial U.S. Approval: 1976

------ RECENT MAJOR CHANGES ------
Warnings and Precautions, Interference with Urine Screen for Methadone, Opiates and Phencyclidine Phosphate (PCP) (5.3) 06/2018

------ INDICATIONS AND USAGE ------
BONJESTA is a fixed dose combination drug product of 20 mg doxylamine succinate, an antihistamine, and 20 mg pyridoxine hydrochloride, a Vitamin B_6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. (1)

---- DOSAGE AND ADMINISTRATION ----
On Day 1, take one tablet at bedtime. On Day 2, if symptoms are not adequately controlled, the dose can be increased to one tablet in the morning and one tablet at bedtime. The maximum recommended dose is two tablets daily, one in the morning and one at bedtime, as described in the full prescribing information. (2)

--- DOSAGE FORMS AND STRENGTHS ---
Extended-release tablets containing 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. (3)

-------- CONTRAINDICATIONS --------
- Known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredient in the formulation (4)
- Monoamine oxidase (MAO) inhibitors (4, 7)

---- WARNINGS AND PRECAUTIONS ----
- Somnolence: BONJESTA may cause somnolence. Avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using BONJESTA until cleared to do so by a healthcare provider (5.1)
- Central nervous system (CNS) depressants: Concurrent use with alcohol or other CNS depressants is not recommended (5.1)
- Anticholinergic actions: Use with caution in patients with asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction (5.2)
- Interference with urine drug screen: BONJESTA may interfere with urine screening for methadone, opiates and PCP (5.3)

-------- ADVERSE REACTIONS --------
The most common adverse reaction (≥ 5 percent and exceeding the rate in placebo) with combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablets is somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Duchesnay Inc. at 1-855-722-7734 or medicalinfo@duchesnayusa.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-------- DRUG INTERACTIONS --------
- Severe drowsiness can occur when used in combination with alcohol or other sedating medications. (7)

----- Use in specific populations -----
BONJESTA is intended for use in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

2. DOSAGE AND ADMINISTRATION

2.1 Dosage Information

Initially, take one BONJESTA extended-release tablet orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking one tablet daily at bedtime only. However, if symptoms persist on Day 2, increase the daily dose to one tablet in the morning and one tablet at bedtime. The maximum recommended dose is two tablets per day, one in the morning and one at bedtime.

Take on an empty stomach with a glass of water *[see Clinical Pharmacology (12.3)]*. Swallow tablets whole. Do not crush, chew, or split BONJESTA tablets.

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

3. DOSAGE FORMS AND STRENGTHS

BONJESTA extended-release tablets are pink, round, film-coated tablets containing 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride, imprinted on one side with the pink image of a pregnant woman and a "D" on the other side.

4. CONTRAINDICATIONS

BONJESTA 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 BONJESTA *[see Drug Interactions (7.1)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Somnolence and Severe Drowsiness

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

BONJESTA 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 (7.1)]*.

5.2 Concomitant Medical Conditions

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

5.3 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 (7.3)]*.

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:
- Somnolence *[see Warnings and Precautions (5.1)]*
- Falls or other accidents resulting from the effect of the combined use of BONJESTA with CNS depressants including alcohol *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trial Experience

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 maculopapular

7. DRUG INTERACTIONS

7.1 Drug Interactions

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

7.2 Drug-Food Interactions

A food-effect trial demonstrated that the delay in the onset of action of BONJESTA may be further delayed, and a reduction in absorption may occur when tablets are taken with food *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*. Therefore, BONJESTA should be taken on an empty stomach with a glass of water *[see Dosage and Administration (2)]*.

7.3 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.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

BONJESTA 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 of doxylamine succinate and

11. DESCRIPTION

BONJESTA extended-release tablets consist
doxylamine succinate and 10 mg pyridoxine h
of 10 mg doxylamine succinate and 10 mg p

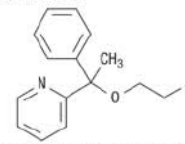
BONJESTA tablets are round, pink, film-coate
ing a total of 20 mg doxylamine succinate a
imprinted on one side with the pink image of

Inactive ingredients are as follows: ammoniu
colloidal silicon dioxide, croscarmellose sod
alcohol, ferrosoferric oxide, FD&C Blue #2 al
propyl alcohol, magnesium stearate, magn
microcrystalline cellulose 102, PEG 3350,
sodium bicarbonate, sodium lauryl sulfate, ta

BONJESTA is certified Kosher, Kosher for Pas

Doxylamine Succinate

Doxylamine succinate is classified as an ant
succinate is ethanamine, N,N-dimethyl-2-[
(1:1). The empirical formula is $C_{17}H_{22}N_2O$ • $C_4H_6O_4$ and the molecular mass is 388.46 g/mol. The structural formula is:



Doxylamine succinate is a white to creamy
alcohol, freely soluble in chloroform and very

Pyridoxine Hydrochloride

Pyridoxine hydrochloride is a vitamin B_6 analo
ride is 3,4-pyridinedimethanol, 5-hydroxy-6-
$C_8H_{11}NO_3$ • HCl and the molecular mass is

Pyridoxine hydrochloride is a white or practi
uble in water, slightly soluble in alcohol and

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of BONJESTA is un

12.3 Pharmacokinetics

The pharmacokinetics of BONJESTA has be
women.

Absorption

(b) (4)

Table 2 – Mean ± SD Single-Dose Pharmacokinetics of BONJESTA in Healthy Premenopausal Adult Women

		BONJESTA Mean±SD				
		AUC_{0-t} (ng•h/mL)	AUC_{0-inf} (ng•h/mL)	AUC_{0-72} (ng•h/mL)	C_{max} (ng/mL)	T_{max}[b] (h)
Doxylamine	N=48	1367.0 ± 356.7	1425.8 ± 405.1	–	92.3 ± 15.7	4.5 (2.5-5.5)
Pyridoxine	N=47	42.3 ± 14.7	42.5 ± 14.7	–	47.1 ± 18.7	0.5 (0.5-4.7)
Pyridoxal[a]	N=48*	203.7 ± 51.7	233.6 ± 55.9	–	58.9 ± 17.0	3.0 (0.8-5.0)
Pyridoxal 5′-phosphate[a]	N=48	–	–	1076.2 ± 382.2	30.1 ± 9.2	9.0 (3.0-16.0)

*N=46 for AUC_{0-inf}
[a] Baseline corrected values
[b] Median (range)

In a multiple-dose, crossover clinical trial conducted in 31 healthy, premenopausal women, one BONJESTA (20 mg doxylamine succinate and 20 mg pyridoxine) tablet given twice daily for 11 days was bioequivalent to one combination tablet of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride given three times daily (1 tablet in the morning, 1 tablet in the afternoon and 2 tablets at bedtime), based on the exposure (AUC) and peak concentration (C_{max}) of doxylamine and baseline corrected pyridoxal 5′-phosphate. Mean ± SD plasma (whole blood for pyridoxal) PK parameters are summarized in Table 3.

Table 3 – Mean ± SD Multiple-Dose (Day 11) Pharmacokinetic Parameters of BONJESTA (given twice daily) in Healthy Premenopausal Adult Women

		BONJESTA Mean±SD				
		AUC_{0-24} (ng•h/mL)	AUC_{0-12} (ng•h/mL)	AUC_{0-6} (ng•h/mL)	C_{max} (ng/mL)	T_{max}[b] (h)
Doxylamine	N=34	2879.4 ± 696.0	1573.2 ± 406.5	883.6 ± 228.5	173.6 ± 45.5	3.5 (1.0-20.0)
Pyridoxine	N=34	80.0 ± 22.7	46.3 ± 15.4	45.3 ± 16.3	48.2 ± 23.7	1.5 (0.3-16.5)
Pyridoxal[a]	N=34	1511.3 ± 300.0	848.1 ± 183.6	647.2 ± 149.6	189.6 ± 48.3	3.0 (2.0-15.0)
Pyridoxal 5′-phosphate[a]	N=34	1742.3 ± 554.3	831.7 ± 274.5	426.2 ± 144.0	85.9 ± 26.2	15.0 (2.0-24.0)

[a] Baseline corrected values
[b] Median (range)

Food Effect

In a single-dose, crossover clinical trial conducted in 23 healthy, premenopausal women, the administration of a high fat, high calorie meal delayed the absorption of doxylamine, pyridoxine, and pyridoxine metabolites. This delay is associated with lower peak concentrations of doxylamine, pyridoxine, and pyridoxal. The extent of absorption for pyridoxine was decreased.

The effect of food on the peak concentration and the extent of absorption of the pyridoxine

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 B_6 concentrations.

Metabolism

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 metabolized in the liver.

Excretion

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 11.9 hours and 0.4 hours, respectively (see Table 5).

Table 5 – Terminal Elimination Half-Life ($T_{1/2el}$) for BONJESTA Administered as a Single Dose under Fasting Conditions in Healthy Premenopausal Adult Women (N=23)

	BONJESTA $T_{1/2el}$ (h)
Doxylamine	11.9 ± 2.2
Pyridoxine	0.4 ± 0.2[a]
Pyridoxal	8.0 ± 1.7[b]

[a] N=12
[b] Baseline corrected value

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.

13. NONCLINICAL TOXICOLOGY

13.1 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.

14. CLINICAL STUDIES

There have been no efficacy and safety trials conducted with BONJESTA.

A double-blind, randomized, multi-center, placebo-controlled study was conducted to support the safety and efficacy of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablets (a different formulation and dosage strength than BONJESTA) 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 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablets or placebo. Two tablets of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride 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

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

BONJESTA extended-release tablets are supplied in a high-density polyethylene bottle with a polypropylene child-resistant cap and a silica gel desiccant canister. Each pink, round, film-coated, extended-release tablet contains 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride, and is imprinted on one side with the pink image of a pregnant woman and a "D" on the other side. BONJESTA tablets are provided as follows:

NDC 55494-120-60 Bottles of 60
NDC 55494-120-10 Bottles of 100

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed and protect from moisture. Do not remove desiccant canister from bottle.

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Somnolence

Inform women to avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using BONJESTA until cleared to do so.

Inform women of the importance of not taking BONJESTA with alcohol or sedating medications, including other antihistamines (present in some cough and cold medications), opiates and sleep aids because somnolence could worsen leading to falls or other accidents.

Interference with urine drug screening

Inform women that use of BONJESTA may result in false positive urine drug screening for methadone, opiates and PCP.

BONJESTA is a registered trademark of Duchesnay Inc.

U.S. Patent Nos. 9,089,489, 7,560,122, 9,375,404 & 9,526,703.

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Patient Information
BONJESTA (bonn jest ah)
(doxylamine succinate and pyridoxine hydrochloride),
extended-release tablets, for oral use

What is BONJESTA?

- BONJESTA is a prescription medicine used to treat nausea and vomiting of pregnancy

How should I take BONJESTA?

- Talk to your healthcare provider about
take it.
- Take BONJESTA everyday as prescribed.
BONJESTA without talking to your health
- **See the following schedule for the rig**
  - Start with 1 tablet by mouth at bedt
controlled on Day 2, continue to take
  - If you still have nausea and vomiting
and 1 tablet at bedtime each day.
- **Do not** take more than 2 tablets (1 in th
- Take BONJESTA on an empty stomach w
- Take BONJESTA tablets whole. Do not cr
swallowing. If you cannot swallow BO
provider.
  - If you take too much BONJESTA (over
restlessness, dry mouth, the pupils of
dizziness, confusion, fast heart rate,
changes and build-up of fluid in the b
severe, they may lead to death. If yo
control center at 1-800-222-1222.

What are the possible side effects of BO
BONJESTA may cause serious side effec
Drowsiness is a common side effect when
- **Do not** drive, operate heavy machinery,
tion unless your healthcare provider say
- **Do not** drink alcohol, or take other centr
and cold medicines, certain pain medici
you take BONJESTA. Severe drowsiness
accidents.

BONJESTA may cause false positive u
opiates and PCP.
These are not all the possible side effects o
Call your doctor for medical advice about si
at 1-800-FDA-1088.

How should I store BONJESTA?

- Store BONJESTA at room temperature bu
- Keep the bottle tightly closed to protect
- The BONJESTA bottle contains a desicca
not throw away the desiccant.
- Safely throw away medicine that is past

Keep BONJESTA and all medicines out o

General information about the safe and
Medicines are sometimes prescribed for p
Information leaflet. You can ask your phan
about BONJESTA that is written for healt
a condition for which it was not prescribed.
if they have the same symptoms that you h

What are the ingredients in BONJESTA?
Active ingredient: doxylamine succinate (a

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
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