CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-222Orig1s000

SUMMARY REVIEW

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 022222 Ultresa (pancrelipase) Delayed-Release Capsules
Aptalis Pharma US Inc. (formerly Axcan Pharma US, Inc.)

Summary

Ultresa (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 Ultresa, 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 Ultresa (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis or other conditions.

The applicant has satisfactorily addressed the following approvability issues specified in my previous review dated November 24, 2010, and in the Complete Response letter dated November 28, 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

Ultresa (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. Ultresa should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences.

Ultresa use in pediatric patients is 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 13,800 USP units of lipase, dosing with Ultresa will not be possible for the lowest weight infants. Product labeling will specify dosing recommendations for children 1 to 4 years of age weighing 14 kg or greater, and for patients 4 years of age and older weighing 28 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 to minimize the risk of colonic stricture, indicative of fibrosing colonopathy, and only if they are documented to be effective by 72-hour fecal fat measures.

[1] Ultresa has been marketed in the US as "Ultrase" since 1991. The to-be-marketed product, Ultresa, is the same formulation as the previously marketed formulation.

Ultresa (pancrelipase) Delayed-Release Capsules are not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Ultresa, 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 Ultresa label will state that "Ultresa is not interchangeable with any other pancrelipase product."

Regulatory History[2]

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 Ultresa (pancrelipase) Delayed-Release Capsules. 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 022222 on September 28, 2007, received on October 1, 2007, and was granted a priority review. A major amendment extended the review clock to July 1, 2008. Concurrent with review of this NDA, FDA reviewed submissions to DMF # (b) (4) from the drug substance manufacturer (b) (4) and to DMF #15681 from the drug product manufacturer, Aptalis Pharma SRL (formerly Eurand SpA), which support this NDA. FDA issued an approvable letter on July 1, 2008 due to unresolved CMC deficiencies.

A complete response was submitted on April 7, 2009, and a proposed REMS on June 2, 2009. 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). Based on these findings, the Office of Compliance recommended withholding NDA approval. FDA issued a complete response letter on September 9, 2009.

An inspection of the drug product manufacturing facility performed in October 2009 was satisfactory.

Axcan Pharma US, Inc. submitted a complete response on November 5, 2009 triggering a third review cycle. 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…" The Office of Compliance again recommended withholding NDA approval and 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. FDA issued a third complete response letter on May 5, 2010. In subsequent testing, CFSAN recovered enterotoxigenic *B. cereus* from 4 of these 7 lots.[3]

On May 28, 2010, Axcan Pharma US, Inc. submitted a complete response triggering a fourth review cycle. Inspections were conducted of (b) (4) (b) (4)) and (b) (4) (b) (4)

[2] Additional details may be found in the review by Dr. Daniel Shames dated July 1, 2008, and my previous reviews dated September 9, 2009, May 5, 2010, and November 24, 2010.
[3] See memo dated October 25, 2010, from Reginald Bennett, Jennifer Hait, and Sandra Tallent.

(b) (4) and FDA form 483s were issued to both firms. There were (b) (4) observations cited for (b) (4) including (b) (4) (b) (4) (4).

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

(b) (4) (b) (4) A re-inspection of the (b) (4) facility was performed (b) (4) On (b) (4), (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 fifth 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 three capsule strengths containing 13,800, 20,700, and 23,000 USP units of lipase, respectively. The capsules contain identical small enteric-coated minitablets of (b) (4) pancreatic enzymes (lipase, amylase and pancrease). 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. Stability studies of the minitablets mixed in soft acidic foods (e.g., applesauce, yogurt) support the use of these foods to administer the tablets.

Drug substance ((b) (4) The drug substance, DS 1286, is a (b) (4) DS 1208.[6] 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 (b) (4) inspection of (b) (4) FDA noted the use of (b) (4) blue drums for drug substance intermediate storage. 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).

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[4] (b) (4) was cited for not adequately investigating a complaint dated (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.

[6] In contrast, the drug substance (b) (4).

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

Axcan Pharma US, Inc. and (b) (4) response received on November 9, 2010, 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, 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) (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 pancreatin matrix, 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 the current 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 Ultresa 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 crossover trial in 31 patients, aged 8-37 years (14 patients aged 8 to 17 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either Ultresa or placebo for 6-7 days, followed by crossover to the alternate treatment for an additional 6-7 days. The mean Ultresa dose during the controlled treatment period was 6,270 lipase units/kg of body weight per day. All patients consumed a high fat diet. Ultresa treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption (CFA) in 72-hour stool samples ($p<0.0001$).

Results from an open-label trial conducted in 9 patients with cystic fibrosis, aged 7 to 11 years, support the efficacy of the product. Patients entered a 15-day screening period on individually-titrated doses of Ultresa not exceeding 2500 lipase units/kg of body weight per meal, followed by a washout period of 7 days (no treatment given). Next, patients entered a 12-day treatment phase on the same previous Ultresa dose. The mean Ultresa dose during the treatment phase was 6,846 lipase units/kg of body weight per day. All patients consumed a high fat diet. Mean CFA during the washout phase was 35% and improved to 83% during the Ultresa treatment phase.

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

Safety

Postmarketing data for Ultresa 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. 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

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

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 Ultresa that will inform patients of this risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study in Ultresa 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 Ultresa is not retained in the mouth. Ultresa should not be crushed or chewed 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 Ultresa to patients with gout, renal impairment, or hyperuricemia.

Potential for Viral Exposure from the Product Source. Like other porcine-derived PEPs, Ultresa 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 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 Ultresa. The Medication Guide for Ultresa will inform patients of this theoretical risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study, 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

On June 10, 2009, the Division of Medication Error Prevention and Analysis (DMEPA) informed Axcan Pharma US, Inc. that the tradenames "Ultrase MT-12", "Ultrase MT-18", and "Ultrase MT-20" are not acceptable. First, the proposed suffixes, MT-12, MT-18, and MT-20, are ambiguous in their meaning and vulnerable to misinterpretation. Second, the last three letters of the proposed proprietary name Ultrase contain the US Adopted Name (USAN) stem "-ase". The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the risk of confusion among those drugs. This confusion may compromise patient safety. Therefore, USAN stems should not be incorporated into proprietary names.

On July 7, 2009, the applicant submitted a different proprietary name for consideration. DMEPA informed the applicant on October 5, 2009, that the proposed tradename "Ultresa" was acceptable. A request for a re-review of the proposed tradename was made during the current review cycle. DMEPA informed the applicant on December 19, 2011, that the proposed tradename "Ultresa" was 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 Ultresa were demonstrated in clinical trials of Ultresa. 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."

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 applicant has fulfilled the pediatric study requirement for patients greater than 1 year to less than 4 years (weighing 14 kg or more) and patients 4 to 17 years (weighing 28 kg or more) for this application.

The pediatric study requirement for patients 1 month to 1 year, patients greater than 1 year to less than 4 years (weighing less than 14 kg), and patients ages 4 to 17 years (weighing less than 28 kg) is not fulfilled due to the lack of an age appropriate formulation.

FDA will defer submission of an age appropriate formulation for pediatric patients 1 month to 1 year, greater than 1 year to 4 years (weighing less than 14 kg), and patients 4 to 17 years (weighing less than 28 kg). This formulation will allow for dosing to the youngest, lowest weight patients who will require 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Postmarketing Requirements under 505(o)

As described in the complete response letter dated September 9, 2009, in accordance with section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that the applicant will be required to conduct the following studies to assess a known serious risk of fibrosing colonopathy and the unexpected risk of potential viral exposure to patients taking Ultresa (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 Ultresa in the US 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 with cystic fibrosis taking Ultresa compared with an appropriate control group.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

Ultresa (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 recent published guidance,[9] FDA will not require a REMS for Ultresa (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.

[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
02/29/2012