CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: February 29, 2012

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022542 Viokace (pancrelipase) Tablets
Aptalis Pharma US Inc. (formerly Axcan Pharma US, Inc.)

Summary

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

The applicant has satisfactorily addressed the following approvability issues specified in my previous review dated November 24, 2010, and in the Complete Response dated November 24, 2010. These issues were: 1)) resolution of ongoing discussions involving proposed modifications to in-process microbial controls for the drug substance manufacturing process and the feasibility of *Bacillus cereus* diarrheal enterotoxin testing, 2) resolution of deficiencies identified during inspection of the drug substance manufacturing facility, and 3) resolution of discussions regarding the product label, REMS, and postmarketing study requirements and commitments.

Dosing

Viokace (pancrelipase) Tablets 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. Viokace should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences. Viokace is not enteric-coated and should be taken in combination with a proton pump inhibitor, so that the acid-labile enzymes contained in the formulation may be protected from the acid contents of the stomach.

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 $\leq$ 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. Usually, half the prescribed dose for a full meal should be given with each snack. The total daily dosage should reflect approximately three meals plus 2-3 snacks per day.

[1] Viokace Tablets have been marketed in the US as "Viokase", "Viokase 8", and "Viokase 16" since 1949. The to-be-marketed product and the previously marketed product have the same formulation.

Viokace (pancrelipase) Tablets are not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Viokace, is pancrelipase, which consists of the enzymes lipase, amylase and protease, as specified in the US Pharmacopeia. However, the animal source of pancreata and the extraction processing differ among products. The **Dosage and Administration** section of the Viokace label will state that "Viokace is not interchangeable with any other pancrelipase product."

Regulatory History

A meeting of FDA's Anti-Viral Advisory Committee on December 2, 2008, discussed the theoretical risk of viral exposure in patients taking porcine-derived PEPs, including Viokace (pancrelipase) Tablets. Recommendations from this Advisory Committee included informing patients of this theoretical risk and monitoring for potential viral exposure in users of these products (see below).

Axcan Pharma US, Inc. (formerly Axcan Scandipharm, Inc.) submitted NDA 022542 on October 29, 2009, received on October 30, 2009, and was granted a standard review. A major amendment extended the review clock by 90 days. A proposed REMS was included in the original submission and amended on August 20, 2010 and September 17, 2010. Concurrent with review of this NDA, FDA reviewed submissions to DMF (b) (4) from the drug substance manufacturer, (b) (4) which support this NDA.

Inspection of the (b) (4) facility in (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483 and involved (b) (4)

A re-inspection of the (b) (4) facility was performed in (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…" The Office of Compliance planned to conduct another pre-approval inspection of this facility to assess the adequacy of additional, yet-to-be-implemented, microbiologic controls of the drug substance manufacturing process. In subsequent testing, CFSAN recovered enterotoxigenic *B. cereus* from 4 of these 7 lots.[2]

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 (b) (4)

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

There were (b) (4) observations cited for (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 recommended withholding NDA approval. On November 28, 2010, FDA issued a Complete Response letter to Axcan Pharma US Inc.

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

On September 1, 2011, Axcan Pharma US Inc. submitted a complete response triggering a second review cycle. On October 24, 2011, the applicant informed DGIEP that it had changed its name to Aptalis Pharma US, Inc.

Product Quality Considerations

The applicant intends to market two tablet strengths containing either 10,440 or 20,880 USP units of lipase. Viokace is not enteric-coated. Viokace should be swallowed whole, without crushing or chewing, and taken in combination with a proton pump inhibitor.

Drug substance (SPL). The drug substance, DS 1252, is a (b) (4) DS 1206.[5] Several CMC deficiencies involving the drug substance have been identified and previously conveyed to (b) (4) 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.

At the most recent inspection of (b) (4) FDA noted the use of (b) (4) blue drums for drug substance intermediate storage.[6] Given that drug substance is stored in (b) (4) in these drums for (b) (4) extractable and leachable 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 (b) (4) on (b) (4) Axcan Pharma US, Inc. and (b) (4) response received on November 9, 2010[7], were reviewed in depth in the current review cycle. At this time there are no outstanding issues related to the drug substance that would preclude approval.

Drug product (Aptalis Pharma SRL, formerly Eurand SpA). There are no outstanding issues related to the drug product that would preclude approval. The applicant has agreed to the following postmarketing commitments: 1) to revise release and stability specifications after 30 lots of drug product have been manufactured, 2) to include accelerated and/or stressed stability conditions in the annual stability protocol

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3 (b) was cited for not adequately investigating a complaint date (b) (4) regarding (b) (4) (b) (4) has been used for release testing and historical testing for BDE in 726 samples since April 13, 2010.

5 In contrast, the drug substance DS 1286 manufactured by (b) (4) for Ultresa (pancrelipase) Delayed-Release Capsules (NDA 02222) is (b) (4) DS 1208. (b) (4) drug substance for Pertzye (pancrelipase) Delayed-Release Capsules (NDA 022175) contains both DS 1206 and DS 1208.

6 (b) (4) did not notify the NDA applicant of this manufacturing change or submit any information to support the change for FDA review.

7 Submitted to NDA 02222

and 3) to evaluate the stability of the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

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) 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, and the drug product manufacturing process (b) (4)

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 (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, since (b) (4) was unable to develop a validated assay for BDE detection, the DMF was amended on October 22, 2010 to replace the action and alert levels with a specification of no more than (b) (4) at (b) (4) and no more than (b) (4) and for the finished API; if the specification is exceeded, the batch would be rejected.

At a meeting held with FDA on November 15, 2010, (b) (4) proposed even tighter in-process microbiologic action limits. In addition to the previously specified TAMC limits, batches would be rejected if the TAMC exceeded (b) (4) argued that these in-process controls would be highly effective since detectable BDE is only produced when *B. cereus* counts exceed (b) (4) /g. (b) (4) further stated that BDE (b) (4) could not be recovered due to (b) (4), suggesting that the positive result from FDA testing could not have been due to the presence of BDE. (b) (4) also speculated that previously reported high in-process microbial counts were not representative of the manufacturing process, but rather the result of microbial contamination of improperly designed sampling ports. (b) (4) has relocated and replaced these ports; these changes were in place at the time of FDA's most recent facility inspection.

At the conclusion of this meeting, Axcan Pharma US, Inc. and (b) (4) agreed to submit 1) their current proposal for TAMC testing and arguments why it will prevent BDE formation during manufacturing, 2) results of all efforts to validate a BDE test method in the pancreatin matrix, 3) information that BDE is (b) (4) present in the (b) (4), 4) information regarding changes made in the ports used for sampling pancreatin during the manufacturing process, and 5) information about the pancreatin product made under the previous manufacturing process that is still on the market and what they intend to do regarding these products.

In this review cycle, results of submitted studies supported the following conclusions: 1) the 3M ELISA kit used to measure BDE in the food industry is not suitable for measuring BDE in the pancrelipase API since (b) (4) and proteases present in the API can lead to false positive and false negative results, respectively, 2) any BDE introduced in the manufacturing process would be rapidly degraded, and 3) multiple in-process microbial controls are now in place to ensure that *B. cereus* cell density is maintained

below a level at which BDE production occurs. Therefore, all microbiology deficiencies have been satisfactorily resolved.

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.

Efficacy

As with other PEP manufacturers, Axcan Pharma US, Inc. was requested to perform at least one controlled clinical trial with Viokace 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*.[8] Axcan Pharma US, Inc. conducted one double-blind, placebo-controlled trial in 50 patients, aged 24-70 years, with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. After a washout period of 6-7 days, patients were randomized to either a fixed dose of Viokace (20,888 USP units of lipase per tablet) or placebo, in combination with a proton pump inhibitor, for an additional 6-7 days. All patients received 22 tablets per day (6 tablets per meal and 2 tablets with 2 of 3 snacks) and consumed a high fat diet of 100 gm of fat per day. Viokace treatment was associated with significantly improved fat absorption compared to placebo at the end of the double-blind period, as measured by the difference between groups in the mean coefficient of fat absorption in 72-hour stool samples ($p<0.0001$).

The applicant has agreed to perform *in vitro* studies to determine the feasibility of administering Viokace (pancrelipase) Tablets in an appropriate solution through a gastrostomy tube.

Safety

Postmarketing data for Viokace have been available since 2003 and are similar to that described for other porcine-derived PEPs used to treat exocrine pancreatic insufficiency. Delayed and immediate release formulations of porcine-derived PEPs 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. The magnitude of this risk in adult patients with chronic pancreatitis or pancreatectomy is unknown. Doses greater than 2,500 lipase units/kg of body weight per meal (or > 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 Viokace that will inform patients of this possible risk.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Viokace is not retained in the mouth to avoid 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 Viokace to patients with gout, renal impairment, or hyperuricemia.

Potential for Viral Exposure from the Product Source. Like other porcine-derived PEPs, Viokace 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

[8] See http://www fda.gov/cder/guidance/6275fnl.htm

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 recently 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 Viokace. The Medication Guide for Viokace will inform patients of this theoretical risk.

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 other PEPs with different formulations of the same active ingredient (pancrelipase).

Potential for Exacerbation of Symptoms of Lactose Intolerance. Viokace Tablets contain lactose monohydrate. Patients with lactose intolerance may not be able to tolerate Viokace.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA) has found the proposed tradename "Viokace" to be acceptable (b) (4)

Pediatric Considerations

Pediatric Use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that "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. 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. 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."

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 all pediatric age groups, since 1) Viokace, a non-enteric-coated product, does not represent a meaningful therapeutic benefit over existing enteric-coated pancreatic enzyme products that are used in pediatric patients, and 2) Viokace is not likely to be used in a substantial number of pediatric patients.

Postmarketing Requirements under 505(o)

Unlike other approved PEPs, postmarketing studies as required under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the potential risks of fibrosing colonopathy and viral exposure will not be required for Viokace (pancrelipase) Tablets for the following reasons.

Fibrosing colonopathy. This rare, serious condition 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. The magnitude of this risk in adult patients with chronic pancreatitis or pancreatectomy is unknown but presumed to be very small.

Viral exposure. DGIEP, in consultation with the Division of Epidemiology in the Office of Surveillance and Epidemiology, has concluded that a study assessing viral exposure in adult patients with chronic pancreatitis or pancreatectomy would not be feasible, given that the estimated number of patients with chronic pancreatitis or pancreatectomy who would receive Viokace for durations of six months or greater for management of steatorrhea would be small. It is our view that assessment of the prevalence of antibody seropositivity to selected porcine viruses in cystic fibrosis patients would prove more fruitful given that PEPs are administered continuously for prolonged periods, if not life-long, in these patients. A multi-sponsor observational study assessing the prevalence of antibody seropositivity to porcine viruses in cystic fibrosis patients using FDA-approved PEPs is expected to launch later this year.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

Viokace Tablets will be required to have a Medication Guide as part of approved labeling under 21 CFR part 208. In accordance with recent published guidance,[9] FDA will not require a REMS for Viokace Tablets since the Medication Guide alone is adequate to address the possible risks of fibrosing colonopathy and viral exposure in patients using the product.

[9] 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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