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

VIOKACE (pancrelipase) tablets, for oral use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

VIOKACE™ is a combination of porcine-derived lipases, proteases, and amylases. VIOKACE, in combination with a proton pump inhibitor, is indicated in adults for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. (1)

DOSAGE AND ADMINISTRATION

VIOKACE is not interchangeable with any other pancrelipase product. VIOKACE tablets should be swallowed whole. Do not crush or chew tablets. (2.1) Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines. (2.2)

- Begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. (2.2)
- Individualize dosage based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet. (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 10,440 USP units of lipase; 39,150 USP units of protease; 39,150 USP units of amylase (3)
- Tablets: 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of VIOKACE exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day). (5.1)
- To avoid irritation of oral mucosa, do not chew VIOKACE or retain in the mouth. (5.2)
- Exercise caution when prescribing VIOKACE to patients with gout, renal impairment, or hyperuricemia. (5.3)
- There is theoretical risk of viral transmission with all pancreatic enzyme products including VIOKACE. (5.4)
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. (5.5)

ADVERSE REACTIONS

- Adverse reactions occurring in at least 2 chronic pancreatitis or pancreatectomy patients (greater than or equal to 7%) receiving VIOKACE are biliary tract stones and anal pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact APTALIS Pharma US, Inc. at 1-800-472-2634 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

USE IN SPECIFIC POPULATIONS

- The safety and effectiveness of VIOKACE in pediatric patients have not been established. (8.4)
- VIOKACE use in pediatric patients may result in suboptimal growth due to tablet degradation in the gastric environment. In general, delayed-release (enteric-coated) capsules should be used for pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: March 2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VIOKACE (pancrelipase) tablets, in combination with a proton pump inhibitor, is indicated in adults for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy.

2 DOSAGE AND ADMINISTRATION

VIOKACE is not interchangeable with any other pancrelipase product.

VIOKACE is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of VIOKACE should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet as described in the Limitations on Dosing below [*see Dosage and Administration (2.2) and Warnings and Precautions (5.1)*].

2.1 Administration

Since VIOKACE is not enteric-coated, it should be taken in combination with a proton pump inhibitor [*see Indications and Usage (1)*].

VIOKACE should be taken during meals or snacks, with sufficient fluid. Tablets should be swallowed whole. Do not crush or chew tablets. Care should be taken to ensure that no drug is retained in the mouth to avoid mucosal irritation.

2.2 Dosage

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences.[1,2,3] VIOKACE should be administered in a manner consistent with the recommendations of the Conferences provided in the following paragraph. Only the adult dosing guidelines are shown below. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.

Additional recommendations for pancreatic enzyme therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy are based on a clinical trial conducted in these populations.

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed VIOKACE dose for an individualized full meal should be given with each snack. The total daily dosage should reflect approximately three meals plus two or three snacks per day.

In one clinical trial, patients received VIOKACE at a dose of 125,280 lipase units per meal while consuming 100 g of fat per day *[see Clinical Studies (14)]*. Lower starting doses recommended in the literature are consistent with the 500 lipase units/kg of body weight per meal lowest starting dose recommended for adults in the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1, 2, 3, 4] The initial starting dose and increases in the dose per meal should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.

Limitations on Dosing

Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1,2,3] If symptoms and signs of steatorrhea persist, the dosage may be increased by the healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age *[see Warnings and Precautions (5.1)]*. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

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3 DOSAGE FORMS AND STRENGTHS

The active ingredient in VIOKACE evaluated in clinical trials is lipase. VIOKACE is dosed in lipase units.

Other active ingredients include protease and amylase. Each VIOKACE tablet strength contains the specified amounts of lipase, protease, and amylase as follows:

- 10,440 USP units of lipase; 39,150 USP units of protease; 39,150 USP units of amylase tablets are tan, round, biconvex and have VIO9111 engraved on one side and 9111 on the other side.
- 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets are tan, oval, biconvex with V^{16} engraved on one side and 9116 on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products.[5,6] Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in children less than 12 years of age.[1] Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs.[1] It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day *[see Dosage and Administration (2.2)]*.

Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

5.2 Potential for Irritation to Oral Mucosa

Care should be taken to ensure that no drug is retained in the mouth to avoid irritation of oral mucosa, and/or loss of enzyme activity. VIOKACE should not be crushed or chewed *[see Dosage and Administration (2.1) and Patient Counseling Information (17.1)]*.

5.3 Potential for Risk of Hyperuricemia

Caution should be exercised when prescribing VIOKACE to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

5.4 Potential for Viral Exposure from the Product Source

VIOKACE is sourced from pancreatic tissue from pigs used for food consumption. Although the risk that VIOKACE will transmit an infectious agent to humans has been reduced by testing for certain viruses during manufacturing and by inactivating certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. Thus, the presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.

5.5 Allergic Reactions

Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase). The risks and benefits of continued VIOKACE treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

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5.6 Potential for Exacerbation of Symptoms of Lactose Intolerance

VIOKACE tablets contain lactose monohydrate. Patients who have lactose intolerance may not be able to tolerate VIOKACE.

6 ADVERSE REACTIONS

The most serious adverse reactions reported with different pancreatic enzyme products of the same active ingredient (pancrelipase) that are described elsewhere in the label include fibrosing colonopathy, hyperuricemia and allergic reactions [*see Warnings and Precautions (5.1, 5.3 and 5.5)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The short-term safety of VIOKACE was assessed in a single, multicenter, randomized, parallel, placebo-controlled, double-blind study of 50 patients, ages 24-70 years, with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis or pancreatectomy. VIOKACE Tablets (20,880 USP units of lipase per tablet) or placebo were administered as 22 tablets per day (6 tablets with 3 meals and 2 tablets with 2 of 3 snacks). Duration of exposure ranged from 6 to 7 days. The majority of the subjects were Caucasian (96%) and male (82%).

The most common adverse reactions (greater than or equal to 7%) were biliary tract stones and anal pruritus. Table 1 enumerates adverse reactions that occurred in at least 1 patient (greater than or equal to 3%) treated with VIOKACE at a higher rate than with placebo. Two adverse reactions reported in greater than one patient were biliary tract stones and anal pruritus.

TABLE 1
Adverse Reactions Occurring in at Least 1 Patient (greater than or equal to 3%) in Chronic Pancreatitis or Pancreatectomy

	Treatment Group	
MedDRA Primary System Organ Class/ Adverse Reactions	**VIOKACE (N=30)**	**Placebo (N=20)**
Blood And Lymphatic System Disorders		
Anemia	1 (3%)	0
Gastrointestinal Disorders		
Anal pruritus	2 (7%)	0
Abdominal pain	1 (3%)	0
Ascites	1 (3%)	0
Flatulence	1 (3%)	0
General Disorders and Administration Site Conditions		
Edema peripheral	1 (3%)	0
Hepatobiliary Disorders		
Biliary tract stones	2 (7%)	0
Hydrocholecystis	1 (3%)	0
Infections and Infestations		
Viral infection	1 (3%)	0
Nervous System Disorders		
Headache	1 (3%)	0
Renal and Urinary Disorders		
Renal cyst	1 (3%)	0
Skin and Subcutaneous Tissue Disorders		
Rash	1 (3%)	0

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6.2 Postmarketing Experience

Post-marketing data for VIOKACE have been available since 2003. The safety data are similar to that described below. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Pancreatic enzyme products (delayed and immediate-release) with different formulations of the same active ingredient (pancrelipase) have been used for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis and other conditions, such as chronic pancreatitis. The long-term safety profile of these products has been described in the medical literature. The most serious adverse events included fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions including anaphylaxis, asthma, hives, and pruritus. The most commonly reported adverse events were gastrointestinal disorders, including abdominal pain, diarrhea, flatulence, constipation and nausea, and skin disorders including pruritus, urticaria and rash.

7 DRUG INTERACTIONS

No drug interactions have been identified. No formal interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

Pregnancy Category C. Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. VIOKACE should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VIOKACE is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency.

8.4 Pediatric Use

The safety and effectiveness of VIOKACE in pediatric patients have not been established. In general, delayed-release (enteric-coated) capsules should be used for pediatric patients. Due to greater degradation in the gastric environment, VIOKACE, a non-enteric-coated, pancreatic enzyme replacement product, may have decreased bioavailability and therefore may be less efficacious than enteric-coated formulations.[7, 8] Thus, use of VIOKACE in pediatric patients may increase the risk of inadequate treatment of pancreatic insufficiency and result in suboptimal weight gain, malnutrition and/or need for larger doses of pancreatic enzyme replacement *[See Warnings and Precautions (5.1)]* The efficacy of VIOKACE was established in adult patients with concomitant proton pump inhibitor (PPI) therapy. The long-term safety of PPI use in pediatric patients has not been established.

8.5 Geriatric Use

Clinical studies of VIOKACE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

There have been no reports of overdose in clinical trials or post-marketing surveillance with VIOKACE. Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures *[see Dosage and Administration (2) and*

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Warnings and Precautions (5.1)]. High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia, and should be used with caution in patients with a history of hyperuricemia, gout, or renal impairment *[see Warnings and Precautions (5.3)]*.

11 DESCRIPTION

VIOKACE is a pancreatic enzyme preparation for oral administration consisting of pancrelipase, an extract derived from porcine pancreatic glands. Pancrelipase contains multiple enzyme classes, including porcine-derived lipases, amylases, and proteases.

Pancrelipase is a beige-white amorphous powder. It is miscible in water and practically insoluble in alcohol.

The active ingredient evaluated in clinical trials is lipase. VIOKACE is dosed by lipase units.

Other active ingredients include protease and amylase.

Inactive ingredients in VIOKACE include: colloidal silicon dioxide, crosscarmellose sodium, lactose monohydrate, microcrystalline cellulose, stearic acid and talc.

10,440 USP units of lipase; 39,150 USP units of protease; 39,150 USP units of amylase tablets are tan, round biconvex and have VIO9111 engraved on one side and 9111 on the other side.

20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase tablets are tan, oval, biconvex with V^{16} engraved on one side and 9116 on the other side.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pancreatic enzymes in VIOKACE catalyze the hydrolysis of fats to monoglycerides, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

12.3 Pharmacokinetics

Pancreatic enzymes are not absorbed from the gastrointestinal tract in appreciable amounts.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase.

14 CLINICAL STUDIES

The short-term safety and efficacy of VIOKACE were evaluated in a randomized, double-blind, placebo-controlled, parallel group study comparing VIOKACE Tablets (20,880 USP units of lipase per tablet) to placebo in 50 patients, ages 24 to 70, with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP) or pancreatectomy. Eighteen patients had a history of pancreatectomy (11 were treated with VIOKACE). All patients were maintained on a controlled high fat diet of 100 grams of fat per day. After a wash-out period (6 to 7 days), patients were randomized to a fixed dose of VIOKACE (22 tablets per day; 6 tablets per meal and 2 tablets with 2 of 3 snacks) or placebo, in combination with a proton pump inhibitor. Forty-nine patients completed the double-blind treatment period (6 to 7 days); 29 patients received VIOKACE, and 20 patients received placebo.

The coefficient of fat absorption (CFA) was determined by a 72-hour stool collection during both treatments, when both fat excretion and fat ingestion were measured.

The wash-out period mean CFA was 48% in the VIOKACE treatment group and was 57% in the placebo group. At the end of the double-blind treatment period, the mean CFA was 86% with VIOKACE treatment compared to 58% with placebo. The mean difference in CFA at the end of the double-blind treatment period was 28 percentage points in favor of VIOKACE treatment with 95% Confidence Interval of (21, 37) and $p \leq 0.0001$.

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Subgroup analyses of the CFA results showed that mean change in CFA with VIOKACE treatment (from the washout period to the end of the double-blind period) was greater in patients with lower wash-out period CFA values than in patients with higher wash-out period CFA values.

Only 2 of the patients with a history of total pancreatectomy were treated with VIOKACE. One of these patients had a CFA of 12% during the wash-out period and a CFA of 90% at the end of the double-blind period; the other patient had a CFA of 38% during the wash-out period and a CFA of 77% at the end of the double-blind period. The remaining 9 patients with a history of partial pancreatectomy treated with VIOKACE had a mean CFA of 56% during the wash-out period and a mean CFA of 86% at the end of the double-blind period.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

VIOKACE tablets

10,440 USP units of lipase; 39,150 USP units of protease; 39,150 USP units of amylase
Each VIOKACE tablet is available as a tan, round, biconvex tablet with VIO9111 engraved on one side and 9111 on the other side supplied in bottles of 100 tablets (NDC 58914-112-10).

VIOKACE tablets

20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase
Each VIOKACE tablet is available as a tan, oval, biconvex tablet with V^{16} engraved on one side and 9116 on the other side supplied in bottles of 100 tablets (NDC 58914-117-10).

Storage and Handling

Avoid heat. VIOKACE tablets should be stored in a dry place in the original container. Store at room temperature (20-25°C, 68-77°F), brief excursion permitted up to 40°C (104°F) for up to 24 hrs. After opening, keep the container tightly closed between uses to protect from moisture.

VIOKACE is dispensed in bottles containing a desiccant. The desiccant packet should not be eaten. The desiccant packet will protect the product from moisture.

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17 PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Medication Guide)"

17.1 Dosing and Administration

- Instruct patients and caregivers that VIOKACE should only be taken as directed by their doctor. Patients should be advised that the total daily dose should not exceed 10,000 lipase units/kg body weight/day unless clinically indicated. This needs to be especially emphasized for patients eating multiple snacks and meals per day. Patients should be informed that if a dose is missed, the next dose should be taken with the next meal or snack as directed. Doses should not be doubled [*see Dosage and Administration (2)*].

- Instruct patients and caregivers that VIOKACE should always be taken with food. Patients should swallow the intact tablets with adequate amounts of liquid at mealtimes [*see Dosage and Administration (2)*].

17.2 Fibrosing Colonopathy

Advise patients and caregivers to follow dosing instructions carefully, as doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures in children below the age of 12 years [*see Dosage and Administration (2) and Warnings and Precautions (5.1)*].

17.3 Allergic Reactions

Advise patients and caregivers to contact their healthcare professional immediately if allergic reactions to VIOKACE develop [*see Warnings and Precautions (5.5)*].

17.4 Pregnancy and Breast Feeding

- Instruct patients to notify their healthcare professional if they are pregnant or are thinking of becoming pregnant during treatment with VIOKACE [*see Use in Specific Populations (8.1)*].
- Instruct patients to notify their healthcare professional if they are breast feeding or are thinking of breast feeding during treatment with VIOKACE *[see Use in Specific Populations (8.3)]*.

Marketed by:
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Manufactured by:
Confab Laboratories, Inc.
St. Hubert, Canada

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