CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-542Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 22542 VIOKACE

PMR/PMC Description: To provide an assessment of the viral inactivation capability of the cleaning agents currently used in the facility.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	09/01/2012
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The sponsor needs to evaluate the ability of the cleaning agents used in the facility to inactivate viral agents. This assessment will take time to design and execute. Since the sponsor has assays in place that will be used to monitor for the presence of viral agents, the absence of a formal evaluation of the inactivation capability of the cleaning agents does not preclude approval of the application. The company currently uses detergents, [redacted] (b) (4) to clean equipment. These agents are known to inactivate viral and microbial agents, and their use thus provide some assurance that viral agents will be inactivated.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

During the inspection of the drug substance manufacturing facility, the inspectors noted that the manufacturer cleaning procedures were not robust, which resulted in a citation. The manufacturer committed to improve the cleaning procedures, but did not provide an evaluation of the viruses-inactivation capability of the cleaning agents. Although the cleaning agents used by the sponsor have the potential to inactivate viral and microbial agents, a formal assessment is necessary to address this issue.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should assess the capability of the cleaning agents to inactivate viruses. This assessment can be conducted as a laboratory study or as a formal risk assessment that takes into consideration the chemical characteristic of the agent and the biology of the viral agents.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 22542 VIOKACE

PMR/PMC Description: To develop and validate an infectivity assay for PCV1.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	03/01/2013
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

The (b) (4) drug substance and all PEP products have been shown to contain PCV1 genome equivalents indicative of the presence of this virus. It is not clear how genome equivalents translate to infectious particles but live virus presents a theoretical risk to patient safety. Although the virus has not been reported to cause human disease (and is probably present in porcine products that are ingested by humans), it is well documented that in extremely rare cases viruses can change species tropism leading to an infectious disease. This risk can be further mitigated by ensuring drug product has minimal live virus present in each dose consistent with manufacturing process history and our understanding of the virus's biology. DTP has established a policy that a PCV 1 infectious assay should be developed and used for lot release for all PEP products as recommended in the advisory committee meeting on viral issues for PEP products. The risk is low and these assays take time to develop so we believe it is appropriate to address this issue as a PMC

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. PCV1 is a non enveloped virus that is likely to be present in these products yet the PEP manufacturing process demonstrates no capability to inactivate non enveloped viruses. Therefore (b) (4) should monitor for the virus and reject lots that contain unusual levels of the infectious agent and present a risk to patient safety.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4) should develop a cell-based assay to monitor for infectious PCV1

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 22542 VIOKACE

PMR/PMC Description: To establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	03/01/2013
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The (b) (4) drug substance and all PEP products have been shown to contain PPV and PCV2 virus. In order to establish appropriate and meaningful specifications, the sponsor will need to manufacture several lots of drug substance to fully understand the capability of the process to reduce the load of these two viruses. . These viruses are not known to infect humans but there is a theoretical risk that mutations or genetic recombination events could change species specificity so control of these viruses is warranted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. PCV2 and PPV are non enveloped virus that are present in these products. PEP manufacturing process demonstrates little or no capability to inactivate non enveloped viruses. Therefore (b) (4) should monitor for the viruses and reject lots that do not meet specifications and contain unusual levels of the infectious agent and present a risk to patient safety. These virus are not associate with human infection and are likely present in porcine meat products consumed by humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement assays to monitor for infectious PPV and PCV2

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 22542 VIOKACE

PMR/PMC Description: To perform additional monitoring of viral load entering the manufacturing process. The control program will include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	05/13/2013
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The current PCR assays sensitivity is sub optimal since the limit of detection is only (b) (4) genome equivalents per gram of drug substance. This level is beyond the capacity of the manufacturing process to inactivate some viruses. While this is an important issue, availability of these products is critical and the risk to product quality has already been greatly reduced as compared to current marketed product. Again the risk is theoretical in that no infectious diseases are known to have been transmitted by the unapproved PEPs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The (b) (4) process demonstrates no capability to inactivate non enveloped viruses. Therefore, the sponsor should monitor for the virus with sensentive assays and reject lots that contain the infectious agents beyond the processes capacity to inactivate these viruses.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should select viruses that have the potential to infect the source material and develop appropriate quantitative, PCR based assays to assess the viral load in incoming materials.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name:	22542 VIOKACE
PMR/PMC Description:	To improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria will be submitted to the Agency.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	04/15/2013
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The current PCR assays sensitivity is sub optimal since the limit of detection is only [(b) (4)] [(b) (4)] genome equivalents per gram of drug substance. The starting material for one lot is [(b) (4)] . Therefore, with the current assays, the sensitivity would be [(b) (4)] genome equivalent per lot. While this is an important issue, availability of these products is critical and the risk to product quality has already been greatly reduced as compared to current marketed product. The risk is theoretical in that no infectious diseases are known to have been transmitted by the unapproved PEPs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The [(b) (4)] process demonstrates no capability to inactivate non enveloped viruses. Therefore, [(b) (4)] should monitor for the virus with sensentive assays and reject lots that contain the infectious agents. All of the virus in this PMC have the potential to cause human infections. This was a PMC for the Creon, Zenpep, and Pancreaze products.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should improve the assays currently in use to increase sensitivity and propose new acceptance criteria based on the improved assays.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 22542 VIOKACE

PMR/PMC Description: To assess the risk to product quality associated with hokovirus, and to submit a control strategy for mitigating the risk to product quality.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	06/01/2012
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Hokovirus has only recently been identified in porcine material in south east Asia but has never been detected in the pig population on the US or Europe. The virus can infect humans, but has never be detected in humans in the US or Europe. Since the source material for pancrelipase is (b) (4) the risk to patients is low. However, the sponsor should work proactively and implement a surveillance program that routinely evaluates the risk from this virus in case it spreads to the (b) (4) pig population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. Hokovirus has only recently been identified in swine and therefore little information is availabe. The sponsor's surveillance program should include continual monitoring of the literature to ensure that quality systems could be updated to control for this viurus (e.g. herd surveillance programs) and other emerging new viral agents that infect humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement a surveillance program to monitor for the emergence of hokovirus in the pig herds.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 22542 VIOKACE

PMR/PMC Description: To revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	03/15/2013
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Ebola virus has only recently been identified in porcine material in south east Asia but has never been detected in the pig population on the US or Europe. The virus can infect humans, but has never been detected in humans in the US or Europe. Since the source material for pancrelipase is [redacted] (b) (4), the risk to patients is low. Additionally, Ebola is an enveloped virus and thus can be inactivated by the [redacted] (b) (4) step in the process, further reducing the risk to patients. Regardless, the sponsor should implement a surveillance program that routinely evaluates the risk from this virus to emerge in the [redacted] (b) (4) swine herds.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The process does have the capability to inactivate enveloped viruses and thus should inactivate the Ebola virus. Ebola viruus has only recently been identified in swine and therefore little information is availabe. The sponsor's surveillance program should include continual monitoring of the literature to ensure that quality systems could be updated to control for this viurus (e.g. herd surveillance programs) and other emerging new viral agents that infect humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement a surveillance program to monitor for the emergence of Ebola virus in pig herds.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

MF #/Product Name: 22542 VIOKACE

PMR/PMC Description: Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	06/01/2012
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

(b) (4) drums are used for drug substance intermediate storage, for (b) (4). Although (b) (4) is a relatively inert material, metal ions could potentially leak into the drug substance. Metal ions have the potential to chemically react with the proteins in the pancrelipase drug substance. Therefore, although the risk to product quality is low, a study to evaluate the potential of metal ions to leak from the (b) (4) containers is warranted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this study is to determine the extent of metal ions leaching into pancrelipase drug substance and to perform a risk assessment and if necessary, develop a control strategy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The type of study that is warranted is inductively coupled plasma mass spectrometry (ICP-MS) as a sensitive way to measure metal ions in pancrelipase drug substance under leachable conditions.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

MF #/Product Name: 22542 VIOKACE

PMR/PMC Description: (b) (4) commits to revise release specifications after 30 lots of 1208 and 1286 drug substance have been manufactured.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	05/15/2013
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   The current release specifications for drug substance are adequate to ensure product quality but more robust programs should be developed to provide a better assurance of product quality. While the lots produced so far have shown acceptable results that are in-line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. To established process capability and reduce the risk to product quality, a larger number of product lots are necessary which could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Assays used for release testing of drug substance are adequate for approval. Proposed acceptance criteria for drug substance release specifications are wide and should be based on manufacturing history and clinical experience, once the sponsor gaines sufficient information through manufacturing of multiple lots.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4) should re-evaluate the release specifications for drug substance and tighten acceptance criteria based on results of lots manufactured with the clinical and commercial processes.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name:	NDA 22542 VIOKACE
PMR/PMC Description:	Revise release and stability specifications after 30 lots of drug product have been manufactured.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	July 2014
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The current release and stability specifications for drug product are adequate to ensure product quality and stability but more robust programs should be developed to provide a better assurance of product quality. While the lots produced so far have shown acceptable results that are in-line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. To establish process capability and reduce the risk to product quality, a larger number of product lots are necessary, and this could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Assays used for release and stability testing of drug product are adequate for approval. Proposed acceptance criteria for drug product release and stability specifications are wide and should be based on manufacturing history and clinical experience, once the sponsor gaines sufficient information through manufacturing of multiple lots.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Aptalis should re-evaluate the release and stability specifications for drug product and tighten acceptance criteria based on results of lots manufactured with the clinical and commercial processes.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: NDA 22542 VIOKACE

PMR/PMC Description: Include accelerated and/or stressed stability conditions in the annual stability protocol.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	June 2012
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   The current annual stability protocol for drug product provides for one lot of drug product to be entered on stability at the approved storage conditions. However, the approved storage conditions are not permissive for significant product degradation and therefore do not provide an adequate level of sensitivity to confirm that routine minor changes in operations or equipment do not have an impact on product quality. Because stress stability studies can detect subtle differences in product quality that may not be ready detectable by release tests or the proposed stability protocol, FDA requested the addition of a stress stability protocol that would be capable of detecting these differences in a timely manner. Considering that the stability protocol will be implemented during the next year and the fact the new protocol will be approved in a post approval supplement before implementation, there is no approval issue.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Release and real time stability testing confirm product quality but are less sensitive to detect minor changes that may occur from changes in manufacturing over time. Performing stress stability studies under accelerated and/or stressed conditions provides a bigger window in which to detect changes to product quality.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

No study is required to be agreed upon. A stability protocol will be updated to include stressing one lot of drug product under accelerated and/or stressed conditions.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Include a protocol to stress one lot of drug product per year.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Appears This Way On Original

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name:	NDA 22542 VIOKACE
PMR/PMC Description:	To submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience. Final report submission by:

PMR/PMC Schedule Milestones:	Final Protocol Submission:	June, 2012
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The stability data provided supports the drug substance and drug product dating periods and current cumulative data for drug product lots that will be marketed but does not include drug product produced with drug substance at the end of its expiry period. The concern is only for material that in the future could exceed current cumulative storage times for drug substance and drug product. Therefore to control this risk the applicant should propose a protocol that places on stability lots of drug product manufactured with drug substance aged past what the manufacturer experience has been.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor has used drug substance of various ages and established a stability profile and expiry for the drug product. However, the sponsor may receive drug substance close to its own expiry date and there is little information on what the cumulative stability of the drug substance might be. For protein products extrapolation of existing stability data is not appropriate and therefore real time, real condition studies should be performed. The goal of this protocol is to confirm that product manufactured with drug substance aged past what the manufacturer experience has been, maintains an adequate stability profile throughout its shelf life.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A stability study will be required each time the manufacturer exceeds the cumulative storage time of the drug substance/drug product. Data supporting the cumulative time will be submitted in the annual report as is typical for these types of studies using an agreed to protocol.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: NDA 022542 Viokace (pancrelipase) Tablets

PMR/PMC Description: Perform *in vitro* studies to determine the feasibility of administering Viokace (pancrelipase) Tablets in an appropriate solution through a gastrostomy tube.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	03/2013
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Patients that require PEPs to be administered via gastrostomy tubes are a small subpopulation affected.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

PEPs, including Viokace, are not approved for administration via gastrostomy tubes. However, a small number of patients may require PEPs to be given through this route. In order to evaluate the feasibility of administering Ultresa via gastrostomy tubes, the Applicant has committed to conducting *in vitro* testing.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant will conduct *in vitro* testing to evaluate the feasibility of administering Viokace via gastrostomy tubes.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
The Applicant will conduct *in vitro* testing to evaluate the feasibility of administering Viokace via gastrostomy tubes.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAGJIT S GREWAL
02/29/2012

ANIL K RAJPAL
02/29/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 022542	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Viokace Established/Proper Name: pancrelipase Dosage Form: Tablets Strengths: 10440/39150/39150 lipase/protease/amylase and 20880/78300/78300 lipase/protease/amylase.		
Applicant: Aptalis Pharma US, Inc.		
Date of Receipt: 10/30/2009		
PDUFA Goal Date: 3/1/2012	Action Goal Date (if different):	
Proposed Indication(s): in combination with a proton pump inhibitor, is indicated in adults for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☒ NO ☐

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Freeman et al, Int J Toxicol, 22(3), pg. 149-157, 2003	Safety evaluation of excipient (croscarmellose sodium)
Kotkoskie et al, J Anat, 95(Suppl 1), pg. 158-159, 1996	Safety evaluation of excipient (microcrystalline cellulose)
Published Literature	Nonclinical Safety

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Clinical:
The Clinical reviewer relies heavily on published literature to approve the Pancreatic Enzyme Products. From a clinical standpoint, per the Guidance, long-term safety and efficacy is based on the large body of information with many different PEPs in the treatment of children with Cystic Fibrosis (CF). CF children grow better, have better nutrition, less morbidity (e.g. infections), and longer lives due to PEP treatment (and other advances). This is felt to have been well established over the years in hundreds-thousands of published papers, and is clearly standard of care. However, literature is not for one PEP specifically (such as Cotazym), but an accumulation of knowledge with the entire PEP experience. Thus, the Guidance states the applicants only have to show short-term safety and efficacy because of the large body of available literature/evidence. Otherwise, these short-term study designs (and acceptance of just one small study) would not have been acceptable for establishing clinical safety and efficacy.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

NOTE: The sponsor did submit a patent statement with their application indicating that NDA 020580 Cotazym has no listed patents in the Orange Book. Cotazym is not being relied upon for approval of this application. Therefore, a patent certification/statement is not required.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAGJIT S GREWAL
02/28/2012

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: NDA 22-542

Name of Drug: Viokace™ (Pancrelipase) Tablets

Sponsor: Aptalis Pharma US, Inc. (Originally submitted under AXCAN PHARMA, US, Inc.)

Material Reviewed: Viokace™ (pancrelipase) Tablets- Carton and Container Labels

Submission Dates: October 29, 2009, September 15, 2010, September 1, 2011, January 9, 2012

EXECUTIVE SUMMARY

The carton and container labels for Viokace™ (pancrelipase) were reviewed and found to comply with the following regulations: 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopoeia, 12/1/11- 4/30/12, USP 34/NF 28. Labeling deficiencies were identified mitigated by the applicant. Please see comments in the conclusions section. The labels are acceptable.

Background:

Viokace™ (Pancrelipase) is a New Drug Application (NDA) intended for combination use with a proton pump inhibitor and is indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis (b) (4). Viokace™ is a pancreatic enzyme product (PEP) consisting of porcine-derived lipase, protease, and amylase formulated in an immediate release tablet.

Labels Reviewed:

Viokace™ (pancrelipase) Tablets- Container and Carton Labels
10,440 Lipase Units - 100ct Trade Bottle

20,880 Lipase Units - 100ct Trade Bottle

I. Container

A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
"Manufactured in Canada for: AXCAN PHARMA US, 22 Inverness Center Parkway, Birmingham, AL 35242 USA"
This conforms to the regulation.

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the Trade name at the top of the label. The NDC number configuration is not displayed and does not conform to 21 CFR 207.35 as either a 3-2 or a 4-1 Product-Package Code configuration. This does not conform to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label "For dosage and other information for use, see accompanying product literature." appears. This conforms to the regulation.

4. 21 CFR 201.6 Drugs; misleading statements- The Trade name appears on the label as "Viokace™". The established name appears as, (b) (4). This does not conform to the regulation.

5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, Pancrelipase, USP is not used in type at least half as large as the most prominent presentation of the proprietary name, Viokace™. This does conform to the regulation.

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements ("Rx Only"). "Protect from moisture", "Avoid excessive heat" and a temperature range does not appear on the label. This does not conform to the regulation.

7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the right side of the label. This conforms to the regulation.

8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the right side of the label with sufficient white space surrounding it to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are not listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation per USP 10/1/10-2/1/11, USP 33/NF 28, however the agency recommends all three enzymes are listed on the label for consistency with the class of products. The agency is working with the USP to reconcile the Pancrelipase tablets monograph with the delayed release monograph.

10. 21 CFR 201.51 Declaration of net quantity of contents – The label does state the net quantity of contents in terms of numerical count in units on the lower portion of the label, below the proprietary and established name. This conforms to the regulation.

11. 21 CFR 201.55 Statement of dosage- The label states "Dosage and Administration: See package insert for dosage." The label does not state that dosing is based on lipase units. This does not conform to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for "Rx Only", identifying lot number, and a reference to the package insert. However, the statements, "Protect from moisture", "Avoid excessive heat", and adequate storage conditions are not present on the label. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to regulation.

II. Conclusions for container labels submitted October 29, 2009

A. Container Label

1. Per 21 CFR 201.2 and 21 CFR 207.35, please provide the NDC configuration as either a 3-2 or 4-1 Product-package code configuration.

2. Per 21 CFR 201.6, Please revise the established name from (b) (4) to (pancrelipase) Tablets.

3. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the statements, "Protect from moisture.", "Avoid excessive heat." and "Store at 20-25°C (68-77°F)" to the storage conditions listed to the storage conditions listed.

4. Per 21 CFR 201.10(g)(2), revise the established name presentation to letters printed at least half as large as the letters comprising the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Defer to DMEPA for color and typography differences.

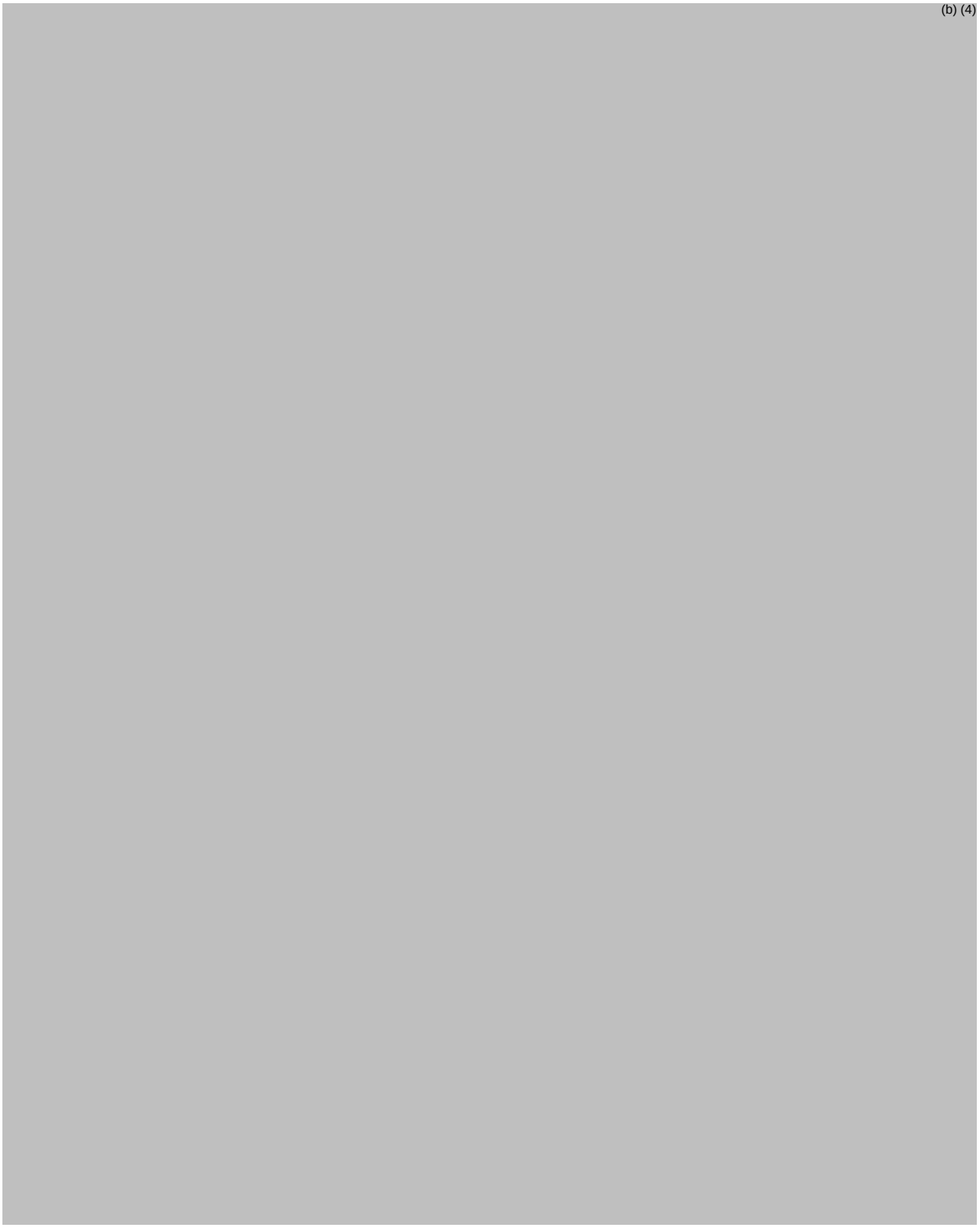
5. Per 21 CFR 201.55 and United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27, Monograph-Pancrelipase Delayed Release Capsules - Please add a statement to the container labels to indicate that dosing is based on lipase units.

Revised labels submitted September 15, 2010

The revised submission includes container and carton labels. The original submission did not include carton labels.

(b) (4)

3 pages of Draft Carton and Container Labels have been Withheld in Full as b4 (CCI/TS) immediately following this page



III. Carton

A. Carton label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:
"Manufactured in Canada for:
Axcan Pharma US, Inc.
Bridgewater, NJ 08807"
This conforms to the regulation

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label "DOSAGE AND ADMINISTRATION: Dose by lipase units. See package insert for dosage information." appears on the carton labels. This conforms to the regulation.

4. 21 CFR 201.6 Drugs; misleading statements – The trade name, "Viokace™" appears with the established name, "(Pancrelipase) (b) (4)" on the carton. The term (b) (4) " does not comply with the USP monograph title for Pancrelipase per the United States Pharmacopoeia, 12/1/11-4/30/12, USP 34/NF 29. This does conform to the regulation.

5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, Viokace™. Defer to DMEPA for color and typography.

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements ("Rx Only", "Protect from moisture", "Avoid excessive heat") appear on the label. This conforms to the regulation.

7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date appears on the carton below the lot number. This conforms to the regulation.

8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of a side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are listed with corresponding units per tablet per 21 CFR 201.10. This conforms to the regulation.

10. 21 CFR 201.51 Declaration of net quantity of contents - The label states the net quantity of contents in terms of numerical count in units near the bottom of the carton. This conforms to the regulation.

11. 21 CFR 201.55 Statement of dosage - The label states "Dose by lipase units. See package insert for dosage information." This conforms to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for "Rx Only", an identifying lot number, storage conditions, and a reference to the package insert. This conforms to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. The following statement appears on the container and carton label, "Dispense the enclosed Mediation Guide to each patient." This conforms to the regulation.

IV. **Conclusions for submissions (**September 15, 2010, September 1, 2011, January 9, 2012**)**

A. Carton and Container

1. Per 21 CFR 201.2 and 21 CFR 207.35, please provide the NDC configuration as either a 3-2 or 4-1 Product-package code configuration. Change made and acceptable.
2. Per 21 CFR 201.6 and the United States Pharmacopoeia, 10/1/10-2/1/11, USP 33/NF 28 Monograph-Pancrelipase Tablets, please revise the established name from [redacted] (b) (4) to (pancrelipase) Tablets. Change made and not acceptable. Presentation changed to [redacted] (b) (4) and does not comply with the official USP monograph title for Pancrelipase Tablets per the United States Pharmacopoeia. Revised presentation submitted January 9 is acceptable.
3. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the statements, "Protect from moisture.", "Avoid excessive heat." and "Store at 20-25°C (68-77°F)" to the storage conditions listed. Change made and acceptable.

4. Per 21 CFR 201.10(g)(2), revise the established name presentation to letters printed at least half as large as the letters comprising the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. In addition, revise the established name to comply with the USP monograph title for Pancrelipase tablets per the United States Pharmacopoeia, 12/1/11-4/30/12, USP 34/NF 29. Change made and acceptable.

5. Per 21 CFR 201.51, Declaration of net quantity of contents, please increase the prominence of the quantity statement. Change made and acceptable.

Note: Manufacturer has been changed to Aptalis Pharma US, Inc., 22 Inverness Center Parkway, Suite 310, Birmingham, AL 35242 on all labeling.

All revisions to the labels are acceptable.

_____
Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

_____
Richard Ledwidge, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP/

_____
Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY M RAINS
02/07/2012

RICHARD LEDWIDGE
02/09/2012

BARRY W CHERNEY
02/15/2012

SEALD Director Sign-Off Memo and Labeling Review

Product Trade Name (Non-Propriety Name)	**VIOKACE (pancrelipase) tablets, for oral use**
Application Number/Supplement Number	NDA 22542
Type of Application	Resubmission Class 2
Indication	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.
Applicant	Aptalis Pharma US, Inc.
Office/Division	ODE III/DGIEP
Division Project Manager	Jagjit Grewal, MPH
Submission Date	September 1, 2011
PDUFA Goal Date	March 1, 2012
SEALD Review Date	February 9, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie B. Burke, RPh, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)**."

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "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 rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). 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."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for "peds only" indications) are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling …

    (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

JEANNE M DELASKO
02/09/2012

LAURIE B BURKE
02/09/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion
Division of Direct-to-Consumer Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 8, 2012

To: Jagjit Grewal, Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Twyla Thompson, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
OPDP

CC: Lisa Hubbard, Professional Group Leader, DDP/OPDP
Shefali Doshi, Direct-To-Consumer Group Leader, DDTCP/OPDP

Subject: NDA 022542
VIOKACE (pancrelipase) tablets, for oral use [Viokace]

OPDP Labeling Consult Response

In response to DGIEP's January 30, 2012, consult request, OPDP has reviewed the draft package insert (PI), carton/container labeling, and Medication Guide for Viokace and offers the following comments.

OPDP's comments on the PI are based on version 8 of the proposed draft marked-up labeling titled, Proposed PI 9-1-11.doc, accessed via the e-Room (last modified February 3, 2012 at 8:25 am). OPDP used the Division of Medical Policy Programs' tracked changes version of the Medication Guide finalized on February 6, 2012 as the base document for review. OPDP's comments on the PI and Medication Guide are provided directly on the document attached below. Please also see below for OPDP's comments on the carton/container labeling.

If you have any questions regarding the PI or carton/container labeling, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Twyla Thompson at 301.796.4294 or Twyla.Thompson@fda.hhs.gov.

Carton/Container Labeling

OPDP has reviewed the following materials, accessed via the EDR (sequence 0037 dated 1/9/12; available at \\CDSESUB1\EVSPROD\NDA022542\022542.enx):

- Viokace Box Label – Lipase 10,440 Units
- Viokace Box Label – Lipase 20,880 Units
- Viokace Bottle Label – Lipase 10,440 Units
- Viokace Bottle Label – Lipase 20,880 Units

OPDP has no comments on these proposed materials.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TWYLA N THOMPSON
02/08/2012

KATHLEEN KLEMM
02/08/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	February 3, 2012
To:	Donna Griebel, MD, Director **Division of Gastrointestinal and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	VIOKACE (pancrelipase)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 22-542
Applicant:	Aptalis Pharma US, Inc.

1 INTRODUCTION

This review is written in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for VIOKACE (pancrelipase) tablets.

The Applicant submitted a Complete Response in response to a Complete Response (CR) letter issued by the Agency on November 28, 2010 for original New Drug Application (NDA) 22-542, for VIOKACE (pancrelipase) tablets. The proposed indication for VIOKACE is as follows: 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.

2 MATERIAL REVIEWED

- Draft VIOKACE (pancrelipase) tablets Medication Guide (MG) received on September 1, 2011.
- Draft VIOKACE (pancrelipase) tablets Prescribing Information (PI) received September 1, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on January 30, 2012.
- VIOKACE (pancrelipase) tablets labeling recommendations sent to Applicant on September 16, 2010.
- Approved Creon (pancrelipase) delayed-release capsules comparator labeling dated July 12, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- performed a side-by-side comparison of MG revisions sent to the Applicant on September 16, 2010 to the MG submitted by the Applicant on September 1, 2011.
- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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SHARON R MILLS
02/03/2012

BARBARA A FULLER
02/06/2012

LASHAWN M GRIFFITHS
02/06/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	October 27, 2011
Reviewer(s):	Manizheh Siahpoushan, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, Pharm.D. Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Viokace (Pancrelipase) Tablets 10,440 U.S.P. Units Lipase 39,150 U.S.P. Units Amylase 39,150 U.S.P. Units Protease and 20880 U.S.P. Units Lipase 78,300 U.S.P. Units Amylase 78,300 U.S.P. Units Protease
Application Type/Number:	NDA 022542
Applicant/sponsor:	Axcan Pharma
OSE RCM #:	2011-3387

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the container labels, carton labeling, Prescribing Information, and the Medication Guide for Viokace (Pancrelipase) Tablets, in response to a consult from the Division of Gastroenterology Products to identify any areas of concern from a medication errors perspective.

1.1 BACKGROUND OR REGULATORY HISTORY

Viokace (Pancrelipase) Tablet (NDA 022542) is the subject of a Class-II resubmission. DMEPA reviewed the container labels and the Prescribing Information for Viokace, as part of the Applicant's original submission pursuant to section 505(b)(2) on October 29, 2009, in OSE Review #2009-2130, dated February 5, 2010. The Applicant submitted revised labels and labeling on September 14, 2010, which were reviewed by DMEPA in OSE review # 2009-2130, dated October 15, 2010. DMEPA's recommendations were communicated to the Applicant in the Complete Response letter that was issued by the Agency on November 28, 2010.

1.2 PRODUCT INFORMATION

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. Viokace contains a combination of porcine-derived lipases, proteases, and amylases; however, it is dosed in lipase units and will be available in two strengths: 10,440 UPS units of lipase and 20,880 USP units of lipase. Viokace is not interchangeable with any other pancrelipase products. Both strengths will be marketed in bottles of 100 tablets. 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/gram fat ingested per day. The tablets should not be crushed or chewed.

2 METHODS AND MATERIALS

Because Pancrelipase is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) to identify medication errors related to the use of Pancrelipase. We also evaluated the container labels, carton labeling, Prescribing Information, and the Medication Guide for Viokace (Panrelipase) Tablets 10,440 USP Units Lipase, 39,150 USP Units Amylase, 39,150 USP Units Protease and 20,880 USP Units Lipase, 78,300 USP Units Amylase, 78,300 USP Units Protease, to identify areas of vulnerability that can lead to medication errors.

2.1 IDENTIFICATION OF MEDICATION ERRORS IN AERS DATABASE

The October 7, 2011 AERS search used the following criteria: Active ingredient 'Pancrelipase', Verbatim term 'Pancrel%' as well as the MedDRA reaction terms 'Medication Errors' (HLGT), 'Product Label Issues' (HLT), and 'Product Quality Issue' (PT). The date limit was set from March 8, 2010 (the date of the last search conducted in OSE review #2009-942, dated April 15, 2010) to October 7, 2011. Those cases not pertaining to errors, pertaining to errors of concomitant drugs, and occurrence of adverse events not due to medication errors were excluded from further analysis.

2.2 LABELS AND LABELING

Using failure Mode and Effects Analysis[1], the principles of human factors, and the lessons learned from postmarketing experience, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the revised container labels, carton labeling, Prescribing Information, and Medication Guide, submitted on September 1, 2011, to identify vulnerabilities that may lead to medication errors. The following were submitted for our evaluation (see Appendices A and B):

- Container labels (10,440 USP Units Lipase and 20,880 USP Units Lipase) submitted 9/1/11
- Carton labeling (10,440 USP Units Lipase and 20,880 USP Units Lipase) submitted 9/1/11
- Prescribing Information submitted 9/1/11
- Medication Guide submitted 9/1/11

3 RESULTS

The following sections describe the results of DMEPA's medication error searches and labels and labeling evaluation.

3.1 IDENTIFICATION OF MEDICATION ERRORS IN AERS DATABASE RESULTS

The October 7, 2011 AERS search identified 3 reports (ISR #'s 6900582, 7767629, and 7798907). After eliminating cases as described in Section 2, no cases remained for further evaluation.

3.2 LABELS AND LABELING RISK ASSESSMENT

Our evaluation of the container labels, carton labeling, Prescribing Information, and the Medication Guide noted that the Applicant implemented DMEPA's recommendations from OSE review #2009-2130, dated February 5, 2010 and October 15, 2010. However, the statement 'Viokace tablets should not be crushed or chewed' can be improved to include positive language (i.e. tell patients they should do something). Additionally, the statement should appear more prominent.

4 CONCLUSIONS

The Applicant implemented DMEPA's recommendations from OSE review #2009-2130, dated February 5, 2010 and October 15, 2010. However, our further evaluation of the proposed labels and labeling identified additional areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations to the Prescribing Information in Section 4.1 *Comments to the Division* for discussion during the labeling meetings. Section 4.2 *Comments to the Applicant* for the container labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact OSE Regulatory Project Manager, Nitin Patel, at 301-796-5412.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004

4.1 COMMENTS TO THE DIVISION

In the Dosage and Administration Section in the Highlights of the Prescribing Information, the warning statement 'Do not crush or chew tablets.' contains negative language. This statement may have the opposite effect of the intended meaning. Patients may overlook the words 'Do not' and interpret this statement to mean the tablets can be crushed or chewed. We recommend revising the warning statement to include a positive language. The statement may appear as follows:

'Viokace tablets should be swallowed whole. Do not crush or chew tablets.'

4.2 COMMENTS TO THE APPLICANT

A. Container Labels and Carton Labeling

1. Revise the warning statement (b) (4) to read 'Viokace tablets should be swallowed whole. Do not crush or chew tablets.' As currently presented, the warning statement only contains negative language which may be overlooked by patients and have the opposite effect of the intended meaning. Patients may overlook the words 'Do not' and interpret this statement to mean the tablets can be crushed or chewed.
2. Relocate the warning statement 'Viokace tablets should be swallowed whole. Do not crush or chew tablets.' (after revised from (b) (4)) to the principal display panels of the container labels and carton labeling. As currently presented, the warning statement lacks prominence and may be overlooked.
3. Include the dosage form (Tablets) immediately following the established name. As currently presented, the dosage form does not appear on the container labels and the carton labeling, where the proprietary name and the established names appear (i.e., on the principal display panel of the container labels and carton labeling, as well as the side panels of the carton labeling). The revised format may appear as follows:

   'Viokace
   (Pancrelipase)
   Tablets'
4. Revise the color of the proprietary name, Viokace to appear less prominent. As currently presented, the color orange distracts attention from other important information such as the NDC number and the products strengths. We recommend using a less prominent color (i.e. the color used for the established name) to minimize medication errors due to product selection (i.e. dispensing the wrong strength).
5. We recommend using tall man lettering scheme for the middle portion of the NDC numbers corresponding to the two different strengths of the product. Since this product is available in two different strengths with very similar NDC numbers, and pharmacists normally rely on the middle portion of the NDC number as part of their checking system, highlighting the middle portion of the NDC numbers by using tall man letters can help distinguish the two similar NDC numbers, making them less prone to mix-ups by the pharmacy staff.

B. Container Labels

Reduce the prominence of 'Rx only' on the container labels. As currently presented, the 'Rx only' is in close proximity and competes in prominence with the NDC number

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/s/

MANIZHEH SIAHPOUSHAN
10/27/2011

ZACHARY A OLESZCZUK
10/27/2011

CAROL A HOLQUIST
10/31/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 15, 2010
Application Type/Number:	NDA 022542
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products
Through:	Melina Griffis, RPh, Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Viokace (Pancrelipase) Tablets 10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease
Applicant:	Axcan Pharma
OSE RCM #:	2009-2130

CONTENTS

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the revised labels and labeling for Viokace submitted by the Applicant on September 14, 2010 and September 17, 2010. DMEPA previously reviewed Viokace labels and labeling in OSE Review #2009-2130 dated February 5, 2010.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the revised labels and labeling submitted on September 14, 2010 and September 17, 2010 (see Appendices A and B). We note that the Applicant has introduced carton labeling with this submission. In addition, we compared the revised labels to those reviewed in OSE Review #2009-2130 dated February 5, 2010 (see Appendix C) to evaluate whether the Applicant addressed our previous label and labeling recommendations.

3 CONCLUSIONS AND RECOMMENDATIONS

In an attempt to address our previous label and labeling recommendations, the Applicant has introduced new areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations for the Division of Gastroenterology Products to consider in Section 3.1 Comments to the Division. We request the recommendations for the carton labeling and container label in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nitin Patel, at 301-796-5412.

3.1 COMMENTS TO THE DIVISION

A. General Comments

1. We note that the Applicant has changed the dosage form on container labels and carton labeling to [redacted] (b) (4) which is not in accordance with the USP monograph for this product. We defer to CMC for the appropriate designation of the dosage form for this product.
2. Per the insert labeling, the Applicant has proposed imprinting the [redacted] (b) (4) on the 10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease strength tablets. However, we note that [redacted] (b) (4) We recommend the Applicant either remove the imprinted [redacted] (b) (4) replace it with an imprint code.

3.2 COMMENTS TO THE APPLICANT

A. RETAIL CONTAINER LABELS (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

As currently presented, the font utilized for the established name appears to be too thin. Revise the established name to be in accordance with 21 CFR 201.10 (g)(2) so that the

established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

B. RETAIL CARTON LABELING (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

1. See comment A above.

2. As currently presented, the "Axcan Parma" logo on the principle display panel appears large and is more prominent than the strength presentation. Minimize or remove this logo.

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/s/

IRENE Z CHAN
10/15/2010

MELINA N GRIFFIS
10/18/2010

CAROL A HOLQUIST on behalf of DENISE P TOYER
10/18/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: August 3, 2010

From: Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Marjorie Dannis, MD, Clinical Reviewer
Anil Rajpal, MD, Clinical Team Leader
Division of Gastroenterology Products (DGP)

Re: Pediatric Labeling

Sponsor: Axcan Pharma, US, Inc.

Drug: Viokace® 16 (pancrelipase)

Application: NDA 22-542

Indication (proposed): Combination therapy with a proton pump inhibitor (PPI) for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis (b) (4) in adults (b) (4)

Indication to be approved: Combination therapy with a proton pump inhibitor (PPI) for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in adults

Dosage form: non-enteric coated tablet (20,880 lipase units per tablet)

Route of administration: oral

Consult Request:
DGP is requesting review of proposed pediatric labeling and the proposed pediatric literature references for inclusion in labeling.

Materials Reviewed:
- PMHS Consult Viokace (February 1, 2010)
- Proposed Labeling (Available in DGP e-room July 16, 2010)

Background:
The approval of Viokace®, a non-enteric coated pancreatic enzyme replacement product (PEP), is anticipated for the treatment of adults for the treatment of exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor (PPI). (b) (4) , given the safety concern that non-enteric coated products are not as efficacious as the enteric-coated products and hence, have the potential to result in inadequate growth and malnutrition.

Given the concern that non-enteric coated PEP products may be less effective than enteric-coated products, the Division has concluded that Viokace® would not represent a therapeutic benefit over the enteric-coated products, and additionally, based on the preferred use of enteric-coated products, Viokace® is not likely to be used in a substantial number of pediatric patients. Therefore, a full waiver of PREA required studies is anticipated based on this criterion in the law. The Pediatric Review Committee (PeRC) is in agreement with the full waiver and recommends including the potential efficacy and, therefore, safety concerns in labeling.

Of note, although PEPs have been available in the U.S. since before the enactment of the Food, Drug, and Cosmetic Act and the Drug Efficacy Study Implementation (DESI) requirements, because of concerns of inconsistencies in the formulation, dosage, and manufacturing processes of enzymes, the Agency announced in 2004 that all PEP drug products are new drugs and that manufacturers who wish to continue to market PEP drug products must submit new drug applications. The Viokace® application is the only new drug application received for an immediate release or non-enteric coated PEP formulation and "Viokase®" was the product marketed without a NDA.

Literature References: Enteric-Coated vs. Non-enteric Coated PEP Products
As discussed in the previous PMHS consult, PEPs were initially marketed as powders, immediate release tablets and capsules, and later, PEPs formulated as microspheres or microtablets coated with an acid-resistant film to prevent inactivation of the enzymes by gastric acid were introduced. Most experts acknowledge that the enteric-coated products represent an advance over non-enteric coated products [5,13]. Difficulties associated with non-enteric coated preparations include excessive inactivation by gastric acids and the association with mouth or perianal excoriation[3,7]. Acid-modifying drugs to protect the

pancreatic enzymes against inactivation have been used, but use has not been demonstrated to be uniformly successful[1,8].

Several small trials and one retrospective study suggest that the enteric-coated enzyme preparations may be more effective than the non-enteric coated enzymes and have fewer associated side effects[1,2,8,11]. In 1981, Gow et al published results of a crossover study of fecal fat and nitrogen excretion in 10 pediatric patients with CF treated with an enteric-coated microsphere PEP compared to a non-enteric coated PEP product. During treatment with the enteric-coated PEP product, fecal fat and nitrogen excretion were both statistically significantly decreased, i.e. $p< 0.001$ for both values[9]. In 1982, Mischler et al published results of a controlled, double-blind, randomized crossover study evaluating fecal fat and nitrogen absorption of an enteric-coated compared to a non-enteric coated PEP in ten boys with CF and concluded that fat absorption was statistically significantly improved during treatment with the enteric-coated product. Of note, although both enzyme preparations caused significantly improved protein absorption as compared to placebo, no significant difference in the degree of azotorrhea was identified[11]. Dutta et al published results in 1988 of a study evaluating the coefficient of fat absorption in 8 adult patients with EPI due to CF treated with an enteric-coated compared to a non-enteric coated product, and concluded that administration of an enteric-coated preparation was accompanied by a statistically significant, $p< 0.05$, reduction in steatorrhea in 7 patients[6]. Ansaldi-Balocco et al published results in 1988 of two studies in children with CF. The first study was a randomized crossover trial of an enteric-coated microsphere preparation compared to a conventional preparation given alone or in combination with cimetidine in 12 patients with CF age 4-14 years. The number of capsules taken per day was significantly less with treatment with the enteric-coated PEP compared to the non-enteric product, both administered alone ($p<0.02$) and with concomitant cimetidine ($p< 0.05$). In addition, the coefficient of fat absorption was statistically superior during treatment with the enteric-coated product. The second study was a retrospective study of the response of 17 patients with CF aged 22 months to 10 years treated with an enteric-coated product for at least 3 months (3-67 months) compared to the response to a non-enteric coated product in the same group of patients. The investigators concluded that while treated with the enteric-coated product, fat absorption was improved and the growth rate of teenage patients was greater, although not statistically significant[1].

Reviewer Comment:
The article by Ansaldi-Balocco et al is not only pertinent due to the data provided on growth in pediatric patients, but also the data on the daily quantity of enzyme replacement needed. Because higher doses of non-enteric formulations may be needed to achieve the same clinical effect as enteric-coated enzymes and high doses of pancreatic enzymes has been associated with fibrosing colonopathy, patients treated with non-enteric coated products may be at higher risk for this complication.

Per Robinson, the introduction of efficient and reliable enteric-coated pancreatic enzyme supplements in the late 1970s allowed a major improvement in CF nutrition[12]. Kraisinger et al concluded that although the microencapsulated formulations differ in content, ability to retard acid inactivation and the pH at which they release enzymes, they are more

effective than conventional products[10]. Dobrilla states that the introduction of enzyme preparations in the form of enteric-coated microspheres in hard gelatin capsules represents a significant advance and that the microspheres are superior to conventional enzyme preparations in improving the symptoms of pancreatic insufficiency, particularly steatorrhea[4].

Reviewer Comment on Literature References:
Although limitations of the studies published in the literature include the small numbers of patients evaluated, the short time period of evaluation and the retrospective design of one of the studies, the studies and literature suggest enteric-coated products may have advantages over non-enteric coated products, based on stool fat and nitrogen content, growth and the need for decreased daily doses of enzyme replacement. As discussed, decreased efficacy may result in inadequate growth, malnutrition and treatment with higher daily doses of enzyme replacement, which may put pediatric patients at higher risk for fibrosing colonopathy. The clinical community appears to have accepted the preferred use of the enteric-coated products.

PMHS agrees with including the publication by Gow et al in labeling as a reference as this article provides data from pediatric patients with CF that suggest improved efficacy of an enteric-coated product compared to a non-enteric coated product based on fecal fat and nitrogen absorption. In addition, including the article by Ansaldi-Balocco et al is recommended as this publication not only provides pediatric data that suggest improved efficacy of an enteric-coated product compared to a non-enteric coated product based on the coefficient of fat absorption, but also provides data that suggest that growth is decreased in some pediatric patients treated with non-enteric coated PEPs and that treatment with an enteric-coated PEP results in the administration of a smaller daily doses of enzyme replacement.

Comments on Labeling:

Division Proposed Labeling:

HIGHLIGHTS:

----------**-----USE IN SPECIFIC POPULATIONS----------**
Pediatric Patients
- The short-term safety and efficacy of VIOKACE has not been assessed in pediatric patients. (8.4)
- Pediatric patients may be at risk for growth retardation with VIOKACE due to tablet degradation in the gastric environment. (8.4)

FULL PRESCRIBING INFORMATION:

Warnings and Precautions (5)
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 (2.1)].

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.

Special Populations (8)
8.4 Pediatric Use
The short-term safety and efficacy of VIOKACE has not been assessed in pediatric patients. Due to greater degradation in the gastric environment of non-enteric-coated formulations, such as VIOKACE, concern exists that pediatric patients may be at a higher risk for growth retardation with a non-enteric-coated formulation than with an enteric-coated formulation.[7]

PMHS Labeling Suggestions**:**
HIGHLIGHTS:

----------**-----USE IN SPECIFIC POPULATIONS----------**
Pediatric Patients
- The safety and effectiveness of VIOKACE have not been established in pediatric patients. (8.4)
- VIOKACE use in pediatric patients may result in suboptimal growth due to tablet degradation in the gastric environment. (8.4)

FULL PRESCRIBING INFORMATION:

Warnings and Precautions (5)
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 (2.1)].

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.

Special Populations (8)
8.4 Pediatric Use
The safety and effectiveness of VIOKACE have not been established in pediatric patients.

Due to greater degradation in the gastric environment, the non-enteric-coated pancreatic enzyme replacement products such as VIOKACE, 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[See Warnings and Precautions (5.1)] [7]
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.

Conclusions and Recommendations:
Approval for Viokace® is anticipated in adult patients in combination therapy with a PPI for the treatment of EPI due to chronic pancreatitis or pancreatectomy. Because the safety and effectiveness of Viokace® have not been established in pediatric patients, this statement should be included in labeling and pediatric information pertaining to the unapproved use should be provided in USE IN SPECIFIC POPULATIONS, Pediatric Use as proposed. Stating that "the safety and effectiveness of Viokace® have not been established in pediatric patients" is preferred over stating that (b)(4) as the former is objective, and the latter can be

subject to interpretation. Given the greater degradation in the gastric environment of non-enteric-coated formulations that may decrease the bioavailability and efficacy of non-enteric coated PEP products, the Pediatric Use section should inform that use of non-enteric coated products may put pediatric patients at higher risk for an inadequate response to enzyme replacement therapy, and therefore at higher risk for suboptimal growth, malnutrition and/or need for higher daily doses of enzyme replacement therapy. Given that high doses of enzyme replacement therapy have been associated with fibrosing colonopathy, Warnings and Precautions Section 5.1, Fibrosing Colonopathy, should be cross referenced. In addition, the approval of Viokace® in adults includes concomitant treatment with a PPI. Although PPIs are approved for use in pediatric patients $\geq$ 1 year for the treatment of GERD, the long-term safety of the PPIs in pediatric patients has not been established and this information is also recommended for inclusion in labeling in the Pediatric Use section. The publications by Gow et al[9] and Ansaldi-Balocco et al[1] are recommended as references for labeling as these articles provide data from studies in pediatric patients that demonstrate the increased risk of suboptimal weight gain, malnutrition and/or need for larger doses of pancreatic enzyme replacement associated with treatment with non-enteric coated products compared to enteric-coated products.

REFERENCES

1. Ansaldi-Balocco N, Santini B, Sarchi C. Efficacy of pancreatic enzyme supplementation in children with cystic fibrosis: comparison of two preparations by random crossover study and a retrospective study of the same patients at two different ages. *J Pediatr Gastroenterol Nutr.* 1988;7 Suppl 1:S40-5.

2. Beker LT, Fink RJ, Hamsa FH. Comparison of Weight-Based Dosages of Enteric-coated Microtablet Enzyme Preparations in Patients with Cystic Fibrosis. Journal of Pediatric Gastroenterology and Nutrition.1994;19:191-97.

3. Borowitz D, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. J Pediatr 1995;127:681–84.

4. Dobrilla G. Management of chronic pancreatitis. Focus on enzyme replacement therapy. *Int J Pancreatol*. 1989;5 Suppl:17-29.

5. Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr Gastroenterol Rep.* 2007;9(2):116-22.

6. Dutta SK, Hubbard VS, Appler M. Critical examination of therapeutic efficacy of a pH-sensitive enteric-coated pancreatic enzyme preparation in treatment of exocrine pancreatic insufficiency secondary to cystic fibrosis. *Dig Dis Sci.* 1988;33(10):1237-44.

7. Ferrone M, Raimondo M, Scolapio JS. Pancreatic Enzyme Pharmacotherapy. *Pharmacotherapy.* 2007;27(6):910–920.

8. George DE, Pinero R, Miller AM, et al. Comparison of Two Pancreatic Enzyme Supplements in Patients with Cystic Fibrosis. *Advances in Therapy.* 1990;7(3):109-118.

9. Gow R, Francis P, Bradbear R, et al. Comparative study of varying regimens to improve steatorrhea and creatorrhea in cystic fibrosis: effectiveness of an enteric-coated preparation with and without antacids and cimetidine. *Lancet;* 1981: 1071-1074

10. Kraisinger M, Hochhaus G, Stecenko A, Bowser E, Hendeles L. Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and in vitro performance of microencapsulated formulations. *J Clin Pharmacol*. 1994. 34(2):158-66. (Abstract only)

11. Mischler EH, Parrell S, Farrell PM, Odell GB. Comparison of effectiveness of pancreatic enzyme preparations in cystic fibrosis. *Am J Dis Child.* 1982;136(12):1060-3.

12. Robinson P. Nutritional status and requirements in cystic fibrosis. *Clinical Nutrition.* 2001;20: 81-86.

13. Waljee AK, Dimagno MJ, Wu BU, Schoenfeld PS, Conwell DL. Systematic review: pancreatic enzyme treatment of malabsorption associated with chronic pancreatitis. *Aliment Pharmacol Ther*. 2009;29(3):235-46.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH L DURMOWICZ
08/10/2010
Because of a linking problem with DARRTS, I need to enter this as a "Consult Review". After signed off, the consult will be entered as a PMHS review and linked to the PMHS consult.

HARI C SACHS
08/11/2010
Addendum: after additional discussion, labeling will reflect tha (b) (4)

LISA L MATHIS
08/17/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: June 29, 2010

To: Elizabeth Ford, Regulatory Health Project Manager
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Sheetal Patel, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Aline Moukhtara, Acting DTC Group Leader
Wayne Amchin, Regulatory Health Project Manager DDMAC

Subject: NDA 022542

DDMAC labeling comments for Tradename (pancrelipase) Tablets, Immediate Release for Oral Use

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In response to DGP's November 12, 2009, consult request, DDMAC has reviewed the draft package insert (PI), Medication Guide, and carton/container labeling for Tradename (pancrelipase) Tablets, Immediate Release for Oral Use. DDMAC's comments on the PI and Medication Guide are based on the proposed draft marked-up labeling titled "Applicant submitted 3-9-2010.doc" that was modified in the e-room on June 28, 2010, at 6:35pm.

DDMAC's comments on the PI and Medication Guide are provided directly in the marked-up document attached (see below). DDMAC's comments on the carton/container labeling follow.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI or carton/container labeling, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

If you have any questions regarding the Medication Guide, please contact Sheetal Patel at 301.796.5167 or Sheetal.Patel@fda.hhs.gov.

<u>Carton/Container Labeling</u>

DDMAC has reviewed the following carton/container labeling pieces, accessed via the e-room on June 28, 2010, and has no comments at this time.

- Tradename-16.pdf
- Tradename-8.pdf

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHEETAL PATEL
06/29/2010

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 24, 2010

TO: Elizabeth Ford, Regulatory, Project Manager
Marjorie Dannis, Medical Officer
Division of Gastroenterology Products

FROM: Khairy W. Malek, M.D., Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA or BLA: 22-542

APPLICANT: Axcan Pharma US, Inc.

DRUG: Viokase (pancreatic enzymes)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Treatment of exocrine pancreatic insufficiency due to chronic Pancreatitis (b) (4).

CONSULTATION REQUEST DATE: December 23, 2009

DIVISION SUMMARY GOAL DATE: July 1, 2010
PDUFA DATE: August 30, 2010

I. BACKGROUND:

The current treatment of exocrine pancreatic insufficiency (EPI) includes enzyme supplementation with pancreatic enzyme concentrate consisting mainly of lipase, amylase and protease. Viokase is an oral supplement of pancreatic enzymes that has been on the market since 1949 and is indicated in the treatment of EPI.

Axcan Pharma submitted this application in support of the efficacy and safety of Viokase 16 tablets for lipid digestion and absorption compared to placebo in patients with EPI.

One pivotal study was submitted in support of the application: VIO16EP107-01 "A Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled, Phase III Study To Assess The Safety And Efficacy Of Viokase 16 For The Correction Of Steatorrhea In Patients With Exocrine Pancreatic Insufficiency". The primary efficacy parameter was the comparison of the coefficient of fat absorption (CFA) percentage between Viokase and placebo groups.

The pivotal study was selected for inspection, and two clinical investigator sites were inspected. These sites were selected because of the large number of subjects and significant primary efficacy results.

II. RESULTS (by Site):

Name of CI & Location	Protocol # and # of Subjects	Inspection Date	Final Classification
Phillip Toskes, M.D. 1600 SW Archer, Room M-411 Gainsville, FL 32610	VIO16EP107-01 6 subjects	March 10-12, 2010	VAI
Grazyna Rydzewska, M.D. Kliniczny MSWIA, W Warszawie ul. Woloska 137, Warszawa 02-507, Poland	VIO16EP107-01 8 subjects	April 26-28, 2010	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Phillip Toskes, M.D.-Site # 42
   Shands Teaching Hospital, University of Florida Division of Gastroenterology, Hepatology and Nutrition.
   1600 SW Archer Road, Room M-411, Gainesville, FL 32610, USA

a. What was inspected: At this site, 13 subjects were screened, 6 subjects were randomized and all completed the study. There were no SAEs reported. The field investigator reviewed the records of all subjects in the study. There were no limitations to the inspection.

b. General observations/commentary: The field investigator reviewed the records of the 6 subjects who completed the study: 34201, 4204, 4205, 4206, 4210 and 4211.

Following the inspection, a one-observation Form FDA-483 was issued to the clinical investigator. The field investigator reported that 4/6 subjects used un-approved concomitant medications;

i. Subject 4205 used "Methadone",
ii. Subject 4201used "Duragesic Patch",
iii. Subject 4206used "Oscal" (Calcium carbonate) and
iv. Subject 4210 used "Calcitrat".

Reviewer's Comments: The inspection was classified as "OAI"; however, following evaluation of the 483, EIR and exhibits, the inspection was reclassified as VAI as the identified issues are not considered importantly to impact data integrity.
After review of the report and the CI response to the Form 483, I found no evidence that Subject 4210 used "Calcitrate" and the CI assured that she did not. Regarding Subject 4201 who used the Duragesic Patch, the CI replied that the effect of the patch on gut motility is less than oral or parenteral administration. Regarding the concomitant use of calcium tablets by Subject 4206, calcium was not absolutely un-allowed by the protocol, but was allowed in a multivitamin preparation (in small amounts). Also Subject 4204 was admitted in error as the sponsor calculated the CFA as 80% on admission and after verification it was found to be actually 93.3% .

c. Assessment of data integrity: The data from the 3 subjects who did not use un-approved concomitant medications (# 4204, 4210 and 4211) can be used for NDA approval, but it is up to the review division to assess the effect of the un-approved concomitant medications on the CFA results. Also, the review division should consider that Subject # 4204 had an admission error in the calculation of CFA (93.3%).

2. Grazyna Rydzewska, M.D.-Site 35
Klinika Chorob Wewnetznychi Gastroenterologii, Centralny Szpital Kliniczny MSWiA, w Warszawie ul. Woloska 137, Warszawa 02-507, Poland

a. What was inspected: The site screened 44 subjects, 26 were screen failures; three subjects withdrew their consent, 7 were wash-out failures and 8 completed the study. The field investigator reviewed the records of 14 subjects. There were no SAEs reported. There was no limitation to the inspection.

b. General observations/commentary: The inspection revealed that the inspection was conducted in accordance with investigational plan. The field investigator did not report any violations and no Form DFA 483 was issued.

c. Assessment of data integrity: The data generated from this site can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites were inspected in support of the application. The data are considered reliable in support of the application; however, the review division may choose to consider the clinical impact, if any, of the use of concomitant medications at Dr. Toske's site in their assessment of the application.

See appended electronic signature page}

Khairy Malek, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

KHAIRY W MALEK
06/29/2010

TEJASHRI S PUROHIT-SHETH
06/30/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 5, 2010
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products
Through:	Melina Griffis, RPh, Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Viokace (Pancrelipase) Tablets 10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease
Application Type/Number:	NDA 022542
Applicant:	Axcan Pharma
OSE RCM #:	2009-2130

CONTENTS

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed retail container labels and insert labeling for Viokace contained in the Applicant's original submission, dated October 29, 2009, and identified areas of vulnerability that can lead to medication errors. We provide recommendations in Section 4 that aim at reducing the risk of medication errors with regard to the proposed product labels and labeling.

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Viokase tablets are currently marketed; therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on December 7, 2009, to identify medication errors involving Viokase.

The MedRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues" were used as search criteria for Reactions. The search criteria used for Products was verbatim substance search "Vioka%". No date limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposures, intentional overdoses, etc.) were excluded from further analysis.

2.2 LABEL AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the labels and labeling submitted as part of the August 21, 2009 submissions (see Appendix A).

3 RESULTS

3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The AERS search conducted on December 7, 2009, yielded 2 cases. Both cases were excluded from further evaluation because they were not applicable to this review. The first case was a wrong drug error where two different medications had been accidentally dispensed in one bottle. There is no indication that labels or labeling were contributing factors in this case.

The second case reported an error due to an order for Viokase that read "Viokase 8 tabs with meals TID." This order was clarified by the pharmacist to read "Viokase-8 three tablets with meals TID." The case identified confusion caused by the use of the suffix "8" in the proprietary name "Viokase 8". This error did not reach the patient.

3.2 LABEL AND LABELING

The label and labeling risk assessment findings indicate the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. These conclusions and their corresponding recommendations are further explained in Section 4 below.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container labels and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1 Comments to the Division. We request the recommendations for the container labels in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nitin Patel, at 301-796-5412.

4.1 COMMENTS TO THE DIVISION

Based on recommendations by the CMC reviewer, the presentation of the established name should be (pancrelipase) tablets throughout all labels and package insert labeling.

4.2 COMMENTS TO THE APPLICANT

A. RETAIL CONTAINER LABELS (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

1. Established Name

   a. Revise the established name to read (pancrelipase) tablets on all labels and package insert labeling.

   b. Revise the established name to be in accordance with 21 CFR 201.10 (g)(2) so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

   c. Remove the color boxing around the established name and change the font color to one color that is legible and provides a sufficient color contrast against the white background. As currently presented, the proprietary name is boxed in green whereas the established name is boxed in gray resulting in an intervening white line separating the proprietary name and the established name boxing.

   d. Ensure that the established name is presented in its entirety on the principle display panel and does not wrap around on the side panel.

2. Revise your container labels so that the three active ingredients are boxed as follows:

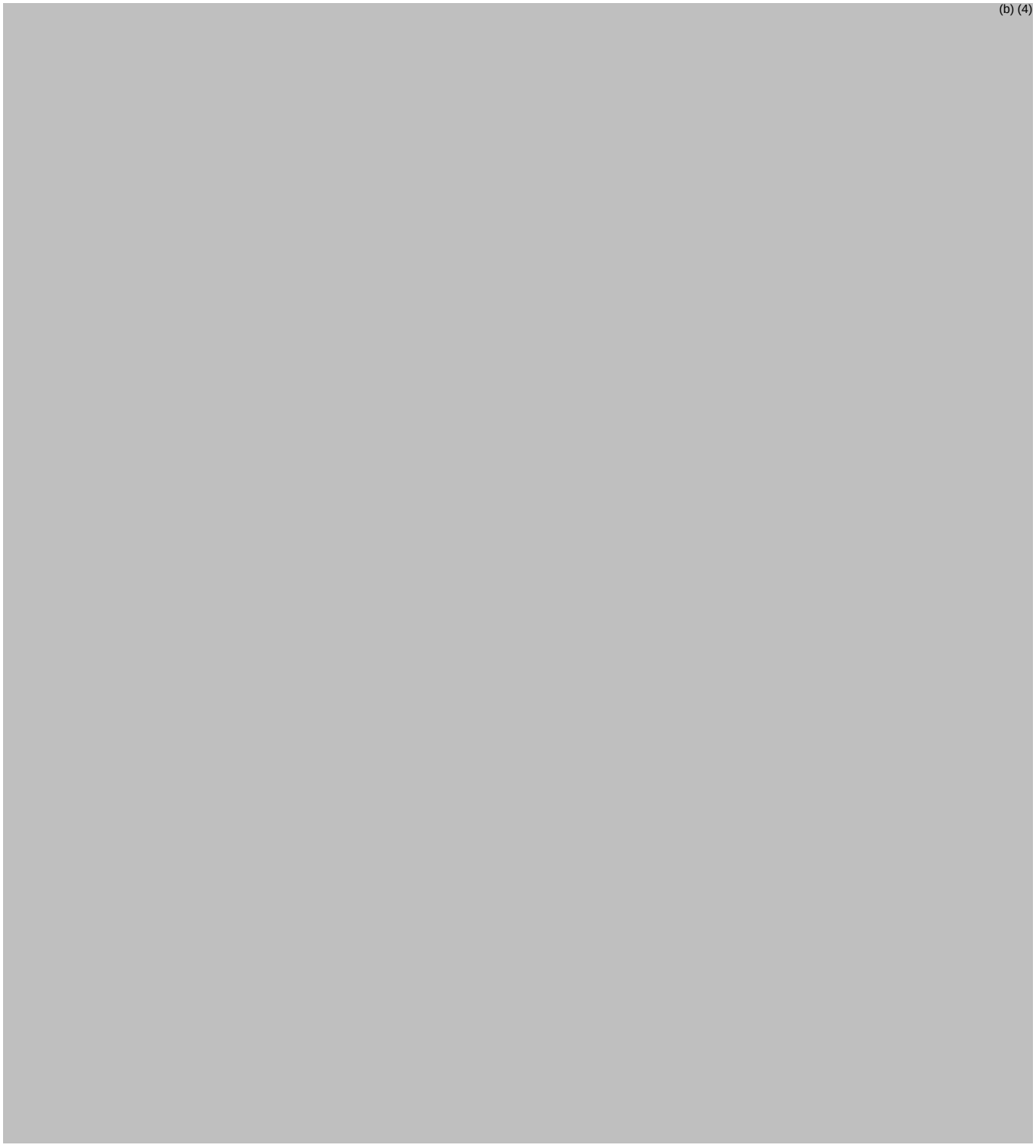
Each tablet contains:	
Lipase	XXXX USP Units
Amylase	XXXX USP Units
Protease	XXXX USP Units

Boxes will represent the product strength on the principle display panel. The boxes should be prominently displayed, following the proprietary and established names, and should incorporate strength differentiation between the two available Viokace strengths. Differentiation may be accomplished through the use of colors, shading, highlighting or some other means. Two unique boxing colors should be utilized for the strength differentiation of Viokace and should not incorporate another color already utilized on the labels. See currently approved pancrelipase product labels and labeling for reference.

3. Include a statement on the principle display panel informing patients and healthcare practitioners that Viokace is dosed based on lipase units.

4. Move the statement "ACCOMPANYING **MEDICATION GUIDE** TO BE DISPENSED TO PATIENT" to a different area of the principle display panel so that it is not intervening between the established name and strength presentation, ensuring that it doesn't wrap around the side panel and is presented in its entirety on the principle display panel. Consider moving the "Rx only" statement to a side panel to ensure adequate room. Remove the bold font from "MEDICATION GUIDE".

<u>Appendix A</u>: Viokace Retail Container Labels for 100 Count Bottles



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/s/

IRENE Z CHAN
02/05/2010

MELINA N GRIFFIS
02/05/2010

DENISE P TOYER
02/05/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST
02/05/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: February 1, 2010

From: Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Marjorie Dannis, MD, Clinical Reviewer
Anil Rajpal, MD, Clinical Team Leader
Division of Gastroenterology Products (DGP)

Re: Use of Viokace®/Viokase® (b) (4)

Sponsor: Axcan Pharma, US, Inc.

Drug: Viokace® 16 (pancrelipase), currently marketed as Viokase®

Application: NDA 22-542

Indication (proposed): Combination therapy with a proton pump inhibitor (PPI) for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis (b) (4) in adults (b) (4)

(b) (4)

Dosage form: (currently marketed) non-enteric coated tablet (8000, 16000 lipase units)
Powder 0.7 g (1/4 teaspoon) = 16,800 lipase units

Dosage form proposed: non-enteric coated tablet (20,880 lipase units per tablet)

Route of administration: oral

Consult Request:
DGP is concerned about the safety and efficacy of non-enteric coated pancreatic enzyme replacement products (PEPs) for the treatment of exocrine pediatric insufficiency (EPI) (b) (4) and the medical necessity of Viokase®, a currently marketed unapproved PEP. PMHS comment is requested about (b) (4) Viokace® in the treatment of EPI and the need for PREA related studies in some or all pediatric age cohorts.

Materials Reviewed:
- PMHS Consult request (December 23, 2009)
- PMHS Review Pancrease MT, December 1, 2008
- Labeling esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs (April 2006)
- Minutes from Meeting with the Sponsor (October 2006)
- Viokace® Clinical Study Report VIO16EPI07-01. October 12, 2009 (From Viokace® NDA application submission)

Regulatory Background:
PEP products are used for the treatment of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF), chronic pancreatitis (CP) and other conditions. PEPs have been available in the U.S. since before the enactment of the Food, Drug, and Cosmetic Act in 1938 and the Drug Efficacy Study Implementation (DESI) requirements of 1962. In April 2004, because of concerns of inconsistencies in the formulation, dosage, and manufacturing processes of enzymes that could significantly compromise the safety and effectiveness of PEP products, the Agency announced that all PEP drug products are new drugs and that manufacturers who wish to continue to market PEP drug products must submit new drug applications. In April 2008, the Agency published a guidance document to assist manufacturers in preparing and submitting NDAs. The PEP guidance indicated that FDA would exercise enforcement discretion for sponsors who submitted INDs by April 28, 2008 and NDAs by April 28, 2009. The deadline for PEPs to be approved or be removed from the market is April 28, 2010 (Federal Register (FR) Notice October 26, 2007). However, the Division is considering enforcement discretion for products anticipating approval immediately before, or just after the FR Notice deadline, specifically Pancrease MT and Ultresa, and for products that may satisfy a unique medical need, specifically Viokace® (See Appendix II: Table of PEPs for which FDA has received an NDA).

Creon® and Zenpep™, enteric-coated PEPs, have been approved in adults and pediatric patients for the treatment of EPI due to CF or other conditions under this process. Another product, Cotazym, was approved under the NDA process in 1996, but is not currently marketed. Four additional NDAs, including the NDA for Viokace® have been submitted. The Viokace® application is the only application received for an immediate release or non-enteric coated PEP formulation (See Appendix II: Table of PEPs for which

FDA has received an NDA). Of note, Viokase® is the name of the currently marketed product, and Viokace® is the proposed name of the product under NDA review.

Exocrine Pancreatic Insufficiency:
Patients with exocrine pancreatic insufficiency have a clinically significant reduction of pancreatic function and are unable to fully digest fats, proteins, and carbohydrates, leading to malabsorption of these nutrients, with resultant malnutrition and secondary complications such as impaired immune response, infections, bleeding tendencies, fat soluble vitamin deficiencies and other signs and symptoms of malnutrition, including impaired growth and development in children. Gastroduodenal and small-intestinal transit can be significantly accelerated, and the available time for digestion and absorption is markedly decreased, further contributing to nutrient malabsorption and perhaps pain in certain patients[8].

EPI can be caused by pancreatic diseases (such as chronic pancreatitis, cystic fibrosis severe acute necrotizing pancreatitis, and pancreatic cancer), extrapancreatic diseases (such as celiac disease and Crohn's disease,) and gastrointestinal and pancreatic resection[6]. Chronic pancreatitis (CP) is an inflammatory disorder results in anatomical changes including chronic inflammatory cell infiltration and gland fibrosis, with loss of exocrine and endocrine functions[12,20]. In CP, pancreatic insufficiency manifests late in the course of the disease secondary to the large functional capacity of the pancreas[8]. The most common cause of CP in adults in developing countries is alcohol[8,12]. In children, CP is rare and the condition behaves differently[20]. The etiology of CP in children is predominantly hereditary or idiopathic, but causes also include trauma, biliary/choledocholithiasis, anatomical abnormalities, drug-induced and hyperlipidemia[12,20].

In cystic fibrosis (CF), pancreatic insufficiency is clinically apparent in 85–90% of patients, usually manifests early in life and may be progressive[8]. Viscous secretions cause luminal obstruction of ducts, which leads to acinar cell destruction, fibrosis, and exocrine pancreatic insufficiency. The resultant pancreatic insufficiency is characterized by a decrease or absence of the exocrine pancreatic enzymes: amylase, proteases, lipase, colipase, and phospholipases. However, salivary and brush border amylase levels are normal or elevated, and lingual lipase levels are elevated resulting in an altered digestive process that can lead to disturbances in motor function of the upper gastrointestinal tract, including an accelerated intestinal transit time that may contribute to further malabsorption of specific vitamins and nutrients[8].

Pancreatic Enzyme Replacement Therapy
Pancreatic enzyme supplementation is standard treatment for patients with pancreatic exocrine deficiency to improve nutrient absorption, improve symptoms of steatorrhea and in some cases, relieve the pain associated with chronic pancreatitis[8,23].

As discussed above, PEPs were initially marketed before 1938 as powders, immediate release tablets and capsules. PEPs formulated as microspheres or microtablets coated

with an acid-resistant film to prevent inactivation of the enzymes by gastric acid were introduced in the 1970s. Although most experts acknowledge that the enteric-coated products represent an advance over non-enteric coated products (see below), neither type of product may completely normalize fat digestions or abolish steatorrhea[6,23].

Difficulties associated with non-enteric coated preparations include excessive inactivation by gastric acids and the association with mouth or perianal excoriation[4,8]. Acid-modifying drugs to protect the pancreatic enzymes against inactivation have been used, but use had not been demonstrated to be uniformly successful[1,10]. Of note, a double-blind, placebo-controlled, crossover study in 12 children and 10 adults with pancreatic-insufficiency secondary to cystic fibrosis did not demonstrate overall significant improvement in fat absorption in patients treated with non-enteric coated pancrelipase and ranitidine compared to patients treated solely with non-enteric coated pancrelipase [8].

Difficulties with the enteric-coated preparations include excessive enzyme protection. Although the enteric coating prevents acid-inactivation of the enzymes in the gastric environment, because patients with pancreatic insufficiency produce decreased amounts of bicarbonate-rich secretions, the duodenum and proximal jejunum may remain acidic, preventing or retarding dissolution of the protective coating until the capsules have passed a significant amount of the intestinal absorptive surface[3,4,8].

Several small trials and one retrospective study suggest that the enteric-coated enzyme preparations may be more effective than the non-enteric coated enzymes and have fewer associated side effects[1,2,7,19]. In 1982, Mischler et al published results of a controlled, double-blind, randomized crossover with washout study of an enteric-coated compared to a non-enteric coated PEP in ten boys with CF and concluded that fat absorption was statistically significantly improved in patients treated with the enteric-coated product[19]. Dutta et al published results in 1988 of a study of 8 patients with EPI due to CF and concluded that administration of an enteric-coated preparation was accompanied by a statistically significant, $p< 0.05$, reduction in steatorrhea[7]. Ansaldi-Balocco et al published results in 1988 of two studies in children with CF. The first study was a randomized crossover trial of 5 days of treatment with an enteric-coated microsphere preparation compared to a conventional preparation given alone or in combination with cimetidine in 12 patients with CF age 4-14 years. The number of capsules taken per day was significantly less in the enteric-coated PEP group ($p<0.02$ compared to the non-enteric product alone and $p< 0.05$ compared to the non-enteric product with cimetidine). In addition, the coefficient of fat absorption, frequency of stools and stool consistency in the enteric-coated treatment group was statistically superior to these efficacy endpoints in patients treated with the non-enteric coated product. The second study was a retrospective study of the response of a group of CF patients treated with an enteric-coated product for at least 3 months (3-67 months) compared to the response to a non-enteric coated product in the same group of patients. The investigators concluded that while treated with the enteric-coated product, fat absorption was improved and the growth rate of teenage patients was greater, although not statistically significant[1].

Reviewer Comment:
Review of the literature identified the above mentioned studies published in the late 1980s investigating the efficacy of the enteric-coated PEPs compared to the non-enteric coated preparations. Limitations of these studies include the small numbers of patients evaluated, the short time period of evaluation and the retrospective design of one of the studies by Ansaldi-Balocco et al. Subsequent studies published in the early 1990s appear to primarily evaluate the superiority of one enteric-coated product over another or the use of PEP treatment in conjunction with acid blocking therapy. This may imply that the clinical community had accepted the superiority of the enteric-coated products.

Per Robinson, the introduction of efficient and reliable enteric-coated pancreatic enzyme supplements in the late 1970s allowed a major improvement in CF nutrition[21]. Kraisinger et al concluded that although the microencapsulated formulations differ in content, ability to retard acid inactivation and the pH at which they release enzymes, they are more effective than conventional products[17]. Dobrilla states that the introduction of enzyme preparations in the form of enteric-coated microspheres in hard gelatin capsules represents a significant advance and that the microspheres are superior to conventional enzyme preparations in improving the symptoms of pancreatic insufficiency, particularly steatorrhea[5].

Of note, although Eudragit L, a resin in the acid-resistant coating of some microtablets, had been implicated in the etiology of fibrosing colonopathy, a complication of pancreatic enzyme replacement therapy, high daily doses of enzyme supplements are currently implicated in the etiology of this condition. FitzSimmons et al state in their sentinel article, High-Dose Pancreatic Enzyme Supplements and Fibrosing Colonopathy in Children with Cystic Fibrosis, that the strength, coating and manufacturers of the products were not associated with the risk of fibrosing colonopathy[9].

This reviewer was unable to find any long-term or recent clinical trials comparing the safety and efficacy of non-enteric PEP products to enteric-coated PEP products.

Clinical Management of EPI

Per the Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis, the microsphere or microtablet preparations are preferable to powders secondary to gastric acid-resistance and the absence of association with mouth or perianal excoriation[3]. The administration of products to alkalinize the duodenal contents, such as bicarbonate, histamine-2 receptor blockers or proton pump inhibitors, are considered by experts to be useful adjuncts in the management of patients with a poor response to therapy[3,4]. In addition, although the review by Borowitz et al and the Consensus Committee published in 1995 state that occasionally the use of non-enteric coated pancreatic powders in combination with enteric-coated enzymes may be helpful[4], a study by Kalnins et al published in 2006, concludes that the addition of powder enzymes to enteric-coated products did not improve nutrient maldigestion compared to treatment with the enteric-coated product alone[14].

Ferrone et al state that patients with rapid gastrojejunal transit and/or those with a hypoacidic stomach are often best treated with powder enzyme preparations. These patients include those who have had a pancreatectomy, associated with either partial gastrectomy or vagotomy and gastroenterostomy, and those with decreased acid secretion, including achlorhydric patients secondary to acid blocking therapy. Ferrone et al also state that Viokase powder may be of benefit in patients receiving continuous enteral feedings via gastrostomy or jejunal tubes, as the powder can be administered through a feeding tube (after dilution in water) or directly into the feeding bag[8]. Of note, this method of enzyme administration is not recommended by the Consensus Committee in the Report on Nutrition for Pediatric Patients with Cystic Fibrosis[3] or by the AAP in the Pediatric Nutrition Handbook[16].

Reviewer Comment:
The few published trials with comparative data and expert opinion appears to support the superiority of the enteric-coated products, and these products appear to be used as standard of care for most children with CF. However, pancreatic enzyme supplementation is managed on a case by case basis[8,14], and the non-enteric coated products may be beneficial in some patients.

Dosing of PEPS is based on published guidelines, individual patient's responses to treatment[8,14] and evaluated subjectively by following growth and stool parameters[3]. The estimated requirement of cumulative prandial intraduodenal lipase in adults is 25,000–40,000 units of lipase based on an estimate of the needed mean lipase activity within the duodenal chyme and a reduction of pancreatic function of 90-95%[8]. In children or young adults with cystic fibrosis, pancreatic enzymes are dosed by units of lipase/ kg/meal or units of lipase/g of fat ingested as outlined in recommendations by the Cystic Fibrosis Foundation, CFF[3]. (See Appendix I: Cystic Fibrosis Foundation Guidelines). This dosing regimen translates into approximately 500–2000 units of lipase/kg/meal or 500–4000 units of lipase/g of fat. To minimize the risk of fibrosing colonopathy, the CFF recommends that Enzyme doses should not exceed 2500 lipase units/kg per meal, 10,000 lipase units/kg per day and 4000 lipase units/gram fat per day[3].

Clinical Development of Viokace®:
The development program for Viokace® includes three clinical studies: a bioavailability study, performed in 20 adult patients with CP, and two safety and efficacy studies. (See Appendix III: Tabular Listing of All Clinical Studies). Study VIO16EPI07-01 is a Phase III, multicenter, randomized, double-blind, parallel group, placebo-controlled study in 50 adult patients with EPI due to CP, partial or total resection of the pancreas to assess the safety and efficacy of Viokace® 16. Patients were treated with 22 tablets per day, 6 tablets with each meal and 2 tablets with two snacks, and with the patient's usual PPI or omeprazole (in patients not being treated with a PPI at study entry). Study STEA-VK00-US01 is a single-center, randomized, parallel group, open-label safety and efficacy study of 17 adult patients with EPI due to CP treated with Viokace® 16. Patients received 8 or 16 tablets per day.

Reviewer Comment:
The dosing in the protocol would deliver 96,000 units of lipase per meal and 32,000 units of lipase per snack, which for a 60 kg young adult is equivalent to 1600 units/kg/meal and approximately 5900 units of lipase/kg/day. Although the quantity of lipase administered in the study is within the CFF dosing recommendations of approximately 500–2000 units of lipase/kg/meal and less than the maximum recommended 10,000 lipase units/kg per day, the dose studied in the clinical trial may be a higher dose than needed to control the signs and symptoms of EPI in pediatric patients. Because patients with CP are likely to have more residual pancreatic function than patients with CF (per information shared via teleconference by David C. Whitcomb, M.D., Ph.D., Medical Director of the National Pancreas Foundation, January 15, 2009), this dose may be more likely to be too high a dose, and thus inappropriate for pediatric patients with CP.

The Sponsor concluded that study VIO16EPI07-01 demonstrated a statistically-significant and clinically meaningful difference between treatment with Viokace® 16 and placebo in patients with EPI who were concomitantly treated with a proton pump inhibitor. The Sponsor also concludes that treatment with Viokace® 16 was also associated with the control of normal stool frequency and was well tolerated.

Reviewer Comment:
PMHS defers the interpretation of safety and efficacy to the Division reviewers.

The proposed indication for labeling is combination therapy with a proton pump inhibitor (PPI) for the treatment of EPI due to chronic pancreatitis (b) (4) in adults (b) (4)

(b) (4)

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(b) (4)

(3) Should pediatric studies be fully waived or partially waived? If you recommend partially waiving studies, please state which ages. Please also state the rationale for your recommendation.

PMHS Response:
Yes. Pediatric studies for Viokace® should be fully waived.

Discussion:
Because the Viokace® NDA application is for a new dosage form, the application is subject to the terms of the Pediatric Research Equity Act and a pediatric assessment is required for the claimed indication in all relevant pediatric subpopulations unless a waiver or a deferral is granted. Waivers can be granted if the Division determines that:

> *(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed);*
>
> *(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or*
>
> *(iii) the drug or biological product--*
>
> *(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and*
> *(II) is not likely to be used in a substantial number of pediatric patients.*

PMHS believes a full waiver of PREA required studies is appropriate for this application. Not only is CP a rare condition in pediatric patients, but given the safety and efficacy concerns of the non-enteric coated products, Viokace® would not represent a therapeutic benefit over the enteric-coated products and based on the preferred use of enteric-coated products, Viokace® is not likely to be used in a substantial number of pediatric patients.

Although the approved indication for Viokace® is likely to include concomitant use of a PPI and the safety of chronic PPI use in children has not been established, this potential safety concern is not sufficiently strong to waive studies based on the second criterion for the waiver of pediatric studies: " there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe". Therefore, PMHS recommends a full waiver based on the third criterion: the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

Appendix I: Cystic Fibrosis Foundation Guidelines[3]

Standard meal dosing

- Infants - 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding
- Children < 4 years old – starting dose of 1000 lipase units/kg per meal
- Children > 4 years old – starting dose of 500 lipase units/kg per meal

Snack dosing - ½ the standard dosing

Total daily dose - should reflect approximately three meals and two or three snacks per day[2].

Enzyme doses should not exceed 2500 lipase units/kg per meal, 10,000 lipase units/kg per day and 4000 lipase units/gram fat per day.

Appendix II: Table of PEPs for which FDA has received an NDA.
Prepared by Elizabeth Ford, RN

NDA Number	Drug Name	Sponsor	DMF Holder	PDUFA	Approvability Issues	Ready for approval by April 28, 2010
N 20725	Creon	Solvay	Solvay	Approved		
N 22210	Zenpep	Eurand	(b) (4)	Approved		
N 22523	Pancrease MT	Johnson & Johnson		4/23/2010		Possible
N 22222	Ultresa	Axcan Pharma US, Inc.		5/5/2010	DMF and manufacturing deficiencies	No
N 22542	Viokase	Axcan Pharma US, Inc.		8/30/2010	DMF and manufacturing deficiencies	No
N 22175	Pancrecarb	Digestive Care Inc.		Awaiting 2nd cycle submission	DMF and manufacturing deficiencies	No

Appendix III: Tabular Listing of All Clinical Studies
From the Sponsor

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Randomized	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	VIO16IP07-01	Evaluation of intraduodenal delivery of lipase, protease and amylase activity	Single-center , open-label, crossover	VIOKASE® 16; Two administrations of a liquid meal with and without a single dose of 3 tablets; phases separated by one day; Oral	20	Chronic pancreatitis patients >18 years of age with EPI (fecal elastase below 100µg/g of stool and CFA% <80% at Screening)	Single dose; Two treatment phases separated by 1 day	Completed; Full report
Efficacy and Safety	VIO16EPI07-01	Efficacy and safety *vs* placebo	Multicenter, randomized, double-blind, parallel, placebo-controlled	VIOKASE® 16; Dose of 22 tablets per day (6 tablets with each meal and 2 tablets with two of the snacks) with usual PPI treatment; Oral.	50	Patients 18-80 years old with EPI (fecal elastase below 100µg/g of stool and CFA% <80% after Washout Phase) caused by Chronic Pancreatitis, partial or total resection of the Pancreas or other condition	At least 6 days on study drug or placebo	Completed; Full report
Efficacy and Safety	STEA-VK00-US01	Efficacy and safety of two dosage regimens	Single-center, randomized, parallel, open-labeled	VIOKASE® 16; 8 or 16 tablets per day; Oral	17	Chronic pancreatitis patients >18 years of age with EPI	3 weeks of study drug	Completed; Full report

Reviewer Comment:
Of note, although the Sponsor's tabular listing of the clinical studies states that Study VIO16EPI07-01 included patients with EPI due to CP, partial or total resection of the pancreas or other conditions, the exclusion criteria specifically excludes causes of EPI other than CP and partial/total pancreas resection and lists the following examples: cystic fibrosis, primary sclerosing cholangitis, hemochromatosis, isolated enzyme deficiency, deficiency in activation of enzymes in the small intestine, etc.

REFERENCES

1. Ansaldi-Balocco N, Santini B, Sarchi C. Efficacy of pancreatic enzyme supplementation in children with cystic fibrosis: comparison of two preparations by random crossover study and a retrospective study of the same patients at two different ages. *J Pediatr Gastroenterol Nutr.* 1988;7 Suppl 1:S40-5.

2. Beker LT, Fink RJ, Hamsa FH. Comparison of Weight-Based Dosages of Enteric-coated Microtablet Enzyme Preparations in Patients with Cystic Fibrosis. Journal of Pediatric Gastroenterology and Nutrition.1994;19:191-97.

3. Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. *Journal of Pediatric Gastroenterology and Nutrition*. 2002;35:246-259.

4. Borowitz D, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. J Pediatr 1995;127:681–84.

5. Dobrilla G. Management of chronic pancreatitis. Focus on enzyme replacement therapy. *Int J Pancreatol*. 1989;5 Suppl:17-29.

6. Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr Gastroenterol Rep.* 2007;9(2):116-22.

7. Dutta SK, Hubbard VS, Appler M. Critical examination of therapeutic efficacy of a pH-sensitive enteric-coated pancreatic enzyme preparation in treatment of exocrine pancreatic insufficiency secondary to cystic fibrosis. *Dig Dis Sci.* 1988;33(10):1237-44. (Abstract only)

8. Ferrone M, Raimondo M, Scolapio JS. Pancreatic Enzyme Pharmacotherapy. *Pharmacotherapy.* 2007;27(6):910–920.

9. FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med* 1998;336:1283–1289.

10. George DE, Pinero R, Miller AM, et al. Comparison of Two Pancreatic Enzyme Supplements in Patients with Cystic Fibrosis. *Advances in Therapy.* 1990;7(3):109-118.

11. Insogna KL. The effect of proton pump-inhibiting drugs on mineral metabolism. *Am J Gastroenterol.* 2009; 104:Suppl 2:S2-4.

12. Iqbal CW, Moir CR, Ishitani MB. Management of chronic pancreatitis in the pediatric patient: endoscopic retrograde cholangiopancreatography vs operative therapy. J*ournal of Pediatric Surgery*. 2009;44:139–143.

13. Kalnins D, Corey M, Ellis L, Durie P, Pencharz P. Combining Unprotected Pancreatic Enzymes with Ph-Sensitive Enteric-Coated Microspheres Does Not Improve Nutrient Digestion in Patients with Cystic Fibrosis. *J Pediatr*. 2005;46:489-93.

14. Kalnins D, Durie P, Pencharz P. Nutritional management of cystic fibrosis patients. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2007; 10:348–354.

15. Kalnins D, Ellis L, Corey M. Enteric-Coated Pancreatic Enzyme with Bicarbonate Is Equal to Standard Enteric-Coated Enzyme in Treating Malabsorption in Cystic Fibrosis. *Journal of Pediatric Gastroenterology and Nutrition*. 2006;42:256-261.

16. Kleinman RE, ed. *Pediatric Nutrition Handbook*. 6th ed, American Academy of Pediatrics. 2009. 1001-1020.

17. Kraisinger M, Hochhaus G, Stecenko A, Bowser E, Hendeles L. Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and in vitro performance of microencapsulated formulations. *J Clin Pharmacol*. 1994. 34(2):158-66. (Abstract only)

18. Laine L. Proton pump inhibitors and bone fractures? *Am J Gastroenterol*. 2009; 104 Suppl 2:S21-6.

19. Mischler EH, Parrell S, Farrell PM, Odell GB. Comparison of effectiveness of pancreatic enzyme preparations in cystic fibrosis. *Am J Dis Child.* 1982;136(12):1060-3. (Abstract only)

20. Nydegger A, Couper RTL, Oliver MR. Childhood Pancreatitis. J*ournal of Gastroenterology and Hepatology*. 2006;21:499–509.

21. Robinson P. Nutritional status and requirements in cystic fibrosis. *Clinical Nutrition.* 2001;20: 81-86.

22. Tolia V, Boyer K. Long-term proton pump inhibitor use in children: a retrospective review of safety. *Dig Dis Sc*i. 2008;53(2):385-93.

23. Waljee AK, Dimagno MJ, Wu BU, Schoenfeld PS, Conwell DL. Systematic review: pancreatic enzyme treatment of malabsorption associated with chronic pancreatitis. *Aliment Pharmacol Ther*. 2009;29(3):235-46.

24. Wright MJ, Proctor DD, Insogna KL, Kerstetter JE. Proton pump-inhibiting drugs, calcium homeostasis, and bone health. *Nutr Rev*. 2008;66(2):103-8.

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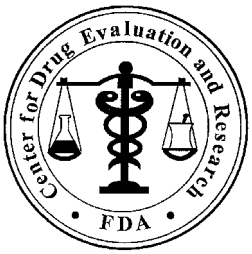
/s/

ELIZABETH L DURMOWICZ
02/01/2010

HARI C SACHS
02/02/2010
I agree with the recommendations in this consult

LISA L MATHIS
02/16/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 22, 2010
To:	Elizabeth A. Ford, Senior Regulatory Project Manager Division of Gastroenterology Products (DGP) Office of Drug Evaluation III
	Anil K. Rajpal, Medical Officer Division of Gastroenterology Products (DGP) Office of Drug Evaluation III
Through:	Laura Governale, Pharm.D., MBA Drug Use Data Analyst Team Leader Division of Epidemiology Office of Surveillance and Epidemiology
From:	Patty Greene, Pharm.D. Drug Use Data Analyst Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Viokase Drug Utilization
Drug Name(s):	Viokase® (pancrelipase)
Application Type/Number:	NDA 22-542
Applicant/sponsor:	Axcan Pharma
OSE RCM #:	2009-2473

1 INTRODUCTION

The Division of Gastroenterology Products (DGP) is evaluating the use of Viokase® (pancrelipase), an oral gastrointestinal agent, generally used for the treatment of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis or other conditions. Viokase® (pancrelipase) and other pancreatic enzyme products will be removed from the market by April 28, 2010 for an unapproved drug class action unless a determination for enforcement discretion is identified. In October 2009, an NDA application was received for *Viokace* (pancrelipase), NDA 22-542, with a proposed indication for the treatment of EPI in combination with a proton pump inhibitor. In support of that assessment, the Division of Epidemiology (DEPI) has been requested to provide total dispensed prescriptions by product form (enteric coated vs. non-enteric coated), total patients and diagnosis data in pediatric patients ages 0-1, 2-11, 12-17, and adults 18 years or older for Viokase® (pancrelipase) and other pancreatic enzyme products for years 2002 to 2009. Diagnosis data comparing the use of pancreatic enzyme products for cystic fibrosis, pancreatitis, and abdominal pain are also provided.

2 METHODS AND MATERIAL

2.1 DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives™ (see ***Appendix 2*** for database descriptions) was used to determine the various retail and non-retail channels of distribution for Viokase® (pancrelipase). The examination of sales data by number of bottles sold for the 12-month period ending in November 2009 indicates that the majority of the sales distribution is toward retail pharmacy settings (50%).[1] Retail pharmacy settings include chain stores, independent pharmacies and food stores. Non-retail settings (mainly federal facilities) accounted for approximately 28% of sales followed by mail order pharmacy with about 22% of sales distribution. For the purpose of this review, we examined outpatient retail pharmacy settings, excluding non-retail and mail order channels.

2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

Outpatient use and patient demographics were measured from SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT). Indications for use were obtained from the SDI's Physician Drug and Diagnosis Audit (PDDA). From these data sources, estimates of the number of dispensed prescriptions and patients by age, as well as the top diagnosis codes associated with the use of Viokase® (pancrelipase) and other pancreatic enzyme products by office-based physicians, were obtained for years 2002-2009, inclusive (***Appendix 2***).

3 RESULTS

3.1 OUTPATIENT DISPENSED PRESCRIPTIONS

Tables 1 and 2 in Appendix 1 provide the total number of dispensed prescriptions for pancreatic enzyme products by product form in outpatient retail pharmacies for years 2002-2009. Enteric coated products accounted for the majority of the market share with ~893,000 prescriptions (90%) in year 2009 compared to non-enteric coated products with ~100,000 prescriptions (10%). Overall, total dispensed prescriptions for pancreatic enzyme products increased by 10% from year 2002 to year 2009. For enteric coated

[1] IMS Health, IMS Nationals Sales Perspectives™, December 2008- November 2009. Data extracted 01/10. File: 1001viok.DVR

products, the number of dispensed prescriptions increased by 18% from 754,000 prescriptions in year 2002 to ~893,000 in year 2009. The number of dispensed prescriptions for non-enteric coated products decreased by 34% from 151,000 prescriptions in year 2002 to 100,000 prescriptions in year 2009. In year 2009, Viokase accounted for approximately 88% of the non-enteric coated pancreatic enzyme market.

Table 3 in Appendix 1 provides the total number of dispensed prescription for Viokase® (pancrelipase) by patient age (0-1, 2-11, 12-17, 18+ years) in outpatient retail pharmacies for years 2002-2009. Prescription utilization increased by 27% for the review period. In year 2009, adult patients aged 18 years and older accounted for the majority of the prescription share with more than 85,000 prescriptions (96%) compared to pediatric patients with ~3,100 prescriptions (less than 4% of the prescription share). Approximately 1,900 prescriptions were dispensed to pediatric patients aged 2-11 years old (2.1% of the prescription share) in year 2009 followed by pediatric patients aged 12-17 years old with 970 prescriptions (1.1% of the prescription share). Pediatric patients aged 0-1 years old accounted for less than 1% of the prescription share in year 2009.

3.2 PROJECTED PATIENTS

Trends for patient data were similar to that of prescription data (***Appendix 1: Table 4***). The total number of patients who received a prescription for Viokase® (pancrelipase) increased by 29% from ~21,000 patients in year 2002 to ~27,000 patients in year 2009. In year 2009, adult patients aged 18 years and older accounted for the majority of the patient share with nearly 25,000 patients (94%) compared to pediatric patients with less than 4% of the patient share. Approximately 600 patients filled a prescription for Viokase® (pancrelipase) in pediatric patients aged 2-11 years old (2.1% of the patient share) during year 2009 followed by pediatric patients aged 12-17 years old with ~400 prescriptions (1.5% of the patient share). Pediatric patients aged 0-1 years old accounted for less than 1% of the patient share in year 2009.

3.3 DIAGNOSIS CODES ASSOCIATED WITH DRUG USE

We also examined the most common diagnosis codes associated with the use of products in the selected market by patient age from January 1, 2002 to November 30, 2009 (***Appendix 1: Tables 5 and 6***). According to office-based physician practices in the U.S., "Acute Pancreatitis" (ICD-9 577.0) was the top diagnosis code associated with the use of pancreatic enzyme products for the review period (22%) for all ages. The second most common use was "Chronic Pancreatitis" (ICD-9 577.1) for the same period (21%) followed by "Pancreatic Disease Nec" (ICD-9 577.8) and "Cystic Fibrosis" (ICD-9 277.0) with 13% and 6% of drug mentions, respectively. Adult patients aged 18 years or older accounted for the majority of use for pancreatic indications. For EPI associated with cystic fibrosis, pediatric patients aged 2-11 years old received the most drug mentions by physician survey (55%) ***(Table 5)***. Drug mentions recorded for "Abdominal pain" (ICD-9 789.0), roughly 3% of drug mentions, were below the acceptable count allowable to provide a reliable estimate of use. No mentions were recorded in pediatric patients for the diagnosis of abdominal pain ***(Table 6)***.

4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Viokase® (pancrelipase) was distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

5 CONCLUSIONS

In the outpatient retail pharmacy setting, enteric coated products accounted for the majority of the market share with ~893,000 prescriptions compared to non-enteric coated products with ~100,000 prescriptions in year 2009. Overall, total dispensed prescriptions for pancreatic enzyme products increased by 10% from year 2002 to year 2009. Prescription and patient utilization for Viokase® (pancrelipase) increased by 27% and 29%, respectively, for the review period. Pediatric patients accounted for less than 4% of the total share. "Acute Pancreatitis" (ICD-9 577.0) was the top diagnosis code associated with the use of pancreatic enzyme products in adult patients aged 18 years or older for the review period. Based on physician survey data, there is limited data to describe pediatric use of pancreatic enzyme products for cystic fibrosis and pancreatic indications. No mentions were recorded in pediatric patients for the diagnosis of abdominal pain.

APPENDIX 1: TABLES

Table 1. Total number of dispensed prescriptions by product form through U.S. outpatient retail pharmacies for selected pancreatic enzyme products, Years 2002 - 2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Market	**905,186**	***100.0%***	**901,219**	***100.0%***	**869,650**	***100.0%***	**845,041**	***100.0%***	**858,580**	***100.0%***	**911,088**	***100.0%***	**982,208**	***100.0%***	**993,011**	***100.0%***
Enteric Coated	753,976	*83.3%*	751,699	*83.4%*	730,866	*84.0%*	716,460	*84 8%*	734,531	*85.6%*	785,969	*86.3%*	855,898	*87.1%*	892,601	*89.9%*
Non-Enteric Coated	151,210	*16.7%*	149,520	*16.6%*	138,784	*16.0%*	128,581	*15 2%*	124,049	*14.5%*	125,119	*13.7%*	126,310	*12.9%*	100,411	*10.1%*

Source: SDI Vector One®: National, Data Extracted January 2010. File: VONA 2009-2473 Viokase Market 01-20-10.xls

Table 2. Total number of dispensed prescriptions through U.S. outpatient retail pharmacies for selected pancreatic enzyme products, Years 2002 - 2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Market	**905,186**	***100.0%***	**901,219**	***100.0%***	**869,650**	***100.0%***	**845,041**	***100.0%***	**858,580**	***100.0%***	**911,088**	***100.0%***	**982,208**	***100.0%***	**993,011**	***100.0%***
Enteric Coated	**753,976**	***83.3%***	**751,699**	***83.4%***	**730,866**	***84.0%***	**716,460**	***84.8%***	**734,531**	***85.6%***	**785,969**	***86.3%***	**855,898**	***87.1%***	**892,601**	***89.9%***
Creon 20	51,669	*6.9%*	46,496	*6.2%*	44,516	*6.1%*	59,724	*8.3%*	79,962	*10.9%*	106,987	*13.6%*	131,892	*15.4%*	124,324	*13.9%*
Creon	67	*0.0%*	34	--	26	--	20	--	2	--	11	--	12	--	110,980	*12.4%*
Creon 10	69,243	*9.2%*	57,507	*7.7%*	49,096	*6.7%*	62,070	*8.7%*	81,050	*11.0%*	96,327	*12.3%*	109,746	*12.8%*	109,097	*12.2%*
Creon 5	17,915	*2.4%*	15,844	*2.1%*	14,970	*2.1%*	16,429	*2.3%*	18,811	*2.6%*	20,481	*2.6%*	23,418	*2.7%*	18,359	*2.1%*
Ultrase MT20	41,379	*5.5%*	41,274	*5.5%*	40,636	*5.6%*	43,018	*6.0%*	44,862	*6.1%*	51,852	*6.6%*	59,561	*7.0%*	90,837	*10.2%*
Ultrase MT12	21,212	*2.8%*	20,511	*2.7%*	20,154	*2.8%*	19,347	*2.7%*	18,858	*2.6%*	17,094	*2.2%*	15,449	*1.8%*	21,288	*2.4%*
Ultrase	8,797	*1.2%*	7,458	*1.0%*	5,381	*0.7%*	7,134	*1.0%*	7,581	*1.0%*	7,692	*1.0%*	8,059	*0.9%*	16,331	*1.8%*
Ultrase MT18	8,982	*1.2%*	9,634	*1.3%*	10,026	*1.4%*	10,054	*1.4%*	11,083	*1.5%*	11,288	*1.4%*	11,146	*1.3%*	13,474	*1.5%*
Ultrase MT6	7	--	11	--	2	--	--	--	--	--	--	--	--	--	--	--
Pancrelipase 4500	--	--	--	--	--	--	--	--	--	--	--	--	400	*0.1%*	76,993	*8.6%*
Pancrelipase 10000	11,329	*1.5%*	2,201	*0.3%*	733	*0.1%*	475	*0.1%*	88	*0.0%*	31	--	3,563	*0.4%*	32,978	*3.7%*
Pancrelipase 20000	887	*0.1%*	210	*0.0%*	151	*0.0%*	14	--	7	--	8	--	1,934	*0.2%*	26,082	*2.9%*
Pancrelipase 16000	1,953	*0.3%*	487	*0.1%*	120	*0.0%*	27	--	2	--	--	--	252	*0.0%*	19,054	*2.1%*
Pancrelipase	15,326	*2.0%*	4,378	*0.6%*	2,989	*0.4%*	4,660	*0.7%*	1,686	*0.2%*	892	*0.1%*	898	*0.1%*	513	*0.1%*
Pancrelipase MT	2,627	*0.4%*	686	*0.1%*	222	*0.0%*	102	*0.0%*	83	*0.0%*	37	--	140	*0.0%*	129	*0.0%*
Pancrease MT 10	22,020	*2.9%*	19,173	*2.6%*	15,616	*2.1%*	14,330	*2.0%*	14,604	*2.0%*	17,061	*2.2%*	31,368	*3.7%*	44,830	*5.0%*
Pancrease MT 16	20,800	*2.8%*	18,945	*2.5%*	16,531	*2.3%*	15,457	*2.2%*	13,920	*1.9%*	14,172	*1.8%*	15,660	*1.8%*	24,847	*2.8%*
Pancrease MT 20	14,225	*1.9%*	13,344	*1.8%*	11,625	*1.6%*	11,848	*1.7%*	12,861	*1.8%*	14,714	*1.9%*	22,762	*2.7%*	31,805	*3.6%*
Pancrease MT 4	14,872	*2.0%*	14,724	*2.0%*	14,830	*2.0%*	15,397	*2.2%*	17,315	*2.4%*	19,868	*2.5%*	23,504	*2.8%*	29,007	*3.3%*
Pangestyme EC	33,065	*4.4%*	48,258	*6.4%*	55,356	*7.6%*	103,632	*14.5%*	132,903	*18.1%*	135,158	*17.2%*	152,640	*17.8%*	41,193	*4.6%*
Pangestyme CN 10	16,888	*2.2%*	23,440	*3.1%*	26,498	*3.6%*	35,795	*5.0%*	37,621	*5.1%*	48,772	*6.2%*	57,145	*6.7%*	15,031	*1.7%*
Pangestyme CN 20	12,649	*1.7%*	16,495	*2.2%*	19,039	*2.6%*	23,756	*3.3%*	25,897	*3.5%*	37,959	*4.8%*	54,178	*6.3%*	13,657	*1.5%*
Pangestyme MT 16	4,616	*0.6%*	7,274	*1.0%*	7,789	*1.1%*	11,275	*1.6%*	14,112	*1.9%*	17,812	*2.3%*	23,754	*2.8%*	6,547	*0.7%*
Pangestyme UL 20	3,619	*0.5%*	5,717	*0.8%*	5,373	*0.7%*	9,518	*1.3%*	8,431	*1.2%*	11,343	*1.4%*	16,673	*2.0%*	3,547	*0.4%*
Pangestyme UL 12	908	*0.1%*	1,506	*0.2%*	1,265	*0.2%*	2,473	*0.4%*	3,283	*0.5%*	3,611	*0.5%*	3,483	*0.4%*	662	*0.1%*
Pangestyme UL 18	954	*0.1%*	1,047	*0.1%*	788	*0.1%*	1,295	*0.2%*	1,367	*0.2%*	1,679	*0.2%*	1,679	*0.2%*	331	*0.0%*
Pancrecarb MS-16	--	--	--	--	258	*0.0%*	3,430	*0.5%*	4,595	*0.6%*	5,554	*0.7%*	5,824	*0.7%*	7,713	*0.9%*
Pancrecarb MS-8	7,174	*1.0%*	9,427	*1.3%*	9,394	*1.3%*	8,449	*1.2%*	6,891	*0.9%*	6,361	*0.8%*	6,280	*0.7%*	5,573	*0.6%*
Pancrecarb MS-4	1,024	*0.1%*	1,454	*0.2%*	1,898	*0.3%*	2,138	*0.3%*	2,430	*0.3%*	2,282	*0.3%*	2,009	*0.2%*	2,496	*0.3%*
Lipram	106,390	*14.1%*	114,741	*15.3%*	115,320	*15.8%*	71,720	*10.0%*	49,681	*6.8%*	36,731	*4.7%*	15,629	*1.8%*	1,090	*0.1%*
Lipram-PN10	9,406	*1.3%*	11,615	*1.6%*	14,654	*2.0%*	14,693	*2.1%*	18,619	*2.5%*	24,992	*3.2%*	13,401	*1.6%*	802	*0.1%*
Lipram-PN20	7,297	*1.0%*	10,375	*1.4%*	11,998	*1.6%*	12,109	*1.7%*	13,027	*1.8%*	15,967	*2.0%*	7,957	*0.9%*	500	*0.1%*
Lipram-PN16	7,307	*1.0%*	9,430	*1.3%*	10,140	*1.4%*	5,811	*0.8%*	5,462	*0.7%*	5,688	*0.7%*	3,599	*0.4%*	150	*0.0%*
Lipram-CR 10	50,183	*6.7%*	61,732	*8.2%*	60,583	*8.3%*	34,360	*4.8%*	22,200	*3.0%*	4,516	*0.6%*	588	*0.1%*	101	*0.0%*
Lipram-UL20	12,423	*1.7%*	16,338	*2.2%*	14,798	*2.0%*	9,247	*1.3%*	7,461	*1.0%*	4,743	*0.6%*	446	*0.1%*	49	*0.0%*
Lipram-CR20	31,495	*4.2%*	42,319	*5.6%*	45,476	*6.2%*	26,100	*3.6%*	18,625	*2.5%*	3,244	*0.4%*	375	*0.0%*	31	--
Lipram-UL12	3,871	*0.5%*	4,942	*0.7%*	4,738	*0.7%*	2,669	*0.4%*	1,078	*0.2%*	157	*0.0%*	14	--	28	--
Lipram-UL18	1,871	*0.3%*	1,982	*0.3%*	2,055	*0.3%*	1,505	*0.2%*	675	*0.1%*	159	*0.0%*	138	*0.0%*	20	--
Lipram-CR5	906	*0.1%*	2,934	*0.4%*	3,524	*0.5%*	2,951	*0.4%*	316	*0.0%*	32	--	11	--	2	--
Zenpep	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**546**	***0.1%***
Ultracaps MT-20	--	--	--	--	--	--	305	*0.0%*	1,315	*0.2%*	1,398	*0.2%*	1,675	*0.2%*	280	*0.0%*
Palcaps 10	--	--	--	--	--	--	638	*0.1%*	2,031	*0.3%*	3,752	*0.5%*	3,488	*0.4%*	252	*0.0%*
Palcaps 20	--	--	--	--	--	--	552	*0.1%*	1,989	*0.3%*	3,802	*0.5%*	4,769	*0.6%*	242	*0.0%*
Lapase	--	--	--	--	1,879	*0.3%*	5,518	*0.8%*	6,324	*0.9%*	8,501	*1.1%*	6,781	*0.8%*	239	*0.0%*
Dygase	--	--	--	--	1,822	*0.3%*	5,054	*0.7%*	5,949	*0.8%*	8,920	*1.1%*	5,270	*0.6%*	183	*0.0%*
Pancrease	103,187	*13.7%*	77,277	*10.3%*	59,345	*8.1%*	32,693	*4.6%*	8,423	*1.2%*	1,131	*0.1%*	454	*0.1%*	181	*0.0%*
Ku-Zyme HP	10,477	*1.4%*	9,268	*1.2%*	8,652	*1.2%*	8,000	*1.1%*	9,736	*1.3%*	10,786	*1.4%*	5,939	*0.7%*	56	*0.0%*
Panocaps MT 16	--	--	--	--	--	--	157	*0.0%*	599	*0.1%*	1,159	*0.2%*	943	*0.1%*	51	*0.0%*
Panocaps MT 20	--	--	--	--	--	--	236	*0.0%*	481	*0.1%*	985	*0.1%*	842	*0.1%*	45	*0.0%*
All Others	4,956	*0.7%*	1,211	*0.2%*	600	*0.1%*	275	*0.0%*	235	*0.0%*	260	*0.0%*	150	*0.0%*	79	*0.0%*
Non-Enteric Coated	**151,210**	***16.7%***	**149,520**	***16.6%***	**138,784**	***16.0%***	**128,581**	***15.2%***	**124,049**	***14.5%***	**125,119**	***13.7%***	**126,310**	***12.9%***	**100,411**	***10.1%***
Viokase	**69,527**	***46.0%***	**62,132**	***41.6%***	**51,076**	***36.8%***	**48,999**	***38.1%***	**50,640**	***40.8%***	**55,265**	***44.2%***	**68,294**	***54.1%***	**88,728**	***88.4%***
Plaretase 8000	3,240	*2.1%*	13,888	*9.3%*	20,737	*14.9%*	30,985	*24.1%*	34,368	*27.7%*	34,990	*28.0%*	37,773	*29.9%*	10,087	*10.1%*
Panokase	44,345	*29.3%*	44,014	*29.4%*	44,331	*31.9%*	35,802	*27.8%*	26,371	*21.3%*	22,832	*18.3%*	13,099	*10.4%*	976	*1.0%*
Panokase-16	--	--	2,319	*1.6%*	6,867	*5.0%*	9,387	*7.3%*	10,948	*8.8%*	11,352	*9.1%*	6,920	*5.5%*	520	*0.5%*
Pancrelipase 8000	--	--	--	--	--	--	77	*0.1%*	327	*0.3%*	415	*0.3%*	98	*0.1%*	52	*0.1%*
Pancrelipase MT	30,886	*20.4%*	25,248	*16.9%*	15,197	*11.0%*	3,193	*2.5%*	1,361	*1.1%*	238	*0.2%*	104	*0.1%*	39	*0.0%*
Pancrelipase	3,206	*2.1%*	1,877	*1.3%*	575	*0.4%*	136	*0.1%*	23	*0.0%*	3	--	16	*0.0%*	9	*0.0%*
Paltrase V8	6	--	42	*0.0%*	1	--	2	--	11	*0.0%*	24	*0.0%*	6	--	--	--

Source: SDI Vector One®: National, Data Extracted January 2010. File: VONA 2009-2473 Viokase Market 01-20-10.xls

Table 3. Total number of dispensed prescriptions by patient age (0-1, 2-11, 12-17, 18+ years) through U.S. outpatient retail pharmacies for Viokase (pancrelipase), Years 2002 - 2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Viokase	**69,845**	***100.0%***	**62,211**	***100.0%***	**51,073**	***100.0%***	**48,985**	***100.0%***	**50,645**	***100.0%***	**55,295**	***100.0%***	**68,267**	***100.0%***	**88,728**	***100.0%***
Age 0-1	170	*0.2%*	226	*0.4%*	142	*0.3%*	59	*0.1%*	163	*0.3%*	182	*0.3%*	172	*0.3%*	243	*0.3%*
Age 2-11	1,371	*2.0%*	1,286	*2.1%*	1,255	*2.5%*	1,449	*3.0%*	1,310	*2.6%*	1,485	*2.7%*	1,467	*2.2%*	1,888	*2.1%*
Age 12-17	784	*1.1%*	699	*1.1%*	701	*1.4%*	735	*1.5%*	803	*1.6%*	985	*1.8%*	939	*1.4%*	970	*1.1%*
Age 18+	66,806	*95.7%*	59,267	*95.3%*	47,945	*93.9%*	45,940	*93.8%*	47,622	*94.0%*	52,335	*94.7%*	65,341	*95.7%*	85,294	*96.1%*
UNSPEC	714	*1.0%*	733	*1 2%*	1,030	*2.0%*	802	*1.6%*	747	*1.5%*	308	*0.6%*	348	*0.5%*	333	*0.4%*

Source: SDI Vector One®: National, Data Extracted January 2010. File: VONA 2009-2473 Viokase by Age 01-15-10. xls

Table 4. Total number of projected patients (ages 0-1, 2-11, 12-17, 18+) who filled a prescription for Viokase (pancrelipase) in U.S. outpatient retail pharmacies, Years 2002 - 2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	Patients	*Share*	Patients	*Share*	Patients	*Share*	Patients	*Share*	Patients	*Share*	Patients	*Share*	Patients	*Share*	Patients	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	**20,649**	***100.0%***	**19,544**	***100.0%***	**15,290**	***100.0%***	**15,199**	***100.0%***	**16,720**	***100.0%***	**17,979**	***100.0%***	**22,650**	***100.0%***	**26,694**	***100.0%***
Age 0-1	99	*0.5%*	122	*0.6%*	84	*0.6%*	39	*0.3%*	83	*0.5%*	108	*0.6%*	126	*0.6%*	113	*0.4%*
Age 2-11	502	*2.4%*	476	*2.4%*	426	*2.8%*	440	*2.9%*	403	*2.4%*	455	*2.5%*	490	*2.2%*	566	*2.1%*
Age 12-17	275	*1.3%*	228	*1.2%*	210	*1.4%*	239	*1.6%*	252	*1.5%*	313	*1.7%*	316	*1.4%*	394	*1.5%*
Age 18+	19,776	*95.8%*	18,488	*94.6%*	14,206	*92.9%*	14,177	*93.3%*	15,676	*93.8%*	16,972	*94.4%*	21,529	*95.1%*	24,985	*93.6%*
UNSPEC	153	*0.7%*	526	*2.7%*	643	*4.2%*	577	*3.8%*	631	*3.8%*	390	*2.2%*	496	*2.2%*	1,288	*4.8%*

*Subtotals may not sum exac ly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.
Source: SDI Total Patient Tracker. File: TPT 2009-2473 Viokase 01-19-10.xls

Table 5. Top 4 Diagnoses associated with the use* of selected market by patient age (0-1, 2-11, 12-17, 18+) as reported by office-based physician practices, January 1, 2002 - November 30, 2009

	1/2002-11/2009									
	Total		Age 0-1		Age 2-11		Age 12-17		Age 18+	
	Uses (000)	Share %	Uses (000)	Horz. Share %	Uses (000)	Horz. Share %	Uses (000)	Horz. Share %	Uses (000)	Horz. Share %
TOTAL MARKET	**1,834**	***100.0%***	**11**	***0.6%***	**62**	***3.4%***	**23**	***1.2%***	**1,738**	***94.8%***
5770 ACUTE PANCREATITIS	398	*21.7%*	--	--	--	--	8	*2.1%*	389	*97.9%*
Viokase	**87**	***21.9%***	**--**	**--**	**--**	**--**	**3**	***2.9%***	**85**	***97.1%***
Pancrease	83	*20.9%*	--	--	--	--	--	--	83	*100.0%*
Pancrease MT 4	39	*9.8%*	--	--	--	--	6	*15.3%*	33	*84.7%*
Pancrease MT 10	29	*7.3%*	--	--	--	--	--	--	29	*100.0%*
Pancrease MT 16	10	*2.5%*	--	--	--	--	--	--	10	*100.0%*
Creon 10	45	*11.3%*	--	--	--	--	--	--	45	*100.0%*
Creon	21	*5.3%*	--	--	--	--	--	--	21	*100.0%*
Creon 20	12	*3.0%*	--	--	--	--	--	--	12	*100.0%*
Pancreatic Enzymes	27	*6.8%*	--	--	--	--	--	--	27	*100.0%*
Ultrase MT20	20	*5.0%*	--	--	--	--	--	--	20	*100.0%*
Pangestyme Unspec	7	*1.8%*	--	--	--	--	--	--	7	*100.0%*
Cotazym	6	*1.5%*	--	--	--	--	--	--	6	*100.0%*
Ultrase MT18	5	*1.3%*	--	--	--	--	--	--	5	*100.0%*
Pancrelipase	4	*1.0%*	--	--	--	--	--	--	4	*100.0%*
All Others	3	*0.8%*	--	--	--	--	--	--	3	*100.0%*
5771 CHRONIC PANCREATITIS	377	*20.6%*	--	--	--	--	4	*1.1%*	373	*98.9%*
Viokase	**80**	***21.2%***	**--**	**--**	**--**	**--**	**--**	**--**	**80**	***100.0%***
Creon	68	*18.0%*	--	--	--	--	--	--	68	*100.0%*
Creon 10	38	*10.1%*	--	--	--	--	--	--	38	*100.0%*
Creon 20	18	*4.8%*	--	--	--	--	--	--	18	*100.0%*
Pancrease	58	*15.4%*	--	--	--	--	--	--	58	*100.0%*
Pancrease MT 10	27	*7.2%*	--	--	--	--	--	--	27	*100.0%*
Pancrease MT 16	10	*2.7%*	--	--	--	--	--	--	10	*100.0%*
Pancrease MT 20	11	*2.9%*	--	--	--	--	--	--	11	*100.0%*
Pancrease MT 25	4	*1.1%*	--	--	--	--	--	--	4	*100.0%*
Pancrease MT 4	9	*2.4%*	--	--	--	--	--	--	9	*100.0%*
Pancrease MT Unspec	4	*1.1%*	--	--	--	--	4	*100.0%*	--	--
Pancreatic Enzymes	4	*1.1%*	--	--	--	--	--	--	4	*100.0%*
Pangestyme Unspec	18	*4.8%*	--	--	--	--	--	--	18	*100.0%*
Pancrelipase	14	*3.7%*	--	--	--	--	--	--	14	*100.0%*
Lipram	13	*3.4%*	--	--	--	--	--	--	13	*100.0%*
5778 PANCREATIC DISEASE NEC	246	*13.4%*	--	--	--	--	--	--	246	*100.0%*
Viokase	**50**	***20.3%***	**--**	**--**	**--**	**--**	**--**	**--**	**50**	***100.0%***
Creon 10	35	*14.2%*	--	--	--	--	--	--	35	*100.0%*
Creon	31	*12.6%*	--	--	--	--	--	--	31	*100.0%*
Creon 20	19	*7.7%*	--	--	--	--	--	--	19	*100.0%*
Pancrease	27	*11.0%*	--	--	--	--	--	--	27	*100.0%*
Pancrease MT 10	26	*10.6%*	--	--	--	--	--	--	26	*100.0%*
Pancrease MT 16	7	*2.8%*	--	--	--	--	--	--	7	*100.0%*
Pancrease MT 4	5	*2.0%*	--	--	--	--	--	--	5	*100.0%*
Pancrease MT 20	3	*1.2%*	--	--	--	--	--	--	3	*100.0%*
Ultrase MT12	11	*4.5%*	--	--	--	--	--	--	11	*100.0%*
Ultrase MT20	5	*2.0%*	--	--	--	--	--	--	5	*100.0%*
Pancreatic Enzymes	11	*4.5%*	--	--	--	--	--	--	11	*100.0%*
Pancrelipase	7	*2.8%*	--	--	--	--	--	--	7	*100.0%*
Lipram	6	*2.4%*	--	--	--	--	--	--	6	*100.0%*
Cotazym	3	*1.2%*	--	--	--	--	--	--	3	*100.0%*
2770 CYSTIC FIBROSIS	114	*6.2%*	11	*9.8%*	62	*54.6%*	10	*9.1%*	30	*26.5%*
Pancreatic Enzymes	37	*32.5%*	--	--	27	*73.2%*	4	*11.1%*	6	*15.7%*
Creon 20	24	*21.1%*	--	--	--	--	--	--	24	*100.0%*
Creon	12	*10.5%*	6	*50.5%*	6	*49.5%*	--	--	--	--
Creon 10	6	*5.3%*	--	--	6	*100.0%*	--	--	--	--
Ultrase MT12	16	*14.0%*	--	--	10	*61.4%*	6	*38.6%*	--	--
Ultrase Unspec	5	*4.4%*	5	*100.0%*	--	--	--	--	--	--
Pancrease	6	*5.3%*	--	--	6	*100.0%*	--	--	--	--
Pancrecarb Unspec	6	*5.3%*	--	--	6	*100.0%*	--	--	--	--

Source: SDI Physician Drug and Diagnosis Audit, Extracted January 2010. File: PDDA 2009-2473 Viokase Dx4 01-20-10.xls

* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular diseas

Table 6. Top 10 Diagnoses associated with the use* of selected market by patient age (0-1, 2-11, 12-17, 18+) as reported by office-based physician practices, January 1, 2002 - November 30, 2009

	1/2002-11/2009									
	Total		Age 0-1		Age 2-11		Age 12-17		Age 18+	
	Uses	Share	Uses	Horz. Share	Uses	Horz. Share	Uses	Horz. Share	Uses	Horz. Share
	(000)	%	(000)	%	(000)	%	(000)	%	(000)	%
TOTAL MARKET	**1,834**	***100.0%***	**11**	***0.6%***	**62**	***3.4%***	**23**	***1.2%***	**1,738**	***94.8%***
5770 ACUTE PANCREATITIS	398	*21.7%*	--	--	--	--	8	*2.1%*	389	*97.9%*
5771 CHRONIC PANCREATITIS	377	*20.6%*	--	--	--	--	4	*1.1%*	373	*98.9%*
5778 PANCREATIC DISEASE NEC	246	*13.4%*	--	--	--	--	--	--	246	*100.0%*
2770 CYSTIC FIBROSIS	114	*6.2%*	11	*9.8%*	62	*54.6%*	10	*9.1%*	30	*26.5%*
7873 FLATUL/ERUCTAT/GAS PAIN	104	*5.7%*	--	--	--	--	--	--	104	*100.0%*
Creon 20	70	*67.3%*	--	--	--	--	--	--	70	*100.0%*
Creon	13	*12.5%*	--	--	--	--	--	--	13	*100.0%*
Creon 10	3	*2.9%*	--	--	--	--	--	--	3	*100.0%*
Pancrease MT 10	9	*8.7%*	--	--	--	--	--	--	9	*100.0%*
Ultrase MT12	5	*4.8%*	--	--	--	--	--	--	5	*100.0%*
Ultrase MT20	3	*2.9%*	--	--	--	--	--	--	3	*100.0%*
7879 GI SYSTEM SYMPTOMS NEC	90	*4.9%*	--	--	--	--	--	--	90	*100.0%*
Ultrase MT20	18	*20.0%*	--	--	--	--	--	--	18	*100.0%*
Ultrase MT12	3	*3.3%*	--	--	--	--	--	--	3	*100.0%*
Pancrease	17	*18.9%*	--	--	--	--	--	--	17	*100.0%*
Pancrease MT 10	10	*11.1%*	--	--	--	--	--	--	10	*100.0%*
Pancrease MT 4	5	*5.6%*	--	--	--	--	--	--	5	*100.0%*
Pancrease MT 16	4	*4.4%*	--	--	--	--	--	--	4	*100.0%*
Creon 20	16	*17.8%*	--	--	--	--	--	--	16	*100.0%*
Creon 10	10	*11.1%*	--	--	--	--	--	--	10	*100.0%*
Creon	2	*2.2%*	--	--	--	--	--	--	2	*100.0%*
Lipram	4	*4.4%*	--	--	--	--	--	--	4	*100.0%*
5368 STOMACH FUNCTION DIS NEC	54	*2.9%*	--	--	--	--	--	--	54	*100.0%*
Creon 10	13	*24.1%*	--	--	--	--	--	--	13	*100.0%*
Pancrease	13	*24.1%*	--	--	--	--	--	--	13	*100.0%*
Pancrease MT 10	5	*9.3%*	--	--	--	--	--	--	5	*100.0%*
Pancrease MT 16	6	*11.1%*	--	--	--	--	--	--	6	*100.0%*
Pancrease MT 4	6	*11.1%*	--	--	--	--	--	--	6	*100.0%*
Lipram	6	*11.1%*	--	--	--	--	--	--	6	*100.0%*
Viokase	**5**	***9.3%***	**--**	**--**	**--**	**--**	**--**	**--**	**5**	***100.0%***
7890 ABDOMINAL PAIN	**51**	***2.8%***	**--**	**--**	**--**	**--**	**--**	**--**	**51**	***100.0%***
Viokase	**15**	***29.4%***	**--**	**--**	**--**	**--**	**--**	**--**	**15**	***100.0%***
Ultrase MT12	13	*25.5%*	--	--	--	--	--	--	13	*100.0%*
Creon 10	9	*17.6%*	--	--	--	--	--	--	9	*100.0%*
Creon 20	7	*13.7%*	--	--	--	--	--	--	7	*100.0%*
Pancrease MT 16	5	*9.8%*	--	--	--	--	--	--	5	*100.0%*
Pancrease	2	*3.9%*	--	--	--	--	--	--	2	*100.0%*
1579 MALIG NEO PANCREAS NOS	41	*2.2%*	--	--	--	--	--	--	41	*100.0%*
Viokase	17	*41.5%*	--	--	--	--	--	--	17	*100.0%*
Pancrease	15	*36.6%*	--	--	--	--	--	--	15	*100.0%*
Pancrease MT 16	6	*14.6%*	--	--	--	--	--	--	6	*100.0%*
Pancreatic Enzymes	3	*7.3%*	--	--	--	--	--	--	3	*100.0%*
5920 CALCULUS OF KIDNEY	30	*1.6%*	--	--	--	--	--	--	30	*100.0%*
Pancrease	30	*100.0%*	--	--	--	--	--	--	30	*100.0%*
All Others	331	*100.0%*	--	--	--	--	--	--	331	*100.0%*

Source: SDI Physician Drug and Diagnosis Audit, Extracted January 2010. File: PDDA 2009-2473 Viokase Dx4 01-20-10.xls

* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease

APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATTY A GREENE
02/01/2010
Data cleared 2/1/2010 IMS/SDI

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022542 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Viokase Established/Proper Name: pancrelipase Dosage Form: Tablets Strengths: 10,440 USP Lipase Units; 20,880 USP Lipase Units		
Applicant: Axcan Pharma US, Inc. Agent for Applicant (if applicable): CanReg Inc.		
Date of Application: 10/29/2009 Date of Receipt: 10/30/2009 Date clock started after UN:		
PDUFA Goal Date: 8/30/2010	Action Goal Date (if different):	
Filing Date: 12/29/2009	Date of Filing Meeting: 12/9/2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7		
Proposed indication(s)/Proposed change(s): Treatment of exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (b) (4)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☒ Fast Track ☒ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 060716	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Paid 4/24/2009: $1,247,200 (FY 2009 fee since first reviewable unit received FY2009)

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small*

business waiver, orphan exemption).

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	X			Axcan claims exclusivity for Viokase (pancrelipase) Tablets, but does not specifically request years of exclusivity.

therefore, requesting exclusivity is not required.				

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?		**X**		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		**X**		
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	

If yes, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?		X		Not located in 1.1 or 1.3.5.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***		X		Partial waiver and partial deferral included, but a pediatric plan is not included.
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***		X		Certifications are missing.
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** February 7, 2007, October 4, 2006 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 17, 2007 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** December 29, 2006 **No Agreement** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		No Agreement on SPA

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 8, 2009

BLA/NDA/Supp #: NDA 022542

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: pancrelipase, USP

DOSAGE FORM/STRENGTH: Uncoated Tablets

APPLICANT: Axcan Pharma US, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (b) (4).

BACKGROUND: NDA 022542 was submitted as a Rolling Review, with the first reviewable unit received on April 28, 2009. The final submission was received on October 30, 2009. A standard review cycle will place the PDUFA goal date outside the October 26, 2007 Federal Register-mandated AP deadline of April 28, 2010.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Ford, R.N.	Y
	CPMS/TL:	Brian Strongin, R.Ph., M.B.A.	Y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal, M.D.		Y
Clinical	Reviewer:	Marjorie Dannis, M.D.	Y
	TL:	Anil Rajpal, M.D.	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial*	Reviewer:		

products)			
	TL:		
Clinical Pharmacology	Reviewer:	Jee Eun Lee, Ph.D.	Y
	TL:	Jang Ik Lee, Ph.D.	Y
Biostatistics	Reviewer:	Mike Welch, Ph.D.	Y
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:	David Joseph, Ph.D.	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Wei Guo, Ph.D.	Y
	TL:	Emanuela Lacana, Ph.D.	Y
Quality Microbiology *(for sterile products)* **Consulted for review of microbial attributes of this NDA (this is not a sterile product).	Reviewer:	Denise Miller, Ph.D.**	N
	TL:	James McVey, Ph.D.	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Donald Obenhuber	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Irene Chan	Y
	TL:	Melina Griffis	N
OSE/DRISK (REMS)	Reviewer:	Steve Morin	N
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		

	TL:		

Other reviewers		
Other attendees	Kathleen Joyce, OC/DNDLC Maria Walsh, ADRA, ODE III Joyce Korvick, DD Safety, DGP Nitin Patel, RPM, OSE	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: No comprehensive table of contents	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

mitigation, treatment or prevention of a disease	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Comments:	

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Agency will request for the environmental assessment from the sponsor.	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: Consulted for review of microbial attributes of this NDA (this is not a sterile product).	☐ Not Applicable ☐ YES ☒ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, M.D. **21st Century Review Milestones (see attached)** (optional): Filing date: 12/29/09, Day 74: 1/12/09, Midcycle meeting: 3/8/2010, Wrap Up meeting: 5/18/09, Target date: 7/7/09. **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Other: Contact sponsor to identify location of, or to submit, the EA/request for categorical exclusion, and a comprehensive table of contents.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH A FORD
12/11/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 022542

Name of Drug: Tradename (pancrelipase) Tablets

Applicant: Axcan Pharma US, Inc.

Material Reviewed:

Submission Date(s): October 29, 2009, November 2, 2009

Receipt Date(s): October 30, 2009, November 2, 2009

Submission Date of Structure Product Labeling (SPL): November 2, 2009

Type of Labeling Reviewed: WORD and SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

I. Highlights of Prescribing Information

a) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

b) The highlights limitation statement must read as follows: "These highlights do not include all the information needed to use Tradename safely and effectively. See full prescribing information for Tradename. [See 21 CFR 201.57(a)(1)]

c) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)] This information is missing in the SPL version of the label.

d) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].

e) Remove the optional heading "Drug Interactions."

f) Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

g) There should be white space between each major heading in Highlights.

h) The patient counseling information statement should read "**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**."

II. Full Prescribing Information: Contents – Table of Contents

a) The Agency recommends use of a two-column format for the Table of Contents, and if possible, that it be limited in length to one-half page. This is adequately formatted in SPL, but not in WORD.

b) If the Highlights and Table of Contents do not fit on one page, insert the Table of Contents on page 2 of the labeling.

c) Since SPL R4 validation does not permit the inclusion of the Medication Guide (MG) as a subsection under the Patient Counseling Information section, do not include the MG as a subsection heading in the Table of Contents.

III. Full Prescribing Information (FPI)

a) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not See *Pediatric Use* (8.4). The cross reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. This is not done consistently throughout the document.

b) Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10), use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

c) In the ADVERSE REACTIONS section, subsection 6.1 is entitled (b) (4) This subsection should be entitled Clinical Trials Experience.

d) In the ADVERSE REACTIONS section, Clinical Trials Experience subsection, include the following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials: "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 rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

e) The Patient Counseling Information must reference any FDA-approved patient labeling. The phrase "See Medication Guide" is appropriately placed at the beginning of the subsection; however, since SPL R4 validation does not permit the inclusion of the MG as a subsection, the MG should not be a subsection under the Patient Counseling Information section. Include at the end without numbering as a subsection.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by March 16, 2010. This updated version of labeling will be used for further labeling discussions.

Elizabeth A.S. Ford, R.N.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

Drafted: EASF/11-24-2009
Revised/Initialed: BKS/11-25-2009
Finalized: EASF/11-27-2009
Filename:
CSO LABELING REVIEW OF PLR FORMAT

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH A FORD
11/27/2009

BRIAN K STRONGIN
11/29/2009