PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ACCEL-SEVELAMER

sevelamer carbonate tablets

Tablets, 800 mg, oral

Phosphate Binder

Accel Pharma Inc.
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Canada

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, [1.2 Geriatrics]	12/2020
4. DOSAGE AND ADMINISTRATION, [4.1 Dosing Considerations]	12/2020
7. WARNINGS AND PRECAUTIONS, [7.1.4 Geriatrics]	12/2020

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACCEL-SEVELAMER (sevelamer carbonate tablets) is indicated for:

- the control of hyperphosphatemia in adults with end-stage renal disease (ESRD) undergoing dialysis.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ACCEL-SEVELAMER in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Careful monitoring and gradual titration practices are recommended for geriatric patients in order to reduce the risk of hypophosphatemia (see 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

Sevelamer carbonate is contraindicated in the following situations:

- patients with hypophosphatemia.
- patients with bowel obstruction, or known active mucosal injury such as necrosis, perforation, ulcerative colitis or gastrointestinal bleeding (see 7 WARNINGS AND PRECAUTIONS).
- patients hypersensitive to sevelamer or one of the other ingredients in the product, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Serious cases of dysphagia, bowel obstruction, and perforation, have been associated with sevelamer carbonate use, some requiring hospitalization and surgery (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- When administering any other medication where a reduction in the bioavailability of that

medication would have a clinically significant effect on safety or efficacy, the physician should consider monitoring blood levels or dosing that medicine apart from ACCEL-SEVELAMER to prevent GI binding (at least one hour before or three hours after ACCEL-SEVELAMER).

- Monitor serum phosphorus, and adjust the dose of ACCEL-SEVELAMER based on the desired target range (see 4.2 RECOMMENDED DOSE AND DOSAGE ADJUSTMENT; Adults).

4.2 Recommended Dose and Dosage Adjustment

- ACCEL-SEVELAMER 800 mg tablets should be taken three times per day with meals at a dosage based on individual patient requirements to control serum phosphate levels (see dosing recommendation for Adults below).
- Adults (≥ 18 years of age)

The recommended dosing to be used when initiating ACCEL-SEVELAMER in adult patients not using another phosphate binder are outlined below in Table 1.

Table 1: Starting Dose for Dialysis Patients Not Taking a Phosphate Binder

Initial Serum Phosphorus	ACCEL-SEVELAMER 800 mg tablet
> 1.8 and < 2.4 mmol/L	1 tablet three times a day with meals (2.4 grams/day)
≥ 2.4 mmol/L	2 tablets three times a day with meals (4.8 grams/day)

For patients previously on sevelamer hydrochloride, ACCEL-SEVELAMER should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses.

In a study in 84 chronic kidney disease (CKD) patients on hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (approximately mg for mg) of sevelamer hydrochloride and calcium acetate. Table 2 gives recommended starting doses of ACCEL-SEVELAMER based on a patient's current calcium acetate dose.

Table 2: Starting Dose for Dialysis Patients Switching from Calcium Acetate to ACCEL-SEVELAMER

Calcium Acetate 667 mg (Tablets per meal)	ACCEL-SEVELAMER 800 mg Tablet (Tablets per meal)
1 tablet	1 tablet
2 tablets	2 tablets
3 tablets	3 tablets

Dose adjustments, when necessary, should be done every 1 to 3 weeks by increasing one tablet per meal (3 tablets per day) until the desired serum levels are met.

The total dose should be divided according to the meal portion during the day.

Maintenance

Serum phosphorus should be monitored on a regular basis with the goal of maintaining serum phosphorus levels consistent with current medical standards (see 4.1 Dosing Considerations).

In clinical trials, the average actual daily dose of sevelamer carbonate, in adults, was approximately 6 g per day. The highest studied daily dose of sevelamer carbonate taken was 14.4 g per day in adult CKD patients.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

- ACCEL-SEVELAMER (sevelamer carbonate) tablets should not be bitten, chewed, or broken apart prior to dosing.
- ACCEL-SEVELAMER should be taken with meals and/or snacks and not on an empty stomach, since its action is to bind ingested phosphate (see 0 Interactions with laboratory tests have not been established.
- CLINICAL PHARMACOLOGY, Mechanism of Action)

4.5 Missed Dose

If a dose is forgotten, it should be skipped. Double dosing is not advisable.

5 OVERDOSAGE

In adult CKD patients on dialysis, the maximum dose studied was 14.4 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy adult volunteers in doses of up to 14.4 grams per day for eight days with no adverse effects. There are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet 800 mg	Diacetylated monoglycerides, hypromellose, lactose monohydrate, silica

		(colloidal anhydrous) and zinc stearate.

ACCEL-SEVELAMER 800 mg tablets are supplied as white, oval, film-coated, tablets, debossed with SVL on one side, containing 800 mg of sevelamer carbonate on an anhydrous basis, diacetylated monoglycerides, hypromellose, lactose monohydrate, silica (colloidal anhydrous) and zinc stearate.

ACCEL-SEVELAMER 800 mg tablets are available in bottles of 180 tablets equipped with pre-mounted desiccant.

ACCEL-SEVELAMER tablets are packaged in white high-density polyethylene bottles (HDPE), with a child resistant polypropylene cap and an induction seal.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Patients with renal insufficiency may develop hypocalcemia. As ACCEL-SEVELAMER does not contain calcium, serum calcium levels should be monitored and elemental calcium should be supplemented whenever considered necessary. In cases of hypocalcemia, patients should be given an evening calcium supplement.

Caution should be exercised to avoid hypophosphatemia, a serum phosphorus of < 0.8 mmol/L (see 4 DOSAGE AND ADMINISTRATION).

Rare serious case reports of difficulty swallowing the sevelamer carbonate tablet have been reported. Many of these cases involved patients with contributing co-morbid conditions affecting the ability to swallow including swallowing disorders or oroesophageal abnormalities. Caution should be exercised when ACCEL-SEVELAMER tablets are used in these patients.

Sevelamer binds to bile acids and, therefore, prevents cholesterol absorption.

The safety and efficacy of sevelamer carbonate in patients with renal disease who are not undergoing dialysis has not been established.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY

Gastrointestinal

Cases of dysphagia and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer carbonate, some requiring hospitalization and intervention.

Cases of bowel obstruction (ileus, subileus) and perforation have also been reported with sevelamer carbonate use. Constipation may be a preceding symptom.

Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery were not included in the sevelamer

carbonate clinical studies.

The safety and efficacy of sevelamer carbonate in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been established. Caution should be exercised when ACCEL-SEVELAMER is used in patients with these GI disorders. These patients should be monitored carefully while being treated with ACCEL-SEVELAMER. ACCEL-SEVELAMER treatment should be re-evaluated in patients who develop severe constipation or other severe GI symptoms (see 8 ADVERSE REACTIONS).

Cases of serious inflammatory disorders of the gastrointestinal tract (with complications including haemorrhage, perforation, ulceration, necrosis, colitis, and colonic/cecal mass) associated with the presence of sevelamer crystals have been reported. (see 8.5 POST-MARKET ADVERSE REACTIONS). Inflammatory disorders may resolve upon ACCEL-SEVELAMER discontinuation. Treatment discontinuation should be considered in patients who develop severe gastrointestinal symptoms. (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS sections).

Monitoring and Laboratory Tests

Bicarbonate and chloride levels should be monitored.

Monitor for reduced vitamins D, E, K and folic acid levels. In preclinical studies in rats and dogs, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, reduced vitamins D, E and K, and folic acid levels at doses 6-10 times the recommended human dose. In short-term clinical trials, there was no evidence of reduction of serum levels of vitamins. However, in a one-year clinical trial, 25-hydroxyvitamin D (normal range 10 to 55 ng/mL) fell from 39 ± 22 to 34 ± 22 ng/mL ($p<0.01$) with sevelamer hydrochloride treatment. Most (approximately 75%) patients in sevelamer hydrochloride clinical trials received vitamin supplements which is typical of patients on dialysis.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of sevelamer carbonate has not been established in pregnant women. In preclinical studies, there was no evidence that sevelamer induced embryolethality, fetotoxicity or teratogenicity at the doses tested (up to 1 g/kg/day in rabbits; up to 4.5 g/kg/day in rats). ACCEL-SEVELAMER should only be given to pregnant women if the benefits outweigh the risks.

7.1.2 Breast-feeding

It is unknown if ACCEL-SEVELAMER (sevelamer carbonate) is excreted in human milk; however, since sevelamer is not absorbed, excretion in breast milk is not expected. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

Pediatrics (<18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ACCEL-SEVELAMER in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Careful monitoring and gradual titration practices are recommended for geriatric patients in order to reduce the risk of hypophosphatemia (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

There are limited data on the safety of sevelamer carbonate. However, because it contains the same active ingredient as the hydrochloride salt, the adverse event profiles of the two salts should be similar. In a cross-over study in patients undergoing hemodialysis with treatment duration of eight weeks each and without a mid-point washout period, the adverse reactions on sevelamer carbonate were similar to those observed on sevelamer hydrochloride.

In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included: vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence, and constipation as shown in Table 4.

Based on studies of 8-52 weeks, the most common reasons for withdrawal from sevelamer hydrochloride were gastro-intestinal adverse reactions (3-16%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In a combined safety database comprised of 483 patients with ESRD undergoing hemodialysis, adverse events reported at an incidence ≥10% are provided in Table 4 below. From this database, adverse events are also presented separately from a single long-term randomized clinical study for sevelamer hydrochloride and calcium. The adverse events presented in the table below are not necessarily attributed to sevelamer hydrochloride treatment. The incidence of these events was not dose related.

Table 4: Adverse Events in Patients with End-Stage Renal Disease undergoing Hemodialysis

	Total AEs reported	52 weeks Study of sevelamer hydrochloride vs. calcium (calcium acetate and calcium carbonate)	
System Organ Class Event	**sevelamer hydrochloride** N = 483 %	**sevelamer hydrochloride** N = 99 %	**calcium** N=101 %
Gastrointestinal Disorders			
Vomiting	24.4	22.2	21.8
Nausea	25.3	20.2	19.8
Diarrhea	21.1	19.2	22.8
Dyspepsia	15.7	16.2	6.9
Constipation	13.3	8.1	11.9
General Disorders and Site Administration Disorders			
Dialysis Access Complication	4.3	6.1	10.9
Pyrexia	8.7	5.1	10.9
Infections and Infestations			
Nasopharyngitis	13.9	14.1	7.9
Bronchitis	5.4	11.1	12.9
Upper Respiratory Tract Infection	7.0	5.1	10.9
Musculoskeletal, Connective Tissue and Bone Disorders			
Pain in Limb	13.7	13.1	14.9
Arthralgia	11.4	12.1	17.8
Back Pain	6.0	4.0	17.8
Nervous System Disorders			
Headache	18.4	9.1	15.8
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnea	15.7	10.1	16.8
Cough	11.6	7.1	12.9
Skin Disorders			
Pruritus	10.4	13.1	9.9
Vascular Disorders			
Hypertension	9.3	10.1	5.9

In 143 patients with ESRD undergoing peritoneal dialysis with treatment duration of 12 weeks (97 on sevelamer hydrochloride and 46 on a calcium-based product), the safety profile was similar to that reported for hemodialysis patients except for peritonitis which is a known complication in these patients.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of sevelamer hydrochloride (which has the same active moiety as sevelamer carbonate): allergic reactions including angioedema, anaphylaxis (some fatal) and erythema, hypersensitivity vasculitis, pruritus, rash, abdominal pain, fecal impaction, and uncommon cases of intestinal obstruction, ileus, subileus and intestinal perforation. Cases of diverticulitis were also reported.

Cases of serious inflammatory disorders of the gastrointestinal tract (with complications including hemorrhage, perforation, ulceration, necrosis, colitis, and intestinal mass) associated with the presence of sevelamer crystals have been reported (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Cases of gastrointestinal mucosal necrosis, gastrointestinal bleeding, and colitis associated with the presence of sevelamer crystals have been reported. However, the causality of the sevelamer crystals in initiating such disorders has not been demonstrated (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS sections).

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

There have been no adequate, well-controlled studies regarding drug-behavioral interactions.

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies. In interaction studies in healthy volunteers, sevelamer hydrochloride had no effect on the bioavailability of a single-dose of digoxin, warfarin, enalapril, metoprolol or iron.

However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer hydrochloride (and thus sevelamer carbonate) should not be taken simultaneously with ciprofloxacin.

During postmarketing experience, reduced concentrations of cyclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride. The possibility of an interaction cannot be excluded and close monitoring of blood concentrations of cyclosporin, mycophenolate mofetil and tacrolimus or dosing these medicines apart from sevelamer carbonate to prevent GI binding (at least one hour before or three hours after ACCEL-SEVELAMER) should be considered during the use of any of these agents in combination with ACCEL-SEVELAMER and after its withdrawal.

During postmarketing experience, very rare cases of increased thyroid stimulating hormone

(TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both medications.

During postmarketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer carbonate.

When administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, the drug should be administered at least one hour before or three hours after sevelamer carbonate, or the physician should consider monitoring blood levels of the drug. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials. Special precautions should be taken when prescribing sevelamer carbonate to patients also taking these medications.

9.5 Drug-Food Interactions

Interactions with food have not been established. There have been no adequate, well-controlled studies regarding the effect of a variety of foods on the intestinal phosphorus binding of sevelamer. In all clinical studies patients were instructed to take sevelamer with meals.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

Patients with chronic kidney disease (CKD) retain phosphorus and can develop hyperphosphatemia. High serum phosphorus can precipitate serum calcium resulting in ectopic calcification. When the product serum calcium and phosphorus concentrations (Ca x P) exceeds 4.4 mmol/L, there is an increased risk that ectopic calcification will occur. Hyperphosphatemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. An increase in parathyroid hormone (PTH) levels is characteristic of patients with chronic renal failure. Increased levels of PTH can lead to osteitis fibrosa. A decrease in serum phosphorus may decrease serum PTH levels.

10.1 Mechanism of Action

Sevelamer carbonate is a non-absorbed phosphate binding crosslinked polymer, free of metal and calcium. It contains multiple amines separated by one carbon from the polymer backbone. These amines exist in a protonated form in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum.

In addition to effects on serum phosphate levels, sevelamer hydrochloride has been shown to bind bile acids *in vitro* and *in vivo* in experimental animal models. Because sevelamer binds bile acids, it may interfere with normal fat absorption and thus may reduce absorption of fat soluble vitamins such as A, D and K as well as other substances such as cholesterol.

In vitro equilibrium studies demonstrated that sevelamer hydrochloride tablets and sevelamer carbonate tablets were equivalent in terms of phosphate binding, with and without acid pre-treatment. Kinetic experiments demonstrated that sevelamer carbonate and sevelamer hydrochloride tablets bind phosphate in a similarly rapid manner. Therefore, these *in vitro* studies have shown that sevelamer carbonate and sevelamer hydrochloride are equivalent in their phosphate binding properties.

Sevelamer does not contain calcium and decreases the incidence of hypercalcaemic episodes as compared to patients using calcium based phosphate binders alone. The effects of sevelamer on phosphorus and calcium were proven to be maintained throughout a study with one year follow-up.

10.2 Pharmacodynamics

A study was conducted to evaluate the safety and tolerability of ACCEL-SEVELAMER compared to Renvela® (Genzyme) tablets in patients with chronic kidney disease (CKD) on hemodialysis based on the evaluation of the incidence of adverse events and serious adverse events as well as compliance. The secondary objective of the study was to prove the equivalence of an oral test preparation containing 800 mg sevelamer carbonate as compared to Renvela® on the control of serum phosphorus in chronic kidney disease patients on hemodialysis. The exploratory objective of the study was to provide further information on the tolerability of ACCEL-SEVELAMER based on the evaluation of vital signs and laboratory parameters (hematology and biochemistry).

The evaluation of the primary endpoint in view of the safety and tolerability of ACCEL-SEVELAMER compared to Renvela® (Genzyme) tablets in patients with CKD on hemodialysis demonstrated no difference regarding the incidence of treatment-emergent adverse events and percentage of subjects who withdrew due to adverse events. The statistical evaluation of time-weighted mean of the serum phosphorus concentration (determined from 4 measurements during the last 2 weeks of each 8-week double-blind treatment period) after treatment with the test and the reference product led to the conclusion that both products are equivalent in view of control of serum phosphorus concentration.

The evaluation of further safety parameters [clinically relevant changes in vital signs from baseline to the end of treatment and clinically relevant changes in safety laboratory parameters from baseline to the end of treatment as well as the laboratory examination (hematology and biochemistry) throughout the trial] provides no evidence for any safety concern.

10.3 Pharmacokinetics

Pharmacokinetic studies have not been carried out with sevelamer carbonate or sevelamer hydrochloride as sevelamer is not absorbed from the GI tract, as confirmed by an absorption

study in healthy volunteers. In this study a mass balance study using ^{14}C-sevelamer hydrochloride in 16 healthy male and female volunteers showed that sevelamer hydrochloride is not systemically absorbed. No absorption studies have been performed in patients with renal disease.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature 15°C to 30°C in original container. Protect from moisture and heat.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Sevelamer carbonate (USAN)

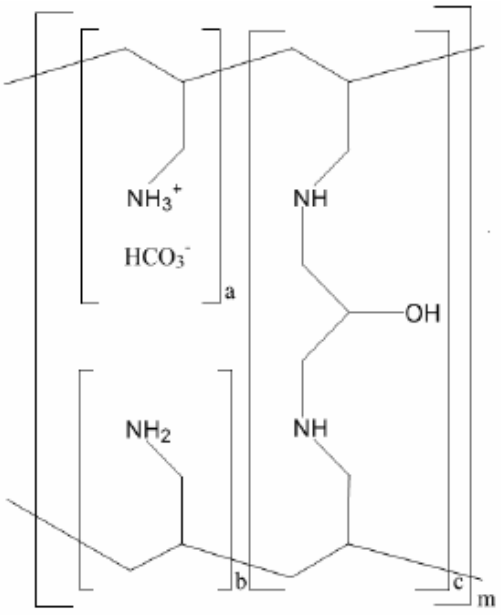
Chemical name:

1. poly(allylamine-*co*-*N,N'*-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt (CAS)
2. Oxirane, (chloromethyl)-, polymer with 2-propen-1-amine, carbonate salt (CAS)
3. 2-Propen-1-amine, polymer with (chloromethyl) oxirane, carbonate salt (CAS)
4. Allylamine polymer with 1-chloro-2,3-epoxypropane, carbonate salt (IUPAC)

Molecular formula and molecular mass: $[(C_4H_9NO_3)_a(C_3H_7N)_b(C_9H_{18}N_2O)_c]_m$, where (a+b):c=9:1

Sevelamer carbonate is a highly cross-linked polymer of varying size, and each particle can be considered as one molecule. Since the molecular weight is equal to the weight of the particle itself, the molecular weight distribution of a cross-linked polymer is a function of the distribution of particle sizes.

Structural formula:



a, b = number of primary amine groups a + b = 9

c = number of crosslinking groups c = 1

m = large number to indicate extended polymer network

Physicochemical properties:

Description: Sevelamer carbonate is a cross-linked poly(allylamine carbonate) polymer. The cross-linking agent is epichlorohydrin (1-chloro-2,3-epoxypropane). The cross-linking groups consist of two secondary amine groups derived from the starting material, poly (allylamine hydrochloride) and one molecule of epichlorohydrin giving 2 hydroxypropyl linkers. A portion of the amine is present as the carbonate salt, at 14 – 21% by weight; this is similar to sevelamer hydrochloride where the chloride salt is present at 15 - 20%, by weight.

Physical Form: White to off-white free flowing powder.

Solubilities: Insoluble in all tested solvents.

Crystallinity: Amorphous, granular.

pH Values: 8 – 10.5 (1% aqueous slurry).

Hygroscopicity: Sevelamer carbonate is hygroscopic.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 5 summarizes the clinical trials using sevelamer in CKD patients on dialysis.

Table 5: Summary of patient demographics for clinical trials in CKD patients on dialysis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)
Sevelamer carbonate vs Sevelamer hydrochloride	Double-Blind Randomized, Cross Over,	Tablet, oral, 2 8 weeks periods	Stage 5 CKD patients: 79
Sevelamer Hydrochloride	Double Blind, Placebo Controlled	Tablet, oral, 2 weeks	24
Sevelamer Hydrochloride	Active Controlled, Open Label, Cross Over	Tablet, oral, 2-week washout periods and 8 weeks periods for Sevelamer and active control	Haemodialysis patients: 84
Sevelamer Hydrochloride	Active Controlled, Parallel	Tablet, oral, 2-weeks washout period and 52 weeks	Haemodialysis patients: 200
Sevelamer Hydrochloride	Active Controlled, Parallel in Peritoneal Dialysis Patients	Tablet, oral, 12 weeks with 2 weeks washout period	Peritoneal Dialysis patients: 143

14.2 Study Results

The safety and efficacy of sevelamer to control serum phosphorus in CKD patients on dialysis was mainly determined by the ability of sevelamer hydrochloride to bind phosphorus from food in one double-blind and several open-label clinical trials in hemodialysis and peritoneal dialysis patients. The tablet formulation of sevelamer carbonate administered three times per day with meals has been shown to control serum phosphorus effectively.

In a double-blind, randomized, two 8-week period cross-over clinical trials in hemodialysis patients, sevelamer carbonate was shown to be therapeutically equivalent to sevelamer hydrochloride.

In this trial, 79 stage 5 CKD patients received, in a random order, sevelamer carbonate 800 mg tablet and sevelamer hydrochloride 800 mg tablets during each 8-week period without an intervening washout phase. The study dose during the cross-over period was based on the sevelamer hydrochloride given during the run-in period. The average actual dose divided among meals during the randomized treatment periods was 6.0 ± 2.8 g/day for both treatment regimens. There was no significant difference in mean serum phosphorus between the two groups during the treatment periods (1.5 ± 0.3 mmol/l during sevelamer carbonate treatment and 1.5±0.3 mmol/l during sevelamer hydrochloride treatment). Following a two-week washout phase after the end of the last period of the cross-over, phosphorus rose significantly to 2.1 ± 0.6 mmol/l.

The ability of sevelamer hydrochloride to lower serum phosphorus in CKD patients on dialysis was demonstrated in six clinical trials: one double-blind placebo controlled 2-week study (sevelamer hydrochloride N=24); two open-label uncontrolled 8-week studies (sevelamer hydrochloride N=220) and three active-controlled open-label studies with treatment durations of 8 to 52 weeks (sevelamer hydrochloride N=256). Three of the active-controlled studies are described here. One is a crossover study with two 8-week periods comparing sevelamer hydrochloride to an active-control. The second is a 52-week parallel study comparing sevelamer hydrochloride with active-control. The third is a 12-week parallel study comparing sevelamer hydrochloride and active-control in peritoneal dialysis patients.

Hemodialysis Patients

Active-Control, Cross-Over Study in Hemodialysis Patients

Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus > 1.9 mmol/L) following a two-week phosphate binder washout period received sevelamer and active-control for eight weeks each in random order. Treatment periods were separated by a two-week phosphate binder washout period. Patients started on treatment three times per day with meals. Over each eight-week treatment period, at three separate time points the dose of sevelamer could be titrated up 1 capsule or tablet per meal (3 per day) to control serum phosphorus, the dose of active-control could also be altered to attain phosphate control. Both treatments significantly decreased mean serum phosphorus by about 0.6 mmol/L (Table 6).

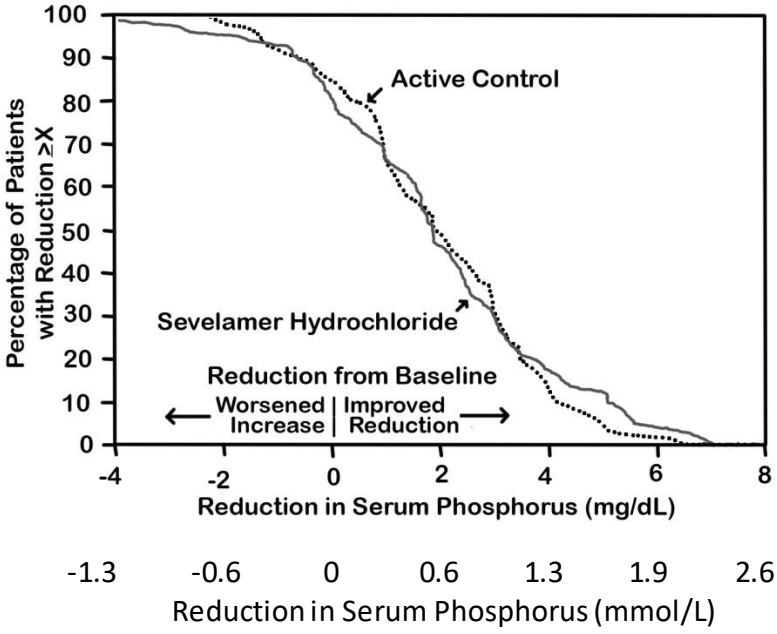
Table 6: Mean Serum Phosphorus (mmol/L) at Baseline and Endpoint

	Sevelamer Hydrochloride (N=81)	Active Control (N=83)
Baseline at End of Washout	2.7	2.6
Endpoint	2.1	1.9
Change from Baseline at Endpoint (95% Confidence Interval)	-0.6* (-0.8, -0.5)	-0.7* (-0.8, -0.5)

*p<0.0001, within treatment group comparison

The distribution of responses is shown in Figure 1. The distributions are similar for sevelamer hydrochloride and active control. The median response is a reduction of about 0.6 mmol/L in both groups. About 50% of subjects have reductions between 0.3 and 1.0 mmol/L.

Figure 1: Percentage of patients (Y-axis) attaining a phosphorus reduction from baseline (mmol/L) at least as great as the value of the X-axis



Average daily sevelamer hydrochloride dose at the end of treatment was 4.9 g (range of 0.0 to 12.6 g).

Active-Control, Parallel Study in Hemodialysis Patients

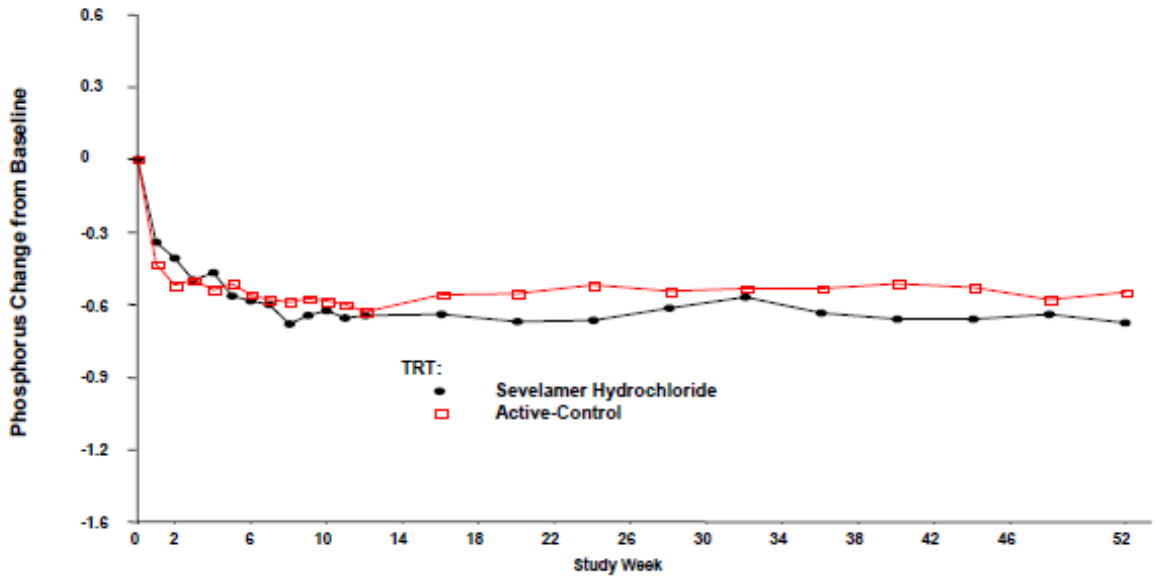
Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >1.8 mmol/L) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride 800 mg tablets (N=99) or an active-control (N=101). The two treatments produced similar decreases in serum phosphorus. At week 52, using last-observation-carried-forward, sevelamer hydrochloride and active-control both significantly decreased mean serum phosphorus (Table 7).

Table 7: Mean Serum Phosphorus (mmol/L) and Ion at Baseline and Change from Baseline to End of Treatment

	Sevelamer HCl (N=94)	Active-Control (N=98)
Phosphorus Baseline	2.4	2.4
Change from Baseline at Endpoint	-0.7	-0.6
Ca x Phosphorus Ion Product Baseline	5.7	5.5
Change from Baseline at Endpoint	-1.6	-1.1

Sixty-one percent of sevelamer hydrochloride patients and 73% of the control patients completed the full 52 weeks of treatment. Figure 2, a plot of the phosphorus change from baseline for the completers, illustrates the durability of response for patients who are able to remain on treatment.

Figure 2: Mean Phosphorus Change from Baseline for Patients who Completed 52 Weeks of Treatment



Average daily sevelamer hydrochloride dose at the end of treatment was 6.5 g (range of 0.8 to 13 g).

Active-Control, Parallel Study in Peritoneal Dialysis Patients

One hundred and forty-three patients on peritoneal dialysis who were hyperphosphatemic (serum phosphorus > 1.8 mmol/L) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride (N=97) or active-control (N=46) open label for 12 weeks. Average daily sevelamer hydrochloride dose at the end of treatment was 5.9 g (range 0.8 to 14.3 g). There were statistically significant changes in serum phosphorus ($p<0.001$) for sevelamer hydrochloride (-0.5 mmol/L from baseline of 2.4 mmol/L), similar to the active-control.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

ACCEL-SEVELAMER contains sevelamer, a non-absorbed phosphate binding crosslinked polymer, free of metal and calcium. ACCEL-SEVELAMER (sevelamer carbonate) was developed as a pharmaceutical alternative to sevelamer hydrochloride (RENAGEL®).

Both sevelamer hydrochloride and sevelamer carbonate salt forms are polymeric anion exchange resins with the same polymeric structure. The amines in the polymer exist in a protonated form and bind to negatively charged phosphates. While the counterions differ for the two salts, the polymer itself, the active moiety responsible for binding of phosphate, remains the same. Since in both resins the active moiety responsible for phosphate binding is the same polymer (sevelamer) and the two salts have been shown to be equivalent both in *in vitro* and *in vivo*, the nonclinical data generated using sevelamer hydrochloride are also applicable to sevelamer carbonate.

To assess nonclinical toxicity, sevelamer was administered orally to Sprague-Dawley rats acutely and for 1, 3, and 6 months at doses up to 10 g/kg/day, and to beagle dogs acutely and for 1, 3, and 12 months at doses up to 2 g/kg/day. In general, sevelamer caused minimal toxicity. In rats, sevelamer produced a dose-dependent decrease in fat-soluble vitamin E and decreased levels of fat-soluble vitamin D and vitamin K (measured by coagulation time) at high doses only. Potentially clinically relevant findings (anemia, focal hemorrhages) due to these decreased serum fat-soluble vitamin levels have only been observed in high-dose (4.5 to 10 g/kg/day) male rats.

In the segment II studies in rats and rabbits, there was no evidence that sevelamer directly induced embryolethality, fetotoxicity, or teratogenicity at the highest doses tested (1.0 g/kg/day in rabbits and 4.5 g/kg/day in rats). In rats, at doses of 1.5 and 4.5 g/kg/day (approximately 8 and 20 times the maximum clinical trial dose of 200 mg/kg/day), sevelamer caused reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D and/or vitamin K depletion at these high doses.

There are no reported overdoses of sevelamer in patients. Since sevelamer is not absorbed, the

risk of systemic toxicity is low.

Studies were conducted with sevelamer carbonate to bridge from the existing toxicology for the hydrochloride salt of sevelamer to the carbonate salt.

To assess nonclinical toxicity, sevelamer hydrochloride and sevelamer carbonate were administered to Sprague Dawley rats and to beagle dogs for four weeks. In rats, two groups received diet mixed with sevelamer carbonate at the dose-level of 1.0 or 4.5 g/kg/day and two other groups received diet mixed with sevelamer hydrochloride at the dose-level of 1.0 or 4.5 g/kg/day. In dogs, treated animals received either sevelamer carbonate or sevelamer hydrochloride once daily by oral gavage at a dose-level of 0.2 or 1.0 g/kg/day. Other than the reduced serum levels of fat soluble vitamins in rats, no systemic toxicity related to administration of sevelamer carbonate or sevelamer hydrochloride was observed. In addition, these findings were comparable to those seen with similar studies conducted with sevelamer hydrochloride.

Carcinogenicity:

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were given sevelamer hydrochloride by diet at 0.3, 1, or 3 g/kg/day. There was an increased incidence of urinary bladder transitional cell papilloma in male rats (3 g/kg/day) at a human equivalent dose 2 times the maximum clinical trial dose of 14.4 g/day. Mice received mean dietary doses of 0.8, 3, or 9 g/kg/day. No increased incidence of tumors was observed in mice at a human equivalent dose 3 times the maximum clinical trial dose of 14.4 g/day.

Genotoxicity:

A series of genotoxicity studies were performed to assess sevelamer's mutagenic potential. In the Salmonella typhimurium reverse mutation assay, sevelamer produced the same mean number of revertants as the negative control in all strains tested with and without metabolic activation. Sevelamer is considered to be non-mutagenic. In the *in vitro* mammalian cytogenetics test, sevelamer, at 5 mg/mL, was concluded to be weakly positive for the induction of structural chromosome aberrations and negative for the induction of numerical chromosome aberrations. The weakly positive effects of sevelamer are thought to be due to sevelamer's ability to absorb the culture medium and not the direct action of the test article. Sevelamer was tested in the *in vivo* mouse micronucleus assay to confirm these results. Since sevelamer is non-absorbed, it was injected intraperitoneally to maximize its potential effects. Sevelamer was administered at doses up to 5 g/kg/day for 2 consecutive days. Under the conditions of this study, sevelamer was concluded to be nonclastogenic

Reproductive and Developmental Toxicology:

Developmental and reproductive toxicity studies have been performed with sevelamer to assess teratogenic potential and effects on fertility. In the segment I study, sevelamer had no adverse effect upon male and female fertility or on early embryonic development at the highest dose tested (4.5 g/kg/day). In the segment III pre- and post-natal study, there was no evidence of maternal toxicity at any dose level. There was no effect on reproductive performance during gestation, parturition or lactation and no effect on the survival, physical development, behavior and reproductive performance of the F_1 generation or on the survival and development of the F_2

generation pups at doses tested (≤ 1.0 g/kg/day). In conclusion, no reproductive toxicity has been observed with sevelamer.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrRenvela® tablets, 800 mg, submission control 238461, Product Monograph, Sanofi-Aventis Canada Inc. (OCT 29, 2020)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ACCEL-SEVELAMER

Sevelamer carbonate tablets

Read this carefully before you start taking ACCEL-SEVELAMER and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ACCEL-SEVELAMER**.**

Serious Warnings and Precautions

ACCEL-SEVELAMER may cause serious side effects that may require hospitalization and surgery. These serious side effects include:

- **Dysphagia** (difficulty swallowing, problems with esophagus)
- **Bowel Obstruction (ileus), Intestinal Blockage, or hole in the intestine**

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

What is ACCEL-SEVELAMER used for?

ACCEL-SEVELAMER is used to lower high blood levels of phosphate in adults who:

- have end-stage kidney disease, and
- are undergoing dialysis.

How does ACCEL-SEVELAMER work?

ACCEL-SEVELAMER is a phosphate binder that is not absorbed in your body. When taken with meals, ACCEL-SEVELAMER binds with the phosphate in the food you ingested and prevents its absorption into your blood. This helps to lower the levels of phosphate in your body.

What are the ingredients in ACCEL-SEVELAMER?

Medicinal ingredients: Sevelamer carbonate

Non-medicinal ingredients: Colloidal anhydrous silica, diacetylated monoglycerides, hypromellose, lactose monohydrate, zinc stearate.

ACCEL-SEVELAMER comes in the following dosage forms:

Tablets: 800 mg

Do not use ACCEL-SEVELAMER if:

- you have abnormally low levels of phosphate in your blood
- you currently have gastrointestinal problems such as:
  - bowel obstruction
  - damage to the lining of the digestive tract caused by tissue death, holes or ulcers (sores)
  - gastrointestinal bleeding
- you are allergic to sevelamer carbonate or to any other ingredients in ACCEL-SEVELAMER. ACCEL-SEVELAMER contains lactose.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ACCEL-SEVELAMER. Talk about any health conditions or problems you may have, including if you:

- have difficulty swallowing. This includes swallowing disorders or problems with your esophagus.
- have an intestinal disorder such as, conditions that slow down the passage of food through the intestine and lead to blockage.
- have had surgery on your intestines.
- have severe or worsening constipation.
- have abnormally low levels of phosphate or calcium in your blood.
- are pregnant, think you may be pregnant, or are planning to become pregnant.
- are breast feeding.
- are taking medicines used to control seizures or epilepsy.
- are taking medicines used to treat heart rhythm problems (arrhythmia).

Other warnings you should know about:
Inflammation of the bowel: ACCEL-SEVELAMER may cause serious bowel inflammation. This can lead to other serious complications such as:

- gastrointestinal bleeding
- damage to the lining of the digestive tract caused by tissue death, holes or ulcers (sores)
- tumours in the intestines
- chronic inflammation of the lining of the digestive tract

See the Serious side effects and what to do about them table, below, for more information on this and other serious side effects.

Pregnancy: Only take ACCEL-SEVELAMER during pregnancy if you and your healthcare professional have discussed the risks and have decided that you should.

Breastfeeding: The effects of ACCEL-SEVELAMER on breast milk and the breastfed baby are not well studied. Talk to your healthcare professional about the best way to feed your baby if you take ACCEL-SEVELAMER.

Check-ups and testing: Your healthcare professional may do blood tests before you start ACCEL-SEVELAMER and/or during your treatment. These tests will check:

- the amount of calcium, phosphate, bicarbonate and chloride in your blood
- the levels of vitamin D, E, K and folic acid in your blood.

Depending on your test results, your healthcare professional may tell you to take supplements during your treatment with ACCEL-SEVELAMER.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ACCEL-SEVELAMER:

- Ciprofloxacin – used to treat bacterial infections
- Cyclosporin, mycophenolate, tacrolimus – used to prevent rejection of organ transplants
- Levothyroxine – used to treat an underactive thyroid gland
- Proton pump inhibitors, such as omeprazole, lansoprazole, pantoprazole – used to relieve symptoms of acid reflux and treat stomach ulcers

Some medicines may need to be taken one hour before or three hours after taking ACCEL-SEVELAMER. Your healthcare professional will give you instructions on how to take your other medications when treated with ACCEL-SEVELAMER.

How to take ACCEL-SEVELAMER:

- Swallow the tablets **whole**. **DO NOT** crush, chew, or break the tablet.
- Tablets should **ONLY** be taken with meals or snacks. You **SHOULD NOT** take it on an empty stomach.
- ACCEL-SEVELAMER should be taken 3 times a day with meals and / or snacks.
- The total daily dose the healthcare professional tells you to take should be divided between the meals or snacks portions you eat during the day.

Usual dose:

Your healthcare professional will:

- determine your dose based on the phosphate levels in your blood.
- monitor your phosphate levels and change the dose as needed.

Take ACCEL-SEVELAMER exactly as directed by your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much ACCEL-SEVELAMER, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, skip it and take the next dose as scheduled. Do not double the dose.

What are possible side effects from using ACCEL-SEVELAMER?

These are not all the possible side effects you may have when taking ACCEL-SEVELAMER. If you experience any side effects not listed here, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Abdominal pain.		✓	
RARE			
Allergic reactions: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
Bowel Obstruction (ileus), Intestinal Blockage, or hole in the intestine: sudden abdominal pain, inflammation and ulcers, abdominal discomfort, cramping and gas pains, diarrhea or difficulty passing stools, bleeding (blood in stools), nausea/vomiting especially after meals, excessive burping, loss of appetite; later symptoms include fever and chills.			✓
Diverticulitis: pain and tenderness in the left lower part of the abdomen, fever, nausea, diarrhea, or constipation.		✓	
Dysphagia: Difficulty swallowing, problems with your esophagus.	✓		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Inflammation of the bowel: Severe abdominal pain, stomach or intestine problems, blood in the stool.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

- Store tablets between 15°C to 30°C in original container.
- Protect from moisture and heat.
- Keep out of reach and sight of children.

If you want more information about ACCEL-SEVELAMER:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.accelpharma.com, or by calling 1-877-822-2235.

This leaflet was prepared by Accel Pharma Inc.

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