COLESEVELAM HCL- colesevelam hcl tablet, film coated
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COLESEVELAM HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for COLESEVELAM HYDROCHLORIDE TABLETS.

COLESEVELAM HYDROCHLORIDE tablets, for oral use.

Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	05/2020
Dosage and Administration, chewable bar dosage form removed (2.2,2.4)	07/2020
Warnings and Precautions (5.1)	05/2020

INDICATIONS AND USAGE

Colesevelam hydrochloride tablets is a bile acid sequestrant indicated as an adjunct to diet and exercise to

· reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia (1.1).
· reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) (1.1)

Limitations of Use (1.3):
•Do not use for treatment of type 1 diabetes or for diabetic ketoacidosis.
•The effect on cardiovascular morbidity and mortality has not been determined.
•Not studied in type 2 diabetes with a dipeptidyl peptidase 4 inhibitor.
•Not studied in Fredrickson Type I, III, IV, and V dyslipidemias.
•Not studied in children less than 10 years of age or in premenarchal girls.

DOSAGE AND ADMINISTRATION

- Obtain lipid parameters, including serum triglyceride (TG) levels before starting colesevelam hydrochloride tablets (2.1)
- The recommended dosage for adults and children 10 to 17 years old with primary hyperlipidemia is 3.75 grams daily. Colesevelam hydrochloride tablets should be taken as follows (2.2, 2.4):

Tablets
Take 6 tablets once daily or 3 tablets twice daily with a meal and liquid.

DOSAGE FORMS AND STRENGTHS

Tablets: 625 mg (3)

CONTRAINDICATIONS

- Patients with serum triglyceride levels greater than 500 mg/dL (4).
- Patients with a history of hypertriglyceridemia-induced pancreatitis (4).
- Patients with a history of bowel obstruction (4).

WARNINGS AND PRECAUTIONS

- *Hypertriglyceridemia and Pancreatitis:*Colesevelam hydrochoride can increase TG. Hypertriglyceridemia can cause acute pancreatitis. Monitor lipids, including TG . Instruct patients to discontinue colesevelam hydrochoride and seek prompt medical attention if the symptoms of acute pancreatitis occur (5.1).
- *Gastrointestinal Obstruction:*Cases of bowel obstruction have occurred. Colesevelam hydrochoride is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction (5.2).
- *Vitamin K or Fat-Soluble Vitamin Deficiencies:*Colesevelam hydrochoride may decrease absorption of fat-soluble vitamins. Patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins may be at increased risk. Patients

on oral vitamin supplementation should take their vitamins at least 4 hours prior to colesevelam hydrochloride (5.3).
- *Drug Interactions:* Due to the potential for decreased absorption of other drugs that have not been tested for interaction, consider administering at least 4 hours prior to colesevelam hydrochloride (5.4, 7, 12.3).

ADVERSE REACTIONS

In clinical trials, the most common (incidence ≥2% and greater than placebo) adverse reactions with Colesevelam hydrochloride included constipation, dyspepsia, and nausea. (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Ascend Laboratories, LLC at 1-877-ASCRX01 (877-272-7901) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use with colesevelam hydrochoride may decrease the exposure of the following drugs: Drugs with a narrow therapeutic index (e.g., cyclosporine), phenytoin, thyroid hormone replacement therapy, warfarin, oral contraceptives containing ethinyl estradiol and norethindrone, olmesartan medoxomil, and sulfonylureas (glimepiride, glipizide, glyburide). Administer these drugs 4 hours prior to colesevelam hydrochloride tablets. For patients on warfarin, monitor International Normalized Ratio (INR) frequently during initiation then periodically (7.1).
Concomitant use with colesevelam hydrochoride may increase the exposure of the following drugs: Metformin extended release. Monitor patients glycemic control (7.2).
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

1.1 Primary Hyperlipidemia

Colesevelam hydrochloride tablets is indicated as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia

Colesevelam hydrochloride tablets is indicated to reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) who are unable to reach LDL-C target levels despite an adequate trial of dietary therapy and lifestyle modification.

1.3 Limitations of Use

- Colesevelam hydrochloride should not be used for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis.
- The effect of colesevelam hydrochloride on cardiovascular morbidity and mortality has not been determined.
- Colesevelam hydrochloride has not been studied in type 2 diabetes in combination with a dipeptidyl peptidase 4 inhibitor.
- Colesevelam hydrochloride has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.
- Colesevelam hydrochloride has not been studied in children younger than 10 years of age or in premenarchal girls

2 DOSAGE & ADMINISTRATION

2.1 Testing Prior to Initiation of Colesevelam Hydrochloride

Obtain lipid parameters, including triglyceride (TG) levels before starting colesevelam hydrochloride. Colesevelam hydrochloride is contraindicated in patients with TG levels greater than 500 mg/dL *[see Contraindications (4) and Warnings and Precautions (5.1)].*

2.2 Recommended Dosage in Primary Hyperlipidemia

The recommended dosage of colesevelam tablets for adults and children 10 to 17 years old with primary hyperlipidemia is 3.75 grams daily. Colesevelam hydrochloride should be taken as follows:

Tablets

Take 6 tablets once daily or 3 tablets twice daily. Due to tablet size, colesevelam hydrochloride for oral suspension is recommended for use in the pediatric population.

2.3 Important Dosing Information for Primary Hyperlipidemia

Colesevelam hydrochloride can be dosed at the same time as a statin or colesevelam hydrochloride and the statin can be dosed apart. Monitor lipid levels within 4 to 6 weeks after initiation of colesevelam hydrochloride.

2.4 Administration Instructions

Tablets

Take colesevelam hydrochloride tablets with a meal and liquid. For patients with difficulty swallowing tablets use colesevelam hydrochloride for oral suspension *[see Warnings and Precautions (5.2)].*

3 DOSAGE FORMS & STRENGTHS

- Off-white to light yellow colored, oval, film coated tablets imprinted "C625" on one side.

4 CONTRAINDICATIONS

Colesevelam hydrochloride is contraindicated in patients with:

- Serum TG concentrations greater than 500 mg/dL *[see Warnings and Precautions (5.1)]*
- History of hypertriglyceridemia-induced pancreatitis *[see Warnings and Precautions (5.1)]*
- A history of bowel obstruction *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Hypertriglyceridemia and Pancreatitis

Colesevelam hydrochloride, like other bile acid sequestrants, can increase serum TG concentrations. Hypertriglyceridemia can cause acute pancreatitis.

Colesevelam hydrochloride had effects on serum TG (median increase 5% compared to placebo) in trials of patients with primary hyperlipidemia.

Obtain lipid parameters, including TG levels before starting colesevelam hydrochloride and periodically thereafter. Colesevelam hydrochloride is contraindicated in patients with TG levels greater than 500 mg/dL or patients with a history of hypertriglyceridemia-induced pancreatitis *[see Contraindications (4)]* . Patients with TG levels greater than 300 mg/dL could have greater increases in serum TG levels with colesevelam

hydrochloride and may require additional TG monitoring. Instruct patients to discontinue colesevelam hydrochloride and seek prompt medical attention if the symptoms of acute pancreatitis occur (e.g., severe abdominal pain with or without nausea and vomiting). Discontinue colesevelam hydrochloride if TG levels exceed 500 mg/dL *[see Adverse Reactions (6.1)].*

5.2 Gastrointestinal Obstruction

Postmarketing cases of bowel obstruction have occurred with colesevelam hydrochloride *[see Adverse Reactions (6.2)].* Because of its constipating effects, colesevelam hydrochloride is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction. Colesevelam hydrochloride is contraindicated in patients with a history of bowel obstruction *[see Contraindications (4)].* Instruct patients to promptly discontinue colesevelam hydrochloride and seek medical attention if severe abdominal pain or severe constipation occurs.

Because of the tablet size, colesevelam hydrochloride tablets can cause dysphagia or esophageal obstruction. For patients with difficulty swallowing tablets use colesevelam hydrochloride for oral suspension.

5.3 Vitamin K or Fat-Soluble Vitamin Deficiencies

Colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins A, D, E, and K. Patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins may be at increased risk when taking colesevelam hydrochloride.

Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to colesevelam hydrochloride .*[see Drug Interactions (7.1)].*

5.4 Drug Interactions

Colesevelam hydrochloride reduces gastrointestinal absorption of some drugs. Administer drugs with a known interaction at least 4 hours prior to colesevelam hydrochloride *[see Drug Interactions (7)].*

Due to the potential for decreased absorption of other drugs that have not been tested for interaction, especially those with a narrow therapeutic index, consider administering at least 4 hours prior to colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*

5.6 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular disease risk reduction with colesevelam hydrochloride.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypertriglyceridemia and Pancreatitis *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Obstruction *[see Warnings and Precautions (5.2)]*
- Vitamin K or Fat-Soluble Vitamin Deficiencies *[see Warnings and Precautions (5.3)]*

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction

rates observed in the clinical studies of a drug cannot be directly compared to rates in clinical studies of another drug and may not reflect the rates observed in practice.

Primary Hyperlipidemia
In 7 double-blind, placebo-controlled, clinical trials, 807 patients with primary hyperlipidemia (age range 18-86 years, 50% women, 90% Caucasians, 7% Blacks, 2% Hispanics, 1% Asians) and elevated LDL-C were treated with colesevelam hydrochloride 1.5 g/day to 4.5 g/day from 4 to 24 weeks (total exposure 199 patient-years).

Table 1

Clinical Studies of Colesevelam Hydrochloride for Primary Hyperlipidemia: Adverse Reactions Reported in ≥ 2% of Patients and More Commonly than in Placebo

	Colesevelam hydrochloride N = 807	**Placebo N = 258**
Constipation	11.0%	7.0%
Dyspepsia	8.3%	3.5%
Nausea	4.2%	3.9%
Accidental injury	3.7%	2.7%
Asthenia	3.6%	1.9%
Pharyngitis	3.2%	1.9%
Flu syndrome	3.2%	3.1%
Rhinitis	3.2%	3.1%
Myalgia	2.1%	0.4%

Pediatric Patients 10 to 17 Years of Age
In an 8-week double-blind, placebo-controlled study boys and post-menarchal girls, 10 to 17 years of age, with HeFH (n=194), were treated with colesevelam hydrochloride tablets (1.9 to 3.8 g, daily) or placebo tablets

Table 2

Clinical Study ofColesevelam Hydrochloridefor Primary Hyperlipidemia in HeFH Pediatric Patients: Adverse Reactions Reported in ≥2% of Patients and More Commonly than in Placebo

	Colesevelam Hydrochloride N = 129	**Placebo N = 65**
Nasopharyngitis	6.2%	4.6%
Headache	3.9%	3.1%
Fatigue	3.9%	1.5%
Creatine Phosphokinase Increase	2.3%	0.0%
Rhinitis	2.3%	0.0%
Vomiting	2.3%	1.5%

The reported adverse reactions during the additional 18-week open-label treatment

period with colesevelam hydrochloride 3.8 g per day were similar to those during the double-blind period and included headache (7.6%), nasopharyngitis (5.4%), upper respiratory tract infection (4.9%), influenza (3.8%), and nausea (3.8%).

A total of 5.3% of colesevelam hydrochloride-treated patients and 3.6% of placebo-treated patients were discontinued from the diabetes trials due to adverse reactions. This difference was driven mostly by gastrointestinal adverse reactions such as abdominal pain and constipation.

One patient in the add-on to sulfonylurea trial discontinued due to body rash and mouth blistering that occurred on the first day of dosing of colesevelam hydrochloride, which may represent a hypersensitivity reaction to colesevelam hydrochloride.

Hypertriglyceridemia

Patients with fasting serum TG levels above 500 mg/dL were excluded from the diabetes clinical trials. In the diabetes trials, 1292 (67.7%) patients had baseline fasting serum TG levels less than 200 mg/dL, 426 (22.3%) had baseline fasting serum TG levels between 200 and less than 300 mg/dL, 175 (9.2%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 16 (0.8%) had fasting serum TG levels greater than or equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 160 mg/dL; the median post-treatment fasting TG was 180 mg/dL in the colesevelam hydrochloride group and 162 mg/dL in the placebo group. Colesevelam hydrochloride therapy resulted in a median placebo-corrected increase in serum TG of 9.7% (p=0.03) in the monotherapy study and of 5% (p=0.22), 11% (p less than 0.001), 18% (p less than 0.001), and 22% (p less than 0.001), when added to metformin, pioglitazone, sulfonylureas, and insulin, respectively. In comparison, colesevelam hydrochloride resulted in a median increase in serum TG of 5% compared to placebo (p=0.42) in a 24-week monotherapy lipid-lowering trial.

Fasting TG concentrations ≥500 mg/dL occurred in 0.9% of colesevelam hydrochloride-treated patients compared to 0.7% of placebo-treated patients in the diabetes trials. Among these patients, the TG concentrations with colesevelam hydrochloride (median 606 mg/dL; interquartile range 570 to 794 mg/dL) were similar to that observed with placebo (median 663 mg/dL; interquartile range 542 to 984 mg/dL). Five (0.6%) patients on colesevelam hydrochloride and 3 (0.3%) patients on placebo developed TG elevations greater than 1000 mg/dL.

Cardiovascular Adverse Reactions

During the diabetes trials, the incidence of patients with serious adverse reactions involving the cardiovascular system was 2.2% (22/1022) in the colesevelam hydrochloride group and 1% (10/1010) in the placebo group. These overall rates included disparate events (e.g., myocardial infarction, aortic stenosis, and bradycardia); therefore, the significance of this imbalance is unknown.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of colesevelam hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse Reactions Resulting from Drug Interactions[see Drug Interactions (7)]:

Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin, reduced International Normalized Ratio (INR) in patients receiving warfarin therapy, and elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy

*Gastrointestinal:*Bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, abdominal distension, exacerbation of hemorrhoids, and increased transaminases.

*Laboratory Abnormalities:*Hypertriglyceridemia

7 DRUG INTERACTIONS

7.1 Colesevelam Hydrochloride Drug Interactions that Decrease the Exposure of the Concomitant Medication

Table 4 includes a list of drugs that decrease exposure of the concomitant medication when administered concomitantly with colesevelam hydrochloride and instructions for preventing or managing them.

Table 4

Colesevelam Hydrochloride Drug Interactions that Decrease the Exposure of the

Concomitant Medication

Drugs with a Narrow Therapeutic Index	
Clinical Impact:	Concomitant use with colesevelam hydrochloride may decrease the exposure of the narrow therapeutic index drug. *In vivo*drug interactions studies showed a decrease in exposure of cyclosporine when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer the narrow therapeutic index drug at least 4 hours prior to colesevelam hydrochloride. Monitor drug levels when appropriate.
Examples:	Cyclosporine
Phenytoin	
Clinical Impact:	There have been postmarketing reports of increased seizure activity or decreased phenytoin levels in patients receiving phenytoin *[see Adverse Reactions (6.2)].*
Intervention:	Administer phenytoin 4 hours prior to colesevelam hydrochloride.
Thyroid Hormone Replacement Therapy	
Clinical Impact:	*In vivo*drug interactions studies

	showed a decrease in exposure of levothyroxine when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)]* . There have been postmarketing reports of elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy *[see Adverse Reactions (6.2)].*
Intervention:	Administer thyroid hormone replacement therapy 4 hours prior to colesevelam hydrochloride.
Warfarin	
Clinical Impact:	There have been postmarketing reports of reduced INR in patients receiving warfarin therapy *[see Adverse Reactions (6.2)].*
Intervention:	Monitor INR frequently during colesevelam hydrochloride initiation then periodically thereafter.
Oral Contraceptives Containing Ethinyl Estradiol and Norethindrone	
Clinical Impact:	*In vivo*drug interactions studies showed a decrease in exposure of ethinyl estradiol and norethindrone when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer oral contraceptives containing ethinyl estradiol and norethindrone 4 hours prior to colesevelam hydrochloride.
Olmesartan Medoxomil	
Clinical Impact:	*In vivo*drug interactions studies showed a decrease in olmesartan medoxomil when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer olmesartan medoxomil 4 hours prior to colesevelam hydrochloride.
Sulfonylureas	
Clinical Impact:	*In vivo*drug interactions studies showed a decrease in sulfonylureas when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Administer sulfonylureas 4 hours prior to colesevelam hydrochloride.
Examples:	Glimepiride, glipizide, and glyburide
Oral Vitamin Supplements	
Clinical Impact:	Colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins A, D, E, and K *[see Warnings and Precautions (5.3)].*

Intervention:	Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to colesevelam hydrochloride.

7.2 Colesevelam Hydrochloride Drug Interactions that Increase the Exposure of the Concomitant Medication

Table 5

Colesevelam Hydrochloride Drug Interactions that Increase the Exposure of the Concomitant Medication

Metformin Extended-Release (ER)	
Clinical Impact:	*In vivo*drug interactions studies showed an increase in metformin extended release (ER) when coadministered with colesevelam hydrochloride *[see Clinical Pharmacology (12.3)].*
Intervention:	Monitor patients glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Colesevelam hydrochloride is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Limited available data on the use of colesevelam hydrochloride are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no evidence of either maternal or fetal toxicity was found in rats or rabbits exposed to colesevelam hydrochloride during the period of fetal organogenesis at 8 and 5 times, respectively, the maximum recommended human dose (MRHD) of 3.75 g/day, based on body surface area (mg/m ^{2}). No adverse effects on offspring survival and development were observed in rats administered 5 times the MRHD (see Data).Colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins *[see Warnings and Precautions (5.3)].* There are no data available on the effect of colesevelam hydrochloride on the absorption of fat-soluble vitamins in pregnant women. If the patient becomes pregnant while taking colesevelam hydrochloride, the patient should be advised of the lack of known clinical benefit with continued use during pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20% respectively.

Data

Human Data

There are no adequate and well-controlled studies of colesevelam hydrochloride use in pregnant women.

In the postmarketing setting there have been infrequent reports of pregnancy with use of colesevelam hydrochloride and a causal association with congenital anomalies has not been established.

Animal Data

In pregnant rats given dietary doses of 0.3, 1.0, 3.0 g/kg/day colesevelam hydrochloride from gestation days 7 through 17, no teratogenic effects were observed. Exposures at 3.0 g/kg/day were 8 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m ^{2}).

In pregnant rabbits given oral gavage doses of 0.1, 0.5, 1.0 g/kg/day colesevelam hydrochloride from gestation days 6 through 18, no teratogenic effects were observed. Exposures at 1.0 g/kg/day were 5 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m ^{2}).

In pregnant rats given oral gavage doses of 0.1, 0.3, 1.0 g/kg/day colesevelam hydrochloride from gestation day 6 through lactation day 21 (weaning), no adverse effects on survival and development were observed. Exposures at 1.0 g/kg/day were 5 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m ^{2}).

8.2 Lactation

Risk Summary
Colesevelam hydrochloride is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to colesevelam hydrochloride

8.3 Females and Males of Reproductive Potential

Contraception
Use of colesevelam hydrochloride may reduce the efficacy of oral contraceptives. Advise patients to take oral contraceptives at least 4 hours prior to taking colesevelam hydrochloride *[see Drug Interactions (7)].*

8.4 Pediatric Use

The safety and effectiveness of colesevelam hydrochloride as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age with HeFH *[see Clinical Studies (14.1)]* . The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent boys or girls relative to placebo [s *ee Adverse Reactions (6.1)*].

Due to tablet size, colesevelam hydrochloride for oral suspension is recommended for use in the pediatric population. Dose adjustments are not required when colesevelam hydrochloride is administered to children 10 to 17 years of age.

Colesevelam hydrochloride has not been studied in children younger than 10 years of age or in premenarchal girls.

8.5 Geriatric Use

Primary Hyperlipidemia
Of the 1350 patients enrolled in the hyperlipidemia clinical studies, 349 (26%) were ≥65 years old, and 58 (4%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the

elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

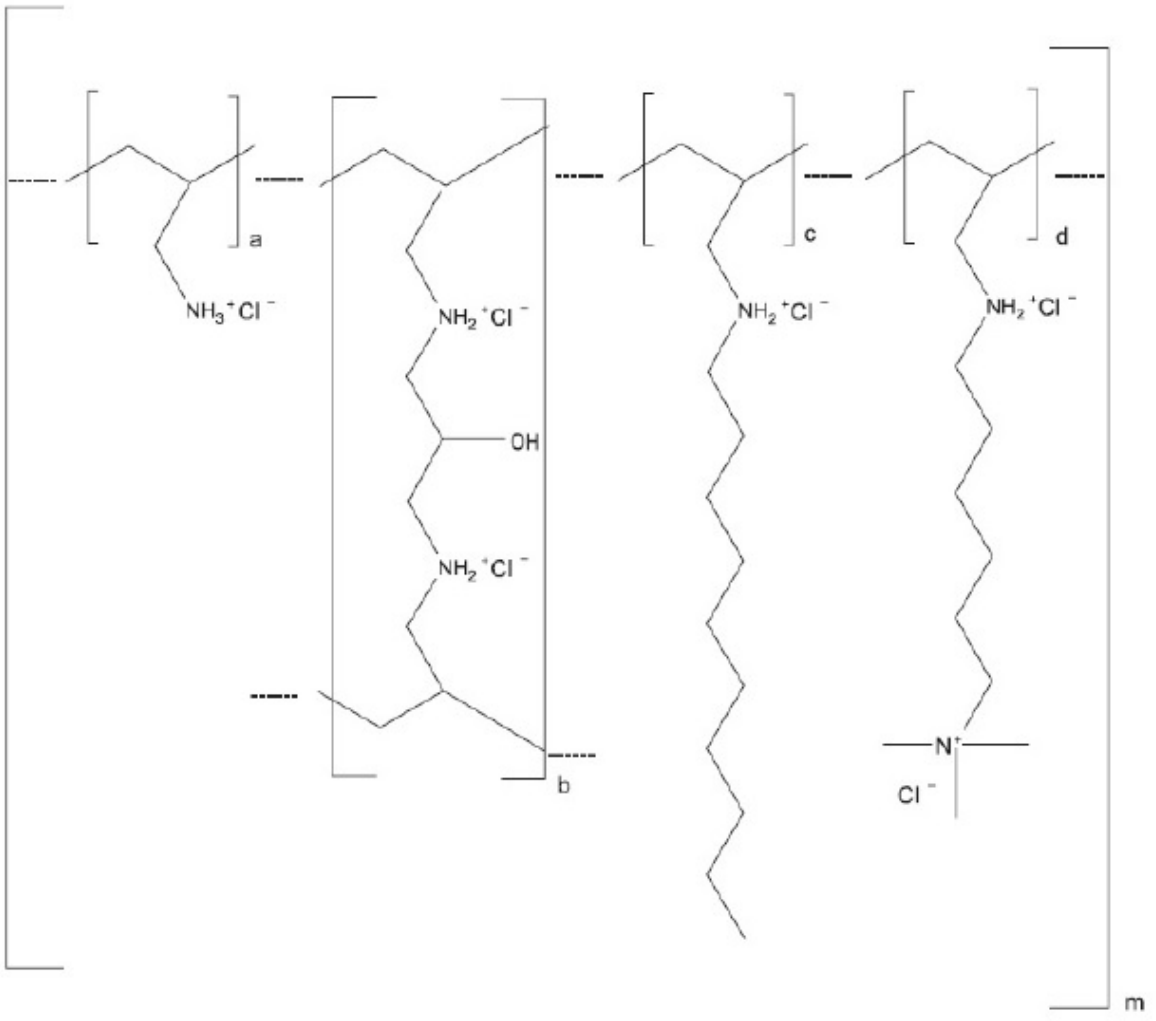
10 OVERDOSAGE

Colesevelam hydrochloride is not absorbed and the risk of systemic toxicity is low. Excessive doses of colesevelam hydrochloride may cause more severe local gastrointestinal effects (e.g., constipation).

11 DESCRIPTION

Colesevelam hydrochloride is a non-absorbed, polymeric, lipid-lowering and glucose-lowering agent for oral administration. Colesevelam hydrochloride is a high-capacity bile acid-binding molecule.

Colesevelam hydrochloride is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. The chemical name (IUPAC) of colesevelam hydrochloride is allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride. The chemical structure of colesevelam hydrochloride is represented by the following formula:



wherein (a) represents allyl amine monomer units that have not been alkylated by either of the 1-bromodecane or (6-bromohexyl)-trimethylammonium bromide alkylating agents or cross-linked by epichlorohydrin; (b) represents allyl amine units that have undergone cross-linking with epichlorohydrin; (c) represents allyl amine units that have been alkylated with a decyl group; (d) represents allyl amine units that have been alkylated with a (6-trimethylammonium) hexyl group, and m represents a number ≥ 100 to indicate an extended polymer network. A small amount of the amines are dialkylated, and are not depicted in the formula above. No regular order of the groups is implied by the structure; cross-linking and alkylation are expected to occur randomly along the polymer chains. A large amount of the amines are protonated. The polymer is depicted in the hydrochloride form; a small amount of the halides are bromide. Colesevelam hydrochloride is hydrophilic and insoluble in water.

Colesevelam Hydrochloride Tablets are an off-white to light yellow colored, oval, film coated tablets imprinted "C625" on one side. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, and sodium stearyl fumarate. The coating material contains hypromellose and propylene glycol. Colesevelam Hydrochloride Tablets are imprinted with edible ink which contains shellac, iron oxide black and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Primary Hyperlipidemia: Colesevelam hydrochloride, the active pharmaceutical ingredient in colesevelam hydrochloride, is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase, and increasing the number of hepatic LDL receptors. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. Serum TG levels may increase or remain unchanged.

12.2 Pharmacodynamics

A maximum therapeutic response to the lipid-lowering effects of colesevelam hydrochloride was achieved within 2 weeks and was maintained during long-term therapy. In the diabetes clinical studies, a therapeutic response to colesevelam hydrochloride, as reflected by a reduction in hemoglobin A1C (A1C), was initially noted following 4 to 6 weeks of treatment and reached maximal or near-maximal effect after 12 to 18 weeks of treatment.

12.3 Pharmacokinetics

Absorption:
Colesevelam hydrochloride is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed.

Distribution:
Colesevelam hydrochloride is not absorbed, and therefore, its distribution is limited to the gastrointestinal tract.

Elimination

Metabolism

Colesevelam hydrochloride is not metabolized systemically and does not interfere with systemic drug-metabolizing enzymes such as cytochrome P450.

Excretion

In 16 healthy volunteers, an average of 0.05% of administered radioactivity from a single ^{14}C-labeled colesevelam hydrochloride dose was excreted in the urine.

Drug Interaction Studies

Drug interactions between colesevelam and concomitantly administered drugs were screened through *in vitro* studies and confirmed in *in vivo* studies. *In vitro* studies demonstrated that cephalexin, metformin, and ciprofloxacin had negligible binding to colesevelam hydrochloride. Therefore, an *in vivo* pharmacokinetic interaction of colesevelam hydrochloride with these drugs is unlikely. Colesevelam hydrochloride was found to have no significant effect on the bioavailability of aspirin, atenolol, digoxin, enalapril, fenofibrate, lovastatin, metoprolol, phenytoin, pioglitazone, quinidine, rosiglitazone, sitagliptin, valproic acid, and warfarin. The results of additional *in vivo* drug interactions of colesevelam hydrochloride are presented in Table 6.

Table 6

Mean Change in Drug Exposure ($AUC_{0-\infty}$ and C_{max}) when Administered with Colesevelam Hydrochloride(3.75 g) *

Drug	Dose	Co-administered		1 hr prior to colesevelam hydrochloride		4 hr prior to colesevelam hydrochloride	
		$AUC_{0 \text{ to } \infty}$	Cmax	$AUC_{0 \text{ to } \infty}$	C_{max}	$AUC_{0 \text{ to } \infty}$	C_{max}
Cyclosporine	200 mg	-34%	-44%	N/A	N/A	N/A	N/A
Ethinyl Estradiol †	0.035 mg	-24%	-24%	-18%	-1%	-12%	0%
Glimepiride	4 mg	-18%	-8%	N/A	N/A	-6%	3%
Glipizide	20 mg	-12%	-13%	N/A	N/A	-4%	0%
Glyburide	3 mg	-32%	-47%	-20%	-15%	-7%	4%
Levothyroxine	600 µg	-22%	-33%	6%	-2%	1%	8%
Metformin ER	1500 mg	44%	8%	N/A	N/A	N/A	N/A
Norethindrone †	1 mg	-1%	-20%	5%	-3%	6%	7%
Olmesartan Medoxomil	40 mg	-39%	-28%	N/A	N/A	-15%	-4%
Repaglinide	2 mg	-7%	-19%	-6%	-1%	N/A	N/A
Verapamil sustained-release	240 mg	-31%	-11%	N/A	N/A	N/A	N/A

*With verapamil, the dose of colesevelam hydrochloride was 4.5 g

†Oral contraceptive containing norethindrone and ethinyl estradiol.

N/A – not available

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility

Carcinogenesis
A 104-week carcinogenicity study with colesevelam hydrochloride was conducted in CD-1 mice, at oral dietary doses up to 3 g/kg/day. This dose was approximately 50 times the maximum recommended human dose of 4.5 g/day, based on body weight, mg/kg. There were no significant drug-induced tumor findings in male or female mice. In a 104-week carcinogenicity study with colesevelam hydrochloride in Harlan Sprague-Dawley rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses greater than 1.2 g/kg/day (approximately 20 times the maximum human dose, based on body weight, mg/kg) (trend test only). A statistically significant increase in thyroid C-cell adenoma was seen in female rats at 2.4 g/kg/day (approximately 40 times the maximum human dose, based on body weight, mg/kg).

Mutagenesis
Colesevelam hydrochloride and 4 degradants present in the drug substance have been evaluated for mutagenicity in the Ames test and a mammalian chromosomal aberration test. The 4 degradants and an extract of the parent compound did not exhibit genetic toxicity in an *in vitro* bacterial mutagenesis assay in S. typhimurium and E. coli (Ames assay) with or without rat liver metabolic activation. An extract of the parent compound was positive in the Chinese Hamster Ovary (CHO) cell chromosomal aberration assay in the presence of metabolic activation and negative in the absence of metabolic activation. The results of the CHO cell chromosomal aberration assay with 2 of the 4 degradants, decylamine HCl and aminohexyltrimethyl ammonium chloride HCl, were equivocal in the absence of metabolic activation and negative in the presence of metabolic activation. The other 2 degradants, didecylamine HCl and 6-decylamino-hexyltrimethyl ammonium chloride HCl, were negative in the presence and absence of metabolic activation.

Impairment of Fertility
Colesevelam hydrochloride did not impair fertility in rats at doses up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg).

13.2 Animal Toxicology and/orPharmacology

Reproductive Toxicology Studies

Reproduction studies have been performed in rats and rabbits at doses up to 3 g/kg/day and 1 g/kg/day, respectively (approximately 50 and 17 times the maximum human dose, based on body weight, mg/kg) and have revealed no evidence of harm to the fetus due to colesevelam hydrochloride.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

Colesevelam hydrochloride reduces total cholesterol (TC), LDL-C, apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) when administered alone or in combination with a statin in patients with primary hyperlipidemia.

Approximately 1600 patients were studied in 9 clinical trials with treatment durations ranging from 4 to 50 weeks. With the exception of one open-label, uncontrolled, long-term extension study, all studies were multicenter, randomized, double-blind, and placebo-controlled. A maximum therapeutic response to colesevelam hydrochloride was achieved within 2 weeks and was maintained during long-term therapy.

Monotherapy
In a study in patients with LDL-C between 130 mg/dL and 220 mg/dL (mean 158 mg/dL), colesevelam hydrochloride was given for 24 weeks in divided doses with the morning and evening meals.

As shown in Table 7, the mean LDL-C reductions were 15% and 18% at the 3.8 g and 4.5 g doses. The respective mean TC reductions were 7% and 10%. The mean Apo B reductions were 12% in both treatment groups. Colesevelam hydrochloride at both doses increased HDL-C by 3%. Increases in TG of 9 to 10% were observed at both colesevelam hydrochloride doses but the changes were not statistically different from placebo.

Table 7

Response to Colesevelam Hydrochloride Monotherapy in a 24-Week Trial - Percent Change in Lipid Parameters from Baseline

Grams/ Day	N	TC	LDL-C	Apo B	HDL-C *	Non-HDL-C	TG*
Placebo	88	+1	0	0	–1	+1	+5
3.8 g (6 tablets)	95	–7 †	–15 †	–12 †	+3 †	–10 †	+10
4.5 g (7 tablets)	94	–10 †	–18 †	–12 †	+3	–13 †	+9

* Median % change from baseline.
†p less than 0.05 for lipid parameters compared to placebo, for Apo B compared to baseline.

In a study in 98 patients with LDL-C between 145 mg/dL and 250 mg/dL (mean 169 mg/dL), colesevelam hydrochloride 3.8 g was given for 6 weeks as a single dose with breakfast, as a single dose with dinner, or as divided doses with breakfast and dinner. The mean LDL-C reductions were 18%, 15%, and 18% for the 3 dosing regimens, respectively. The reductions with these 3 regimens were not statistically different from one another.

Combination Therapy

Co-administration of colesevelam hydrochloride and a statin (atorvastatin, lovastatin, or simvastatin) in 3 clinical studies demonstrated an additive reduction of LDL-C. The mean baseline LDL-C was 184 mg/dL in the atorvastatin study (range 156 to 236 mg/dL), 171 mg/dL in the lovastatin study (range 115 to 247 mg/dL), and 188 mg/dL in the simvastatin study (range 148 to 352 mg/dL). As demonstrated in Table 8, colesevelam hydrochloride doses of 2.3 g to 3.8 g resulted in an additional 8% to 16% reduction in LDL-C above that seen with the statin alone.

Table 8

Response to Colesevelam Hydrochloride in Combination with Atorvastatin, Simvastatin, or Lovastatin -Percent Change in Lipid Parameters

Dose/Day	N	TC	LDL-C	Apo B	HDL-C *	Non-HDL-C	TG*
Atorvastatin Trial (4-week)							
Placebo	19	+4	+3	–3	+4	+4	+10
Atorvastatin 10 mg	18	–27 †	–38 †	–32 †	+8	–35 †	–24 †
Colesevelam hydrochloride 3.8 g/ Atorvastatin 10 mg	18	–31 †	–48 †	–38 †	+11	–40 †	–1
Atorvastatin 80 mg	20	–39 †	–53 †	–46 †	+6	–50 †	–33 †
Simvastatin Trial (6-week)							
Placebo	33	–2	–4	–4 †	–3	–2	+6 †
Simvastatin 10 mg	35	–19 †	–26 †	–20 †	+3 †	–24 †	–17 †
Colesevelam hydrochloride 3.8 g/ Simvastatin 10 mg	34	–28 †	–42 †	–33 †	+10 †	–37 †	–12 †
Simvastatin 20 mg	39	–23 †	–34 †	–26 †	+7 †	–30 †	–12 †
Colesevelam hydrochloride 2.3 g/ Simvastatin 20 mg	37	–29 †	–42 †	–32 †	+4 †	–37 †	–12 †
Lovastatin Trial (4-week)							
Placebo	26	+1	0	0	+1	+1	+1
Lovastatin 10 mg	26	–14 †	–22 †	–16 †	+5	–19 †	0
Colesevelam hydrochloride 2.3 g/ Lovastatin 10 mg Together	27	–21 †	–34 †	–24 †	+4	–27 †	–1
Colesevelam hydrochloride 2.3 g/ Lovastatin 10 mg Apart	23	–21 †	–32 †	–24 †	+2	–28 †	–2

*Median % change from baseline.

†p less than 0.05 for lipid parameters compared to placebo, for Apo B compared to baseline.

In all 3 studies, the LDL-C reduction achieved with the combination of colesevelam hydrochloride and any given dose of statin therapy was statistically superior to that achieved with colesevelam hydrochloride or that dose of the statin alone. The LDL-C reduction with atorvastatin 80 mg was not statistically significantly different from the combination of colesevelam hydrochloride 3.8 g and atorvastatin 10 mg.

Pediatric Therapy

The safety and efficacy of colesevelam hydrochloride in pediatric patients were evaluated in an 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study followed by an open-label phase, in 194 boys and postmenarchal girls 10 to 17 years of age (mean age 14.1 years) with HeFH, taking a stable dose of an FDA-approved statin (with LDL-C greater than 130 mg/dL) or naïve to lipid-lowering therapy (with LDL-C greater than 160 mg/dL). This study had 3 periods: a single-blind, placebo stabilization

period; an 8-week, randomized, double-blind, parallel-group, placebo-controlled treatment period; and an 18-week, open-label treatment period. Forty-seven (24%) patients were taking statins and 147 (76%) patients were statin-naïve at screening. The mean baseline LDL-C at Day 1 was approximately 199 mg/dL.

During the double-blind treatment period, patients were assigned randomly to treatment: colesevelam hydrochloride 3.8 g/day (n=64), colesevelam hydrochloride 1.9 g/day (n=65), or placebo (n=65). In total, 186 patients completed the double-blind treatment period. After 8 weeks of treatment, colesevelam hydrochloride 3.8 g/day significantly decreased plasma levels of LDL-C, non-HDL-C, TC, and Apo B and significantly increased HDL-C. A moderate, non-statistically significant increase in TG was observed versus placebo (Table 9).

Table 9

Response to Colesevelam Hydrochloride 3.8 g Compared to Placebo in Pediatric Patients 10 to 17 Years of Age–Mean Percent Change in Lipid Parameters from Baseline to Week 8

Treatment Difference	**TC (N=128)**	**LDL-C (N=128)**	**Apo B (N=124)**	**HDL-C (N=128)**	**Non-HDL-C (N=128)**	**TG *(N=128)**
Colesevelam Hydrochloride 3.8 g vs Placebo	-7 †	-13 †	-8 †	+6 †	-11 †	+5

*For triglycerides, median % change from baseline.
†p≤0.05 for lipid parameters compared to placebo Values represent LS mean. Only patients with values at both study baseline and endpoint are included in this table. Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.

Results were based on the ITT population with LOCF

During the open-label treatment period patients were treated with colesevelam hydrochloride 3.8 g/day. In total, 173 (89%) patients completed 26 weeks of treatment. Results at Week 26 were consistent with those at Week 8.

16 HOW SUPPLIED/STORAGE AND HANDLING

Colesevelam Hydrochloride Tablets are Off-white to light yellow colored, oval, film coated tablets imprinted "C625" on one side.

Bottle of 180: NDC 72162-1846-2

Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Brief exposure to 40°C (104°F) does not adversely affect colesevelam hydrochloride tablets.

Repackaged/Relabeled by:
Bryant Ranch Prepack, Inc.
Burbank, CA 91504

17 PATIENT COUNSELING INFORMATION

Hypertriglyceridemia and Pancreatitis

Inform patients that colesevelam hydrochloride may increase their serum triglycerides which can lead to hypertriglyceridemia and pancreatitis. Instruct patients to discontinue colesevelam hydrochloride and seek prompt medical attention if the symptoms of acute pancreatitis occur (e.g., severe abdominal pain with or without nausea and vomiting) *[see Warnings and Precautions (5.1)].*

Gastrointestinal

Inform patients that colesevelam hydrochloride may cause bowel obstruction. Instruct patients to promptly discontinue colesevelam hydrochloride and seek medical attention if severe abdominal pain or severe constipation occurs *[see Warnings and Precautions (5.2)].*

Drug and Vitamin Interactions

Advise patients that colesevelam hydrochloride has drug interactions and colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins A, D, E, and K. Instruct patients to take oral vitamins at least 4 hours prior to colesevelam hydrochloride. Instruct patients to inform their physician about all the drugs and vitamins that they are prescribed or take over the counter *[see Warnings and Precautions (5.3) and Drug Interactions (7)].*

Hypertriglyceridemia and Cardiovascular Disease

Inform patients that colesevelam hydrochloride may increase serum triglycerides and that the long-term effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain *[see Warnings and Precautions (5.1)].*

Administration *[see Dosage and Administration (2.2,2.4)]*

Tablets
Advise patients to take colesevelam hydrochloride tablets with a meal and liquid. Inform patients that colesevelam hydrochloride tablets can be taken as 6 tablets once daily or 3 tablets twice daily.

Females of Reproductive Potential

Advise females of reproductive potential that colesevelam hydrochloride may reduce the effectiveness of oral contraceptives, and to take oral contraceptives at least 4 hours before taking colesevelam hydrochloride *[see Drug Interactions (7.1) and Use in Specific Populations (8.3)].*

Manufactured by:

Alkem Laboratories Ltd.,

INDIA.

Distributed by:

Ascend Laboratories, LLC

Parsippany, NJ 07054

Revised: November, 2021

PT 2632-04

Colesevelam HCL 625 mg Tablet #180

Each tablet contains: Active Ingredient: Colesevelam Hydrochloride 625 mg.

Keep this and all medication out of the reach of children.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.

Brief exposure to 40°C (104°F) does not adversely affect the product.

Usual Dosage: Scan Package Insert QR Code.

NDC 72162-**1846**-2

Colesevelam Hydrochloride Tablets

625 mg

BRP PHARMACEUTICALS

Rx only
180 Tablets

Relabeled by:
Bryant Ranch Prepack, Inc.
Burbank, CA 91504 USA

Manufactured by:
Alkem Laboratories Ltd.

COLESEVELAM HCL

colesevelam hcl tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72162-1846(NDC:67877-506)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
COLESEVELAM HYDROCHLORIDE (UNII: P4SG24WI5Q) (COLESEVELAM - UNII:1XU104G55N)	COLESEVELAM HYDROCHLORIDE	625 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
HYPROMELLOSE 2910 (15 MPA.S) (UNII: 36SFW2JZ0W)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	yellow (Off-white to light yellow)	**Score**	no score
Shape	OVAL	**Size**	19mm
Flavor		**Imprint Code**	C625
Contains			

Packaging				
			Marketing Start	**Marketing End**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72162-1846-2	180 in 1 BOTTLE; Type 0: Not a Combination Product	04/20/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209038	10/06/2018	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	repack(72162-1846) , relabel(72162-1846)