

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-175Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 17, 2012
FROM: Julie Beitz, MD
SUBJECT: Approval Action
TO: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules
Digestive Care, Inc.

Summary

Pertzye (pancrelipase) Delayed-Release Capsules are an exogenous source of porcine-derived pancreatic enzymes. Pancreatic enzyme products (PEPs) serve as replacement therapy for digestive enzymes physiologically secreted by the pancreas and have long been considered the main stay of therapy for exocrine pancreatic insufficiency (EPI). Several PEPs, including Pertzye, have been marketed in the US for many years and have not undergone review under new drug applications (NDAs).¹ In 2004, to address concerns about variability in potency across products and within product lines, FDA published a Federal Register Notice which stated that PEPs must be marketed under approved NDAs.

This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Product's (DGIEP's) recommendation for an approval action for Pertzye (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions.

The NDA applicant has satisfactorily addressed the approvability issues discussed in my previous review and in the Complete Response letter, both dated January 27, 2011. In addition, for the drug substance manufacturing process, the DMF holder submitted: 1) adequate information supporting a new change in the intermediate storage containers, and 2) adequate in-process microbial controls. There has been satisfactory resolution of deficiencies identified during inspections of the drug substance and drug product manufacturing facilities, and resolution of discussions regarding the product labeling, REMS, and postmarketing study requirements and commitments.

Dosing

Pertzye (pancrelipase) Delayed-Release Capsules are dosed by lipase units. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Pertzye should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences.

Pertzye use in pediatric patients will be limited by the available capsule dosage strengths and their ability to provide the recommended dose based on age and weight. Since the lowest available dosage strength will be 8000 USP units of lipase, dosing with Pertzye will not be possible for the lowest weight infants. Product labeling will specify dosing recommendations for patients 1 to 4 years of age weighing 8 kg or greater, and for patients 4 years of age and older weighing 16 kg or greater. Doses greater than 2500 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 72-hour fecal fat measures. Doses greater than 6000 lipase units/kg of body weight per meal have been associated with colonic strictures, indicative of fibrosing colonopathy, in children with cystic fibrosis less than 12 years of age.

¹ Pertzye has been marketed in the US under the name "Pancrecarb" in three strengths, MS-4, MS-8, and MS-16, since 1995, 2000, and 2004, respectively.

Pertzye (pancrelipase) Delayed-Release Capsules are not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Pertzye, is pancrelipase, which consists of the enzymes lipase, amylase and protease, as specified in the U.S. Pharmacopeia. However, the animal source of pancreata and the extraction processing differ among products. The **Dosage and Administration** section of product labeling will state that “Pertzye is not interchangeable with any other pancrelipase product.”

Regulatory History

- **Cycle 1**

On October 27, 2008, Digestive Care, Inc. submitted NDA 022175 and was granted a standard review. A meeting of FDA’s Anti-Viral Advisory Committee on December 2, 2008, focused on the theoretical risk of viral exposure to patients administered porcine-derived PEPs, including Pertzye (pancrelipase) Delayed-Release Capsules.

Inspection of Digestive Care, Inc.’s drug product manufacturing facility on (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483 involving failure to thoroughly investigate the root cause and identify corrective actions when batches fail, and absent records documenting qualified, approved cleansing procedures for equipment and utensils. Based on these findings, the Office of Compliance recommended withholding NDA approval.

Concurrent with this review, FDA reviewed submissions to DMF (b) (4) from the drug substance manufacturer, (b) (4) which supports this NDA. Inspection of the (b) (4) facility in (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483, involving quality systems, production systems, equipment and facilities, laboratory systems and material systems. Based on these findings, the Office of Compliance recommended withholding NDA approval.² FDA issued a Complete Response letter on August 27, 2009.

A re-inspection of the (b) (4) facility was performed in (b) (4); (b) (4) deficiencies were identified on an FDA form 483. During that inspection, FDA obtained and conducted microbiological testing on samples from three drug substance lots; 4 out of 5 test samples tested positive for *E. coli*. An outside laboratory retained by (b) (4) tested the same lots using the same assay that FDA had used and all were found to be negative. In January 2010, FDA collected additional samples from seven lots; analysis showed that none of the samples tested positive for *E. coli*, but all seven contained low levels of *Bacillus cereus* and one of the seven tested positive for *B. cereus* diarrheal enterotoxin (BDE) (b) (4) retained (b) (4) to retest these lots; they found that all seven lots tested negative for BDE. According to arguments set forth by (b) (4), trace amounts of (b) (4) intrinsic to the pancreatin drug substance could interfere with the BDE assay and produce false positive results.

In a review dated April 30, 2010, the Division of Microbiology, CFSAN, did not agree that the positive assay results could represent false positive results. The review further stated that if the drug substance lots were “...made with any level of consistency and the batches are homogeneous, it seems that 7/7 samples would have tested positive...” In subsequent testing, CFSAN recovered enterotoxigenic *B. cereus* from 4 of these 7 lots.³

- **Cycle 2**

² (b) (4) is also the drug substance manufacturer for Aptalis Pharma US, Inc.’s (formerly Axcan Pharma US, Inc.’s) Ultresa (pancrelipase) Delayed Capsules submitted under NDA 022222, and Viokace (pancrelipase) Tablets submitted under NDA 022542. The recommendation of the Office of Compliance to withhold NDA approval applied to these NDAs as well.

³ See memo dated October 25, 2010, from Reginald Bennett, Jennifer Hait, and Sandra Tallent.

On July 29, 2010, Digestive Care, Inc. submitted a complete response triggering a second review cycle. Inspections were conducted of (b) (4) and (b) (4) and FDA form 483s were issued to both firms. There were (b) (4) observations cited for (b) (4) including reporting results of BDE testing of pancreatin samples to (b) (4) as negative, when in fact the results were positive, and inadequate BDE test methods (e.g., lack of a test protocol and documentation that the test method was performed in a consistent manner), and failure to appropriately qualify analytical equipment used for BDE testing. (b) (4)

There were (b) (4) observations cited for (b) (4) one regarding the manufacture of (b) (4) and three regarding the manufacture of pancreatin drug substance: 1) (b) (4) had implemented a change in the drug substance intermediate storage containers, from (b) (4) white drums to (b) (4) blue drums, however, the latter were either not of appropriate design or not qualified to ensure product quality, 2) failure to adequately evaluate and qualify the contract laboratory, (b) (4), and 3) failure to adequately evaluate several suppliers of raw ingredients (i.e., slaughterhouses). (b) (4) response dated (b) (4) addressing the deficiencies listed on FDA form 483 dated (b) (4), was not deemed adequate and lacked sufficient corrective actions. The Office of Compliance again recommended withholding NDA approval. (b) (4)

A re-inspection of Digestive Care, Inc.'s drug product manufacturing facility on (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483 involving quality systems, production systems, equipment and facilities. The Office of Compliance again recommended withholding NDA approval. On January 27, 2011, FDA issued a Complete Response letter to Digestive Care Inc.

A re-inspection of the (b) (4) facility was performed (b) (4). On August 17, 2011, (b) (4) was notified by FDA's (b) (4) District Office that the violations contained in the (b) (4) had been addressed.

- **Cycle 3**

On November 18, 2011, Digestive Care Inc. submitted a complete response triggering a third review cycle. Re-inspection of Digestive Care, Inc.'s drug product manufacturing facility on (b) (4) found the facility to be acceptable.

Product Quality Considerations

Digestive Care, Inc. intends to market two capsule strengths containing 8000 and 16,000 USP units of lipase, respectively. The capsules contain bicarbonate-buffered enteric-coated microspheres of pancreatic enzymes (lipase, amylase and pancrease). The microspheres range in size from 0.8 to 2.2 mm in diameter. The enteric coating minimizes destruction or inactivation in gastric acid. The capsules are designed to release most of the enzymes *in vivo* at pH greater than 5.5.

Digestive Care, Inc. previously marketed the product as "Pancrecarb" in three capsule strengths: MS-4, MS-8, and MS-16. (b) (4)

(b) (4)

During the second review cycle, the applicant reformulated the previously marketed Pancrecarb MS-8 capsules and provided process validation, release and stability data for the new MS-8 capsules. In this review cycle, the applicant pursued approval of the MS-8 and MS-16 capsule strengths.

Drug substance. During the first review cycle, several product quality deficiencies involving the drug substance were identified and conveyed to . At this time, the Division of Therapeutic Proteins has determined that deficiencies involving the capacity of the manufacturing process to clear viruses and monitor viral load can be addressed as postmarketing commitments and do not preclude approval of the NDA. During the inspection of FDA noted the use of blue drums for drug substance intermediate storage. Given that drug substance is stored in in these drums for , leachable/extractable studies, evaluation of product quality, stability data, and validation studies to support re-use of the containers are needed. These information requests were conveyed to on October 27, 2010.

response dated , received on November 9, 2010, was reviewed in the current review cycle and found to be adequate. Although the leachable/extractable studies performed for drug substance stored in drums revealed only negligible amounts of , decided to switch to containers. Enzyme activities and microbial counts were unchanged during storage in containers for , a duration that is longer than the allowed holding time of . At this time, there are no deficiencies involving the drug substance that preclude approval. Postmarketing commitments will include: 1) a leachable/extractable study to address the potential for metals to leach into the pancreatin drug substance, and 2) revision of release specifications after 30 lots of drug substance have been manufactured.

Drug product (Digestive Care, Inc). During the first review cycle, several deficiencies involving the drug product were identified that precluded approval of the NDA. These deficiencies involved the applicant's release testing program, stability testing program, manufacturing process and process validation, acceptance criteria and reference standards, control of excipients, particularly the cellulose acetate phthalate and diethyl phthalate used for , a comparison of the currently marketed and to-be-marketed formulations, and discrepancies between manufacturing dates and signature dates on Certificates of Analysis. A total of 17 deficiencies were communicated in the August 27, 2009 Complete Response letter to Digestive Care, Inc.

In the second review cycle, several of the previously identified deficiencies were adequately addressed by the applicant. The remaining deficiencies involved the applicant's release testing program, stability testing program, process validation, qualification of internal reference standards, and proposed expiry of MS-8 drug products. A newly identified deficiency was identified involving the need to perform accelerated and/or stressed stability studies in the stability testing program. These deficiencies were conveyed in the January 27, 2011 Complete Response letter to Digestive Care, Inc.

In the current re-submission, the applicant's response was sufficient to allow approval with the following postmarketing commitments involving the drug product: 1) revise release and stability specifications after 30 lots of drug product have been manufactured, 2) submit a stability protocol to evaluate and extend the maximum cumulative storage time of the drug substance and drug product, 3) establish an expiration date for the RP-HPLC column, and 4) establish a primary reference standard against which future reference

⁶ Reformulation of the MS-8 capsule strengths would obviate the need for clinical trials to demonstrate the efficacy and safety of these lower strengths, although additional process validation, release and stability data would be needed. See the August 27, 2009 Complete Response letter for further details.

⁷ did not notify the NDA applicant of this manufacturing change or submit any information to support the change for FDA review.

standards will be qualified. In addition, the applicant agrees to conduct dissolution testing and set the buffer stage dissolution acceptance criterion for the drug product.

Microbiology Concerns

Staff in several divisions and offices in CDER and in CFSAN's Division of Microbiology have determined that the presence of any BDE in the resulting drug product could cause gastrointestinal adverse events, including systemic illness, particularly in immunocompromised patients. (b) (4)

(b) (4) could be responsible for *B. cereus* growth and BDE production during drug substance processing. Further, relatively (b) (4) employed at (b) (4) (as compared to other pancreatin drug substance manufacturers) may allow the heat labile toxin to survive processing.

On May 3, 2010 (b) (4) was informed that they will need to implement additional microbiologic controls of the drug substance manufacturing process, and provide 1) a justification for all in-process holding times associated with manufacture of the drug substance, 2) the maximum storage time for the (b) (4) (b) (4) 3) information on total aerobic microbial count (TAMC) alert and action levels at particular points in the manufacturing process, 4) a commitment to test each batch of drug substance for BDE prior to release, and 5) a description of the BDE test method, the validation procedure, and a summary of the supporting validation data.

At a meeting with FDA on May 20, 2010, it was agreed that when the TAMC fell between the alert and action levels of (b) (4) the materials would be tested for BDE biochemically; this agreement was reflected in an amendment to DMF (b) (4) on June 6, 2010. However, (b) (4) was unable to develop a validated assay for BDE detection. The 3M ELISA kit used to measure BDE in the food industry was found not suitable for measuring BDE in the pancreatin drug substance since (b) (4) and proteases present in the API could lead to false positive and false negative results, respectively. In addition, (b) (4) (b) (4) pancreatin samples was rapidly degraded even in the presence of protease inhibitors, further suggesting that previously reported positive results were falsely positive.

To address FDA's concerns about microbiologic controls, (b) (4) amended the DMF on October 22, 2010 to replace the alert and action levels with a specification of no more than (b) (4) at both (b) (4) (b) (4) and no more than (b) (4) (b) (4) and for the finished API. If the specification is exceeded, the batch will be rejected.

Published data suggest that BDE production typically begins once cell density reaches 10^8 cells/ml in rich media, and at a minimal level at 10^5 cells/g. FDA has set a risk threshold of 10^6 cells/g in food. (b) (4) manufacturing process and in-process time points at which samples are taken for microbial counts were reviewed. It was concluded that (b) (4) newly implemented TAMC alert and action levels would ensure that *B. cereus* cell density is maintained below a level at which BDE production occurs.⁸

Clinical Pharmacology

Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount. For this reason, a thorough QT assessment for this product has not been requested.

Given the importance of using applesauce as a means to deliver the capsule contents via feeding tubes or to young pediatric patients who cannot swallow whole capsules, the August 2009 Complete Response letter requested that Digestive Care, Inc., repeat the *in vitro* stability study in applesauce using lipase and amylase assays in which a minimum of five data points are used to assess assay linearity. This request is consistent with other requests made in the letter to enhance analytic methodologies used for lipase and amylase assays. In the second review cycle, the applicant submitted results of a repeat applesauce compatibility

⁸ See reviews filed in DARRTS by Stephen Langille, dated June 7, 2011 and January 31, 2012, filed under DMF (b) (4) by Vinayak Pawar, dated February 3, 2012, filed under NDA 022175; by Emanuela Lacana, dated May 16, 2012, filed under NDA 022175; and by Richard Ledwidge, dated February 1, 2012, filed under NDAs 22222 and 22542.

study, but the report was not deemed complete. In addition, the applicant did not simultaneously run quality control samples to check in-process lipase assay performance.

In the current review cycle, the applicant verified that the test method used for lipase activity was suitable for determining lipase activity of Pertzye microspheres when exposed to applesauce, and demonstrated that microspheres exposed to applesauce at room temperature for 20 minutes remained stable. Thus, there are no clinical pharmacology deficiencies that preclude approval.

Efficacy

As with other PEP manufacturers, Digestive Care, Inc., was requested to perform at least one controlled clinical trial with Pertzye to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*.⁹

The short-term safety and efficacy of Pertzye were evaluated in a double-blind, placebo-controlled crossover trial in 24 patients, aged 8-43 years (11 patients aged 8 to 17 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either previously marketed Pancrecarb MS-16 or placebo for 6-8 days, followed by crossover to the alternate treatment for an additional 6-8 days. All patients consumed a high fat diet. Pertzye treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption in 72-hour stool samples (83% vs. 46%, $p < 0.001$).

The applicant has agreed to perform *in vitro* post-approval studies to determine the feasibility of administering the contents of Pertzye (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

Safety

Formulations of porcine-derived PEPs used to treat exocrine pancreatic insufficiency have been generally well tolerated. The most common adverse events reported relate to the patients' underlying disease and are referable to the gastrointestinal tract. Pancreatic enzyme products are not absorbed from the gastrointestinal tract and are not systemically active.

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of PEPs, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. 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. Patients receiving doses higher 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. A Medication Guide will be required as part of approved labeling for Pertzye to inform patients of this risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study in Pertzye users to assess the incidence of and potential risk factors for developing fibrosing colonopathy.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Pertzye is not retained in the mouth. Pertzye should not be crushed or chewed or mixed with foods having a pH greater than 4.5 since these actions can disrupt the enteric coating and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

Risk of Hyperuricemia. Porcine-derived PEPs contain purines that may increase blood uric acid levels. Caution should be exercised when prescribing Pertzye to patients with gout, renal impairment, or hyperuricemia.

⁹ See <http://www.fda.gov/cder/guidance/6275fnl.htm>

Potential for Viral Exposure from the Product Source. Like other porcine-derived PEPs, Pertzze is derived from porcine pancreas tissue obtained as a by-product from the slaughter of pigs as a source of food. Audit procedures are in place to ensure that the pancreas raw material is derived from pigs certified as fit for human consumption and to ensure that legal requirements regarding e.g., hygienic factors, health certification of slaughtered animals, and surveillance for animal diseases are met. Two broad categories of porcine viruses, enveloped and non-enveloped viruses, may be transmissible to humans (i.e., have zoonotic potential). In addition, viruses with zoonotic potential such as HEV, the causative agent for hepatitis E, have emerged in pigs. The required enhancements to the manufacturing process will inactivate most enveloped viruses that could be present in the drug substance but will have limited capacity to inactivate non-enveloped viruses.

Although there has been no documentation of viral transmission to humans, FDA's Anti-Viral Advisory Committee concluded that there was a theoretical risk of transmission of viral disease to patients treated with porcine-derived PEPs, including Pertzze. A Medication Guide will be required as part of labeling for Pertzze to inform patients of this theoretical risk. In addition, the applicant will be required to conduct a postmarketing observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in Pertzze users, and be requested to conduct postmarketing commitments to ensure that the manufacturing process effectively controls viral load.

Allergic Reactions. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported in patients with a known allergy to proteins of porcine origin who are treated with PEPs.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA) has concluded that the tradenames (b) (4) "Pancrecarb MS-8", and "Pancrecarb MS-16" are not acceptable. (b) (4)

(b) (4)
DMEPA informed the applicant on June 11, 2010, that the proposed alternative tradename "Pertzze" was acceptable. The "Pertzze" tradename was re-reviewed during the current review cycle and found acceptable.

Pediatric Considerations

Pediatric Use. The Use in Specific Populations section, **Pediatric Use** subsection, of the product label will state the ages of pediatric patients with cystic fibrosis for which the short-term safety and effectiveness of Pertzze were demonstrated. In addition, the label will state that "The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredients (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience." Dosing of pediatric patients will be limited by the available capsule dosage strengths.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA will waive the pediatric study requirement for ages birth to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed below 1 month of age, so there would not be enough eligible patients in this age range to study.

The pediatric study requirement is fulfilled for patients greater than 1 year to less than 4 years (weighing 8 kg or more) and for patients 4 to 17 years (weighing 16 kg or more). The pediatric study requirement for patients 1 month to 1 year, patients greater than 1 year to less than 4 years (weighing less than 8 kg), and patients ages 4 to 17 years (weighing less than 16 kg) is not fulfilled due to the lack of an age appropriate formulation.

FDA will defer submission of an age appropriate formulation that will allow for dosing to the youngest, lowest weight patients, including infants less than 12 months of age, who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Postmarketing Requirements under 505(o)

Digestive Care, Inc. will be required to conduct the following postmarketing studies for Pertzye (pancrelipase) Delayed-Release Capsules to assess a known serious risk of fibrosing colonopathy and an unexpected serious risk of potential viral exposure to patients taking Pertzye (pancrelipase) Delayed-Release Capsules:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Pertzye (pancrelipase) Delayed-Release Capsules in the U.S. and to assess potential risk factors for the event.
2. An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Pertzye (pancrelipase) Delayed-Release Capsules compared with an appropriate control group.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

Pertzye (pancrelipase) Delayed-Release Capsules will be required to have a Medication Guide as part of approved labeling under 21 CFR part 208. In accordance with recently published guidance,¹⁰ FDA will not require a REMS for Pertzye (pancrelipase) Delayed-Release Capsules since the Medication Guide alone is adequate to address the possible risks of fibrosing colonopathy and viral exposure in patients using the product.

¹⁰ See *Guidance: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies*, November 2011.

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/s/

JULIE G BEITZ
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