SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

BONJESTA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pyridoxine hydrochloride 20 mg

Doxylamine succinate 20 mg

For the full list of excipients, see section 12.

3. PHARMACEUTICAL FORM

Extended release tablets.

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. ClINICAL PARTICULARS

4.1 Therapeutic indications

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

Limitations of Use

BONJESTA has not been studied in women with hyperemesis gravidarum.

4.2 Posology and method of administration

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.

4.3 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. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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 combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablets compared to placebo was studied 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 (14)]*. Adverse reactions that occurred at an incidence ≥5 percent and exceeded the incidence for placebo are summarized in Table 1.

Table 1 – Number (Percent) of Women with ≥ 5 Percent Adverse Reactions in a 15-Day Placebo-Controlled Trial of Combination 10 mg Doxylamine Succinate and 10 mg Pyridoxine Hydrochloride Tablets (Only Those Adverse Reactions Occurring at an Incidence ≥ 5 Percent and at a Higher Incidence than Placebo are Shown)

Adverse Reaction	**Combination 10 mg Doxylamine Succinate and 10 mg Pyridoxine Hydrochloride Tablets** (N = 133)	**Placebo** (n = 128)
Somnolence	19 (14.3%)	15 (11.7%)

6.2 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 maculopapular

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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

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 Posology and method of administration (4.2), Clinical Pharmacology (12.3)]*. Therefore, BONJESTA should be taken on an empty stomach with a glass of water *[see Posology and method of administration (4.2)]*.

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 pyridoxine hydrochloride with or without dicyclomine hydrochloride.

8.2 Lactation

Risk Summary

Women should not breastfeed while using BONJESTA.

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 BONJESTA 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.

8.4 Pediatric Use

The safety and effectiveness of BONJESTA 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.

10. OVERDOSAGE

10.1 Signs and Symptoms of Overdose

BONJESTA is an extended-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.

10.2 Management of Overdose

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

11. DESCRIPTION

BONJESTA extended-release tablets consist of an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and an immediate release coating of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

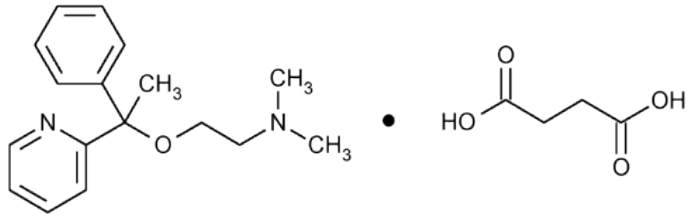
BONJESTA tablets are round, pink, film-coated, multilayer, extended-release tablets containing a total of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. Tablets are imprinted on one side with the pink image of a pregnant woman and a “D” on the other side.

Inactive ingredients are as follows:
Tablet core:
Microcrystalline cellulose PH 102
Magnesium Trisillicate
Magnesium Stearate
Croscarmellose Sodium
Colloidal Silicone Dioxide

Tablet coating:
Opadry Clear 02O0190000
Acryl-Eze Clear
Opadry II Pink
Triethyl Citrate
Carnauba Wax Powder
Simethicone Emulsion 30%
Opacode S-1-14022 Pink

Doxylamine Succinate

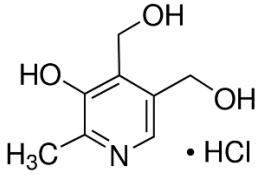
Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1). The empirical formula is $C_{17}H_{22}N_2O \bullet C_4H_6O_4$ and the molecular mass is 388.46. The structural formula 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 B_6 analog. The chemical name for pyridoxine hydrochloride is 3,4-pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride. The empirical formula is $C_8H_{11}NO_3$ • 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.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of BONJESTA is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of BONJESTA has been characterized in healthy non-pregnant adult women.

Absorption

In a single-dose, crossover clinical trial conducted in 48 healthy, premenopausal women under fasting conditions, one BONJESTA (20 mg doxylamine succinate and 20 mg pyridoxine) tablet was bioequivalent to two combination tablets of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride 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) pharmacokinetic (PK) parameters are summarized in Table 2.

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 component is more complex because the pyridoxine metabolites such as pyridoxal, pyridoxamine, pyridoxal 5′-phosphate, and pyridoxamine 5′-phosphate also contribute to the biological activity. Food significantly reduces the bioavailability of pyridoxine, lowering its C_{max} and AUC by approximately 67% and 37%, respectively, compared to fasting conditions. Similarly, food significantly reduces pyridoxal C_{max} by approximately 46% compared to fasting conditions. In contrast, food did not affect pyridoxal 5′-phosphate C_{max} and AUC.

Table 4 – Mean ± SD Pharmacokinetic Parameters of Doxylamine and Pyridoxine Metabolites Following a Single Dose Administration of BONJESTA Under Fed and Fasted Conditions in Healthy Premenopausal Adult Women

		BONJESTA N=23				
		AUC_{0-t} (ng•h/mL)	**AUC_{0-inf} (ng•h/mL)**	**C_{max} (ng/mL)**	**T_{max}[b,c] (h)**	**$T_{1/2el}$ (h)**
Doxylamine Mean±SD	**Fasted**	1273.7 ± 276.2	1321.9 ± 315.5	85.9± 10.6	3.5 (2.5-5.5)	11.9 ± 2.2
	Fed	1242.8 ± 254.0	1281.4 ± 282.9	64.5 ± 15.2	6.5 (2.0 – 24.0)	12.7 ± 2.60
Pyridoxine Mean±SD	**Fasted**	34.7 ± 10.6	35.1 ± 8.5	38.9 ± 19.3	0.8 (0.3-4.3)	0.4 ± 0.2
	Fed	22.8 ± 9.9	27.0 ± 10.1	12.7 ± 5.7	8.0 (1.0 – 21.0)	1.2 ± 2.4
Pyridoxal[a] Mean±SD	**Fasted**	209.4 ± 30.0	244.0 ± 32.5	62.0 ± 17.8	2.3 (0.8-5.0)	8.0 ± 1.7
	Fed	204.2 ± 25.7	249.2 ± 43.0	33.1 ± 6.1	6.0 (1.0-21.0)	12.5 ± 7.6
Pyridoxal 5′-phosphate[a] Mean±SD	**Fasted**	1021.7 ± 318.5	---	27.4 ± 7.7	5.0 (3.0-71.8)	---
	Fed	1064.6 ± 386.9	---	30.2 ± 10.0	16.0 (6.0-22.0)	---

[a] Baseline corrected values
[b] Profile of Subject 20 was excluded
[c] Median (range)

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 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 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablet-treated women 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 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablets 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 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablets 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*	Combination 10 mg Doxylamine Succinate and 10 mg Pyridoxine Hydrochloride Tablets N=131	Placebo N=125	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.

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:

Pack sizes: Bottles containing 50, 60 or 100 extended-release tablets.
Not all pack sizes may be marketed.

16.2 Storage and Handling

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

16.3 Shelf life

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

17. MANUFACTURER

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

18. REGISTRATION HOLDER

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

19. DRUG REGISTRATION NUMBER

167-52-36428-00

Approved in June 2021