Summary Basis for Regulatory Action

Date	03 Jan 2011
From	L. Ross Pierce, M.D., Committee Chair
Subject	Summary Basis for Regulatory Action
BLA Supplement#	STN 125267/312
Applicant	ViroPharma Inc.
Date of Submission	11 March 2011, plus various subsequent amendments through 13 December 2011
PDUFA Goal Date	09 January 2012
Proprietary Name / Established (USAN) names	Cinryze/ C1 Esterase Inhibitor (Human), Nanofiltered
Proposed Indication(s)	For routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE))
Recommended Action:	Approval
Signatory Authorities Action:	**Approval** **Basil Golding**_____ *Offices Signatory Authority:* □ *I concur with the summary review* □ *I concur with the summary review and include a separate review or addendum to add further analysis* □ *I do not concur with the summary review and include a separate review or addendum*

Reviewer Names
Clinical: L. Ross Pierce, M.D.
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Epidemiology: Not applicable
Pharmacology/ Toxicology: Not applicable.
BioResearch Monitoring: Not applicable
Facilities: Not applicable
Advisory Committee Transcript: Not applicable

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1. Introduction

This submission is a Biologics License Prior Approval Supplement (PAS) from ViroPharma Inc. to the Biologics License Application (BLA) for Cinryze (C1 Esterase Inhibitor (Human) (STN 125267). Cinryze is available in a lyophilized formulation, and has been licensed since 2008 for the following indication:

- CINRYZE is a C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

This PAS labeling supplement, as amended, updates the package insert (PI) with safety data from an open-label uncontrolled routine prophylaxis extension study, LEVP2006-4 ("Change 3" study). This study was an extension to the randomized, placebo controlled pivotal trial which supported licensure. This BLA supplement, as amended, contains the final study report for clinical study LEVP2006-4.

While the original supplement had requested updating the PI with both safety and efficacy data from the Change 3 study, the sponsor revised the submitted draft PI at FDA's request to eliminate the additions of efficacy data regarding routine prophylaxis as the study was uncontrolled and lacked any pre-specified test hypotheses for efficacy. For these same reasons, the study could not have supported a new indication for treatment of HAE attacks.

The application is not subject to PREA because the product has orphan designation as a therapeutic for HAE attacks.

2. Background

C1-INH products represent replacement therapy for HAE patients with inadequate functional C1-INH levels, aimed at aborting or preventing acute HAE attacks. When the product is infused to treat an acute HAE attack that has already begun, it is called "treatment." In contrast, routine prophylaxis therapy involves the administration of a C1-INH product at appropriate

regular intervals in an attempt to prevent or greatly reduce the frequency of acute HAE attack episodes. Cinryze is approved for routine prophylaxis to reduce the frequency of acute HAE attacks. Another plasma-derived C1-INH product, Berinert, was subsequently approved for treatment of acute abdominal or facial (or, later, laryngeal) HAE attacks but is not approved for prophylaxis to prevent HAE attacks.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The original Berinert BLA was approved in 2008 (STN 125267).

Cinryze is presented as a lyophilized powder in single use vials containing the following nominal amount of C1 Esterase Inhibitor (Human): 500 U and is to be reconstituted with 5 mL of Sterile Water for Injection USP (not supplied).

Each vial is labeled with the C1-INH activity expressed in Units (U) per vial. Potency is determined using an *in vitro* assay which employs an in-house C1-INH concentrate standard. One Unit of the standard is approximately equal to the level of C1-INH activity found in 1 mL of fresh human plasma.

The active component of the product is a purified single-chain glycoprotein consisting of 478 amino acid residues. The product is prepared from large pools of plasma from U.S. donors. The purification process includes 2 validated and designated steps designed and shown via *in vitro* spiking experiments to reduce the risk of viral transmission by the product. These are heat treatment in aqueous solution at 60 degrees C x 10 hours in solution with stabilizers and nanofiltration using 2 sequential 15 nm filters in series. An additional validated step in the manufacturing process is precipitation in polyethylene glycol solution.

Each vial of 500 U of C1-INH when reconstituted contains the following stabilizers and excipients in the listed concentration ranges:

- NaCl 4.1 mg/mL
- Sucrose 21 mg/mL
- Trisodium Citrate 2.6 mg/mL

- L-Valine 2.0 mg/mL
- L-Alanine 1.2 mg/mL
- L-Threonine 4.5 mg/mL

The product contains no preservative.

Cinryze is to be stored at 2 – 25 deg. C in powder form.

The PI included in the submission proposes increasing the dating period for the product to 24 months, based on stability data previously submitted. FDA approved the 24 month expiration period for the product in May 2010 (Dr. F. D'Agnillo, email communication dated26 December 2011).

b) CBER Lot Release

Section is not applicable for this supplement.

c) Facilities review/inspection

There are no ongoing or pending investigations or compliance actions with respect to the facility used in the Manufacture of Cinryze or other products made at this facility. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission.

4. Nonclinical Pharmacology/Toxicology

There were no new toxicology data submitted with this PAS. Toxicology studies in support of the initial Cinryze approval were submitted under the original BLA STN 125267.

5. Clinical Pharmacology

a) Mechanism of Action

C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors known as serpins. As with the other inhibitors in this group, C1 esterase inhibitor has an inhibiting potential on several of the major cascade systems of the human body, including the

complement, the intrinsic coagulation (contact), and the fibrinolytic systems, as well as the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation and consumption of the C1 esterase inhibitor.

C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation Factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation Factor XIa of the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that the increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and Factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.

Administration of Cinryze to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients. The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L.

b) Pharmacokinetics

The pharmacokinetics of Cinryze were evaluated in a randomized, parallel group, open-label study performed in subjects with non-symptomatic hereditary angioedema (HAE). The subjects received either a single dose of 1,000 Units or 1,000 Units followed by a second 1,000 Units 60 minutes later. Table 1 (below) summarizes the pharmacokinetic parameters for functional C1-INH activity calculated from this study (data submitted in the original BLA).

Table 1
Mean pharmacokinetic parameters of Functional C1 Inhibitor

Parameters	Single Dose	Double Dose
$C_{baseline}$ (units/mL)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C_{max} (units/mL)	0.68 ± 0.08 (n = 12)	0.85 ± 0.12 (n = 13)
T_{max} (hrs)	3.9 ± 7.3 (n = 12)	2.7 ± 1.9 (n = 13)
$AUC_{(0-t)}$ (units*hr/mL)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
CL (mL/min)	0.85 ± 1.07 (n = 7)	1.17 ± 0.78 (n = 9)
Half-life (hours)	56 ± 36 (n = 7)	62 ± 38 (n = 9)

Numbers in parenthesis are number of subjects evaluated
Single dose = 1,000 Units
Double dose = 1,000 Units followed by a second 1,000 Units 60 minutes later
* One Unit is equal to the mean C1 inhibitor concentration of 1 mL of normal human plasma

The maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased from the single to double dose, although the increase was not dose proportional. The mean half-lives of CINRYZE were 56 hours (range 11 to 108 hours) for a single dose and 62 hours (range 16 to 152 hours) for the double dose.

In the Change 3 trial, C1-INH serum functional levels increased from 25.0 to 32.4% in adult subjects and 22.0 to 45.9% in subjects less than 18 years of age, according to the sponsor's analysis. Mean increases from baseline at one hour post-infusion for antigenic C1-INH ranged from 5.6 to 8.4 mg/dL in adult subjects over 18 and from 6.7 to 15 mg/dL in subjects < 18 years of age. These results are not included in the updated PI and were therefore not evaluated by the FDA pharmacokinetic reviewer.

Studies have not been conducted to specifically evaluate the pharmacokinetics of Cinryze in special patient populations identified by gender, race, pediatric or geriatric age, or the presence of renal or hepatic impairment.

6. Clinical/ Statistical

a) Clinical Program

ViroPharma, Inc. completed and submitted the final study report for the single-arm, open-label, uncontrolled extension study (Change 3 Study) into which subjects were eligible to enroll following completion of the pivotal placebo-controlled randomized study.

Summary of the Design of Extension Protocol No. LEVP2006-4 (Change 3)

Study Title:

> Change 3 Trial (C1 inhibitor in Hereditary Angioedema Nanofiltration Generation Evaluating Efficacy): Open-Label Use of C1 Inhibitor (Human) for the Prophylactic Treatment to Prevent Hereditary Angioedema (HAE) Attacks and as Treatment in Acute HAE Attacks

This prospective, single-arm, single period, open label, uncontrolled, multi-dose, multi-center phase III-IV extension of a phase III randomized placebo controlled crossover clinical trial was conducted in 47 U.S. centers and was designed to enroll subjects aged 1 year and greater with C1-Esterase Inhibitor (C1-INH) deficiency who had qualified for the pivotal trial LEVP2005-1, as well as selected subjects who did not qualify for study LEVP2005-1 (see study inclusion criteria below). Subjects were evaluated by study personnel at least weekly and received their Cinryze C1-INH infusion in the clinic. There was no fixed minimum duration of participation of each subject. There was a 3 month follow-up visit at the conclusion of the period of routine prophylaxis with Cinryze. Subjects in the extension trial (with Type I or II HAE) were administered a single dose of 1000 U Cinryze IV every 3 to 7 days for the duration of routine prophylaxis during the study. The inter-dose time interval window of 3 – 7 days in the Change 3 extension study was more extended than had been in the case for pivotal study LEVP2005-1, where Cinryze had been given every 3-4 days. The sponsor states it based this longer upper limit for the dosing interval for the Change 3 trial on the recommended dosing in the label of another C1-Esterase Inhibitor product, Cetor, marketed in Europe and on the PK and PD properties of various C1-INH products. [The sponsor did not request a

change in the recommended dosing interval for routine prophylaxis in the PI included in this PAS.] Subjects were also treated with Cinryze 1000 U IV, with the possibility of a 2nd 1000 U IV dose one hour later, for any HAE attacks which occurred despite routine prophylaxis with Cinryze. The Change 3 protocol did not pre-specify any primary, secondary, or exploratory efficacy endpoints.

Study Objectives:

> To evaluate the safety and efficacy of prophylactic use of Cinryze for the prevention of HAE attacks.

Study Inclusion Criteria:

- History of at least 1 HAE attack per month, or any history of laryngeal edema
- May have completed participation in Part B of the pivotal randomized placebo-controlled cross-over study, LEVP2005-1 anytime after the final prophylactic treatment in Part B
- May have been enrolled but not randomized in LEVP2005-1 Part A after Part A has closed.
- May have been enrolled and randomized in LEVP2005-1 Part A after Part B has closed (after the day 3 f/u visit).
- May have been excluded from LEVP2005-1 for the following reasons:
  - Pregnancy or lactation
  - Age < 6 years
  - Narcotic Addiction
  - Presence of anti-C1-INH antibody
- May not have been enrolled in LEVP2005-1 (may enter after LEVP2005-1 has closed) under the following circumstances:
  - Evidence of a low C4 level plus either a low C1-INH antigenic level or a low C1-INH functional level, or
  - Subject has known HAE-causing C1-INH mutation, or
  - Subject has a diagnosis of HAE based on a strong family history of HAE as determined by the clinical investigator.
- Age ≥ 1 year
- Signed informed consent

Study Exclusion Criteria:

- History of allergic reaction to C1-INH or other blood products
- Current participation in any other investigational drug study within the past 30 days other than those sponsored by Lev Pharmaceuticals
- Received blood or a blood product in the past 60 days other than C1-INH-nf.

Treatment Plan

The protocol specified that subjects were to be given prophylactic infusions of C1-INH (Cinryze) every 3-7 days (approximately 1-2 times per week. The infusion schedule was determined by the investigator based on the subject's response to therapy.

Treatment of Breakthrough HAE Attacks

HAE attacks which occurred despite routine prophylaxis were treated with 1000 U open-label Cinryze IV infusion over 10 min. If the attack had not "abated" by the 1 hour time point, a 2nd 1000 U open-label Cinryze IV infusion over 10 min was able to be administered. The subjects were allowed to leave the clinic after it was "safe to do so."

Visit Procedures

At each prophylaxis visit the following were performed:

- Medication history recorded
- AEs assessed
- Vital signs immediately prior to prophylactic treatment and again at 30 min post infusion.
- Pre- and 60 min post-infusion labs q 12 weeks starting at the first visit

Subjects were released from the clinic after the 30 min post infusion vital signs were taken, unless post-infusion blood samples were to be taken.

Definition of Angioedema Attack

An angioedema attack was defined as a discrete episode during which the subject progresses from no angioedema to symptoms of angioedema. Attacks that progress from one site to another were to be considered a single attack. Attacks that begin to regress and then worsen before complete resolution were to be considered one attack.

Documentation of HAE attacks

All HAE attacks were documented on subject diary cards at approximately the same time each day, evaluating symptoms over the past 24 hours, indicating attack anatomical location, severity, and duration of the "swelling" in minutes. Subjects also rated their HAE attack symptoms using visual analogue scales (100mm).

HAE attack symptoms were assessed prior to and q 15 min from 0 to 4 hours after administration of open-label study product for attacks (or until "substantial" symptom relief occurs. Substantial relief was defined as at least 3 consecutive reports that symptoms were "absent now but present before" or "present, symptoms better," of the defining symptoms.

Safety Monitoring:

Laboratory Evaluation

Viral serologies were drawn at baseline and pre-infusion at 3 months following the end of Cinryze dosing.

- HBsAg
- Anti-HCV
- Anti-HIV
- Parvovirus B19 prior to each infusion unless positive at baseline)

PCR for viral pathogens

- HIV NAT
- HCV NAT
- Parvovirus B19

Special studies

The following were drawn at the initial infusion and q 12 weeks thereafter:

- C1-INH antigenic – pre-infusion, 60 min post-infusion
- C1-INH functional - pre-infusion, 60 min post-infusion
- C4 – Pre-infusion, 60 min post-infusion

Immunogenicity testing

A single (post-baseline) blood sample for anti-C1-INH antibody testing was obtained from consenting subjects at selected study sites at the discretion of the investigator. This optional evaluation was added in an amendment at FDA's request and was not part of the original protocol.

Planned statistical analyses

Statement of Primary efficacy endpoint hypothesis test: none.

"The efficacy will be analyzed by the number of all angioedema attacks that occur during the treatment irrespective of whether the subject obtained open label C1-INH-nf or not and will be summarized."

Planned subgroup analyses: None.

Secondary efficacy analyses: None stated.

Robustness analyses: Not addressed.

Exploratory analyses: None stated.

Safety: The number and severity of AEs were summarized. Change in clinical safety labs and vital signs from pre- to post-infusion were analyzed by paired t-test.

Results of Change 3 Study

- The first subject enrolled in June 2006.
- The last subject completed the study in March 2009.

The extension study was conducted at 47 U.S. sites. A total of 146 subjects were enrolled and treated for a total of 1085 attacks.

Exposure to the product

A total of 12,019 infusions were administered to 146 subjects during the study over a median of 243.5 (range 8 – 959) days (10,617 infusions for routine prophylaxis, 874 first infusions for acute treatment, and 528 2nd infusions for acute treatment). (Note that the fact that more than half of subjects treated with the product for acute HAE attacks required a 2nd dose suggests that the starting dose may have been inadequate. The sponsor is conducting a separate post-marketing dose-ranging study to better evaluate doses for routine prophylaxis.) Sixty-five percent of subjects (n = 95/146) also received Cinryze for acute HAE attacks despite prophylactic treatment.

The median number of exposure days of the product was 46 (range 2-286 days).

Dose Escalation during the Change 3 Trial

Although the protocol did not provide for dose escalation, 2 subjects were escalated to 2000 U Cinryze IV twice weekly in an attempt to reduce HAE attack frequency. In one of these subjects HAE attack frequency was reported to fall from 1.13 to 0.37 HAE attacks per month following dose escalation. In the other subject, no reduction in HAE attack frequency was observed over 3 months at the higher dose. This subject experienced 2 laryngeal HAE attacks during the period of dosing with 2000 U twice weekly which were classified by the investigator as serious adverse events unrelated to Cinryze.

Subject Disposition in Change 3 Trial

Seventy-nine of 146 subjects (54%) completed the study. Subjects who discontinued the study prematurely were recorded as having stopped for the following reasons as noted in Table 2 below:

Table 2
Reasons for Premature Subject Discontinuation in the Change 3 Trial (n = 146 enrolled)

Reason for Discontinuation of Participation in Change 3 Study	**Number (%) of Subjects**
Death	2 (1.4%)
Investigator deemed in best interest of subject	1 (0.7%)
Lost to follow-up	10 (6.8%)
Subject withdrew consent	8 (5.5%)
Transitioned to commercial Cinryze	40 (27.4%)
Transferred to Protocol LEVP 2006-1	3 (2.1%)
Logistical reasons	1 (1.4%)
Change to treatment with Cetor	1 (0.7%)

Demographics:

Females: 112 subjects (76.7%), Males: 34 subjects (23.3%)

Median age: 36 years, Mean age: 36.5 years

Age range : 3 – 82 years; Age 2 to < 6 years: 2 subjects, Age 6 to < 12 years: 9 subjects, Age 12 to < 18 years: 12 subjects, Age 18 - < 65 years: 114 subjects, Age > 64 years: 9 subjects

Caucasian: 83% , Black: 8 subjects, Hispanic/Latino: 15 subjects
Other: 2 subjects

Concomitant Medications

Thirty nine subjects took Danazol during the study. However, the sponsor's Table 10 in the study report lists only 18 subjects as taking anabolic steroids. Nineteen subjects were listed as having taken other therapeutic products for HAE during the study, including Berinert and Cetor. **This use of concomitant products having activity in HAE further complicates and biases any efficacy (both prophylaxis and treatment) inferences which might otherwise be drawn from the Change 3 study data.**

Results - Efficacy analyses of Impact II Study (treatment and prophylaxis)

Given that the extension study lacked a concurrent control group and was open-label, the sponsor's analyses were descriptive in nature and performed on both per-subject and per-attack bases. Per subject analyses averaged individual attack times over all treated attacks for each subject. In a calendar quarter-by-quarter analysis of HAE attack frequency during routine prophylaxis with Cinryze, the breakthrough HAE attack frequency appeared to be constant, averaging 0.34 attacks per subject-month. Prior to enrollment in the trial, subjects reported a median attack frequency of 3.0 HAE attacks per month (range 0.08 to 28.0 attacks per month). Per attack analyses were presented descriptively, with 2-sided 95% CIs for median time to onset of HAE symptom relief and median time to complete resolution of HAE attack symptoms. As noted below, however, the protocol lacked any hypothesis testing for evaluating the efficacy of Cinryze administration for either prophylaxis or treatment of HAE attacks.

Pre-specified Efficacy Analyses (all HAE anatomical locations): none.

Despite the fact that one of the study objectives was to assess the efficacy of the product in routine prophylaxis to prevent acute HAE attacks, no provision for hypothesis testing related to efficacy was found in the protocol. The sponsor's descriptive statistics for efficacy measures are not further summarized in this memorandum because they are subject to bias and are not possible to interpret satisfactorily due to the lack of a suitable control.

Due to the lack of a concurrent control group and potential for bias, given that subjects and investigators knew they were receiving prophylaxis and

treatment for any breakthrough HAE attacks with active product in this single-arm study, the sponsor agreed to remove from the draft PI a statement it had proposed commenting on lack of evidence for a diminution of therapeutic effect over the course of the study.

Protocol Violations/Deviations

Twenty-two of 146 subjects (15.1%) enrolled and treated subjects did not meet one or more protocol eligibility criteria. This included 15 subjects who had received blood or a blood product in the past other than Cinryze. Four subjects had participated in another study of an investigational drug not sponsored by Lev Pharmaceuticals within the past 30 days.

Viral follow-up testing was incomplete in a number of instances.

BIMO Inspections: None.

7. <u>Safety:</u>

The safety of Cinryze 1000U IV every 3 to 7 days for the routine prophylaxis to prevent acute HAE attacks in adults and adolescents was demonstrated in pivotal study LEVP2005-1 prior to the original BLA licensure. The data presented from the Open label extension Change 3 study include a safety signal of concern for thrombotic and thrombotic events which was reported for 5/146 subjects (not including additional reported cases of thromboses of indwelling central venous catheters). This risk had been identified in the Warnings and Precautions section of the package insert at the time of original product licensure in the U.S. and the package insert had already been strengthened in this regard, based on the data from the completed Change 3 study, prior to submission of this PAS.

Safety monitoring in the Change 3 study included vital signs, and laboratory studies for viral serology at baseline and at 3 months following the final Cinryze dose. Routine hematology and serum chemistries were not performed. Antibodies to C1-INH measured by central laboratory were obtained only at investigator discretion following amendment of the protocol.

SAFETY RESULTS – CHANGE 3 EXTENSION STUDY

Adverse Events (AEs)

Deaths: 2/146

Neither death was considered by the investigators to be related to prior Cinryze administration.

Subject 45-002, a 34 year-old female died due to pulmonary arterial embolization of foreign material due to IV injection of oral medication (diphenhydramine and /or hydroxyzine) (autopsy conclusion).

Subject 05-028, a seventy-one year-old male died of progressive hepatocellular carcinoma.

Serious AEs (SAEs):

Twenty-one percent (n = 31/146) of subjects reported at least 1 Treatment Emergent SAE during the study. Two subjects' SAEs were considered of unknown relationship to Cinryze administration by the investigators. The sponsor classified these 2 Treatment Emergent SAEs as possibly related. These 2 possibly related Treatment Emergent SAEs were musculoskeletal chest pain and major depression.

Most Treatment Emergent SAEs consisted of symptoms consistent with HAE attack.

Among the Treatment Emergent SAEs not considered by the investigators to be related to Cinryze administration were the following SAEs of interest:

Table 3
SAEs of Interest based on FDA's Review of SAEs from Change 3 Study

Treatment Emergent SAE	Number of Subjects reporting SAE
CVA	2 (1.4%)
MI	1 (0.7%)
PE	1 (0.7%)

DVT	1 (0.7%)
CHF	1 (0.7%)
Acute febrile neutrophilic dermatosis	1 (0.7%)
Chest pain	1 (0.7%)
Cholelithiasis	**1 (0.7%)**
Pancreatitis	**1 (0.7%)**
Anaphylactic reaction (ascribed to shellfish)	**1 (0.7%)**
Angioneurotic edema	**1 (0.7%)**

Timing of Thrombotic/Thrombo-embolic (TE) events in relation to day of participation in the Change 3 Study:

Subject	TE event	Day of Onset of AE
16-010	**DVT**	**282**
28-003	**CVA**	**109**
45-002	**PE**	**349**
05-028	**MI**	**104**
55-001	**CVA**	**211**

The investigators classified the above 5 TE events as unrelated to administration of Cinryze, however the possible contribution of Cinryze to the TE events in 4 of these 5 subjects cannot be excluded at this time. All reported TE events in Change 3 occurred in adults.

Note that that the package insert for C1-Esterase Inhibitor (Human), Cinryze, was recently changed under another STN reviewed by Dr. Maplethorpe of this Division to indicate that, in the open-label prophylaxis study extension study which is the subject of this supplement, involving 146 adult and adolescent hereditary angioedema subjects, there were a total of 5 thrombotic/thrombo-embolic (TE) events (incidence of 3.4%) which occurred following administration of the recommended dose of the product. The incidence of TE events exceeded 5% when indwelling-central venous catheter-associated thromboses of the subclavian and internal jugular veins were included. This safety signal emerged post-licensure, but the potential for thrombotic events as a potential class effect had been mentioned in the PI at the time of original licensure.

Discontinuation due to AE: none.

Overall Incidence of AEs:

Seventy-eight percent (n = 114/146) of subjects reported one or more Treatment-Emergent AEs (TEAEs) during the study.

Severity/Intensity of AEs:

> Of the TEAEs, 86% (n = 967/1118) were considered mild or moderate in intensity; 14% were rated severe in intensity

The most commonly reported TEAEs were URI, sinusitis, UTI, bronchitis, nausea, diarrhea, vomiting, rash and headache. These common AEs occurred with an incidence of 11-23% of subjects, depending on the AE type.

Possibly-related TEAEs according to investigator assessment numbered 129 (12% of all 1118 TEAEs reported). The most commonly reported AE considered related to Cinryze administration by the investigator was headache (incidence 5.5% of subjects).

Outcomes during pregnancy

Eleven women received Cinryze during pregnancy in the trial. Six subjects delivered 7 healthy neonates (including 1 set twins). One subject (29-001) had a spontaneous abortion (ectopic pregnancy suspected). One subject (28-005), exposed to Cinryze after week 16 of gestation, had a stillborn child with multiple congenital anomalies. Neither adverse fetal outcome was ascribed to Cinryze by the investigators.

Immunogenicity Testing Results from the Change 3 Trial:

Post-baseline samples were obtained at a single time point (variable) for 74/146 (50.6%) subjects for anti-C1-INH antibodies. No antibodies were detected. These subjects had received a median of 48 doses of Cinryze prior to antibody testing.

Vital Signs: no clinically relevant changes

Adverse Reactions

Adverse reactions for the purpose of this review are adverse events that are considered at least possibly related to administration of the investigational product. Because the Change 3 trial design lacked a concurrent placebo or other suitable control group, no gold standard exists by which to judge whether a given AE was a adverse reaction. Therefore, the following definition of adverse reaction was used to prepare Table 3 of the revised package insert which provides data on adverse reactions reported in the Change 3 study:

All adverse events beginning the day of or within 3 days of an infusion are considered at least possibly related to administration of Cinryze, and therefore are termed adverse reactions, plus those AEs considered by either the investigator or sponsor as at least possibly related to administration of Cinryze, as well as those for which the causality assessment is missing or indeterminate.

Adverse reactions in the open-label Change 3 trial (n=146) that occurred in at least three subjects (≥2%) receiving CINRYZE, are given in the following table, which was introduced into the revised PI at FDA's request:

Table 3
Adverse Reactions in the Open-Label Follow-On Change 3 Trial

Adverse Reaction	**Number (%) of Subjects (N=146) with Adverse Reaction**	**Number (%) of Infusion Days (N=11,435) with Adverse Reaction**
Headache	28 (19)	62 (0.5)
Nausea	26 (18)	29 (0.3)
Rash	15 (10)	30 (0.3)
Vomiting	15 (10)	17 (0.1)
Pyrexia	7 (5)	7 (<0.1)
Catheter Site Pain	4 (3)	5 (<0.1)
Dizziness	3 (2)	4 (<0.1)
Erythema	3 (2)	3 (<0.1)
Pruritus	3 (2)	4 (<0.1)

Note that the sponsor's CRF did not have a space for recording the time of onset of AEs, but rather only the day of onset. Hence, the timeframe for defining temporal relationship between infusion and ADR onset was expressed in days rather than hours.

Viral Safety:

No transmissions of HIV, HBV, HCV, or parvovirus B19 were observed in Change 3. Not all subjects had all protocol-required viral follow-up testing, but the majority underwent such testing (See clinical review memo pp 14-16).

Anti-C1-INH Antibodies:

Note that comprehensive immunogenicity testing was not required by the study protocol. A single blood sample for anti-C1-INH antibody testing was obtained from consenting subjects (50% of all study subjects) at selected study sites at the discretion of the investigator and tested at Sanquin diagnostic services using a validated assay to detect IgA, IgM, and IgG antibodies directed against C1-INH. All antibody testing was negative.

Comment on safety of Cinryze in Adolescents

The safety of Cinryze in the dose of 1000 U/kg twice weekly for adolescents for prevention of HAE attacks already has been established from the data submitted in the original BLA.

Postmarketing Experience

Cinryze has been approved in the U.S. since 2008. Postmarketing adverse events in the FDA AERs database were reviewed for a recently approved Cinryze labeling supplement, which strengthened statements in the package insert concerning thrombotic and thromboembolic events to indicate that such events have been observed after administration of Cinryze at the recommended dose for the prevention of acute HAE attacks.

The package insert states "Postmarketing thrombotic events have been reported, including catheter-related and deep venous thromboses, transient ischemic attack, and stroke. Patients with known risk factors for thrombotic

events should be monitored closely. (*See Section 5.2 Thrombotic events in WARNINGS AND PRECAUTIONS)*"

Postmarketing adverse reactions include local infusion site reactions (including pain, rash, erythema, inflammation or hematoma at the infusion site).

FDA concluded that recently examined postmarketing AERs database for Cinryze does not change the favorable risk: benefit balance for the existing indication, routine prophylaxis for the prevention of acute HAE attacks, for any age group.

Safety Conclusion:

The overall safety profile of Cinryze is acceptable for the current indication for routine prophylaxis to prevent acute HAE attacks. Safety is supported by results from the Change 3 study, the pivotal study reviewed in the original BLA, and by postmarketing experience, but thrombotic and thrombotic events at the recommended doses have been observed for both members of this class, including Cinryze, and will be the subject of ongoing surveillance. No pattern of unusual safety signals was evident among the pediatric study population from the data presented. The benefits of treatment with Cinryze at 1000 U appear to outweigh the risks for the studied age populations.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this PAS.

10. Labeling

Prescribing Information (PI): APLB and the medical reviewer from the Clinical Review Branch, HFM-392 reviewed the draft package insert (PI) submitted by the sponsor. Comments from a promotional and comprehension perspective were provided to OBRR from APLB. FDA comments regarding the draft PI were sent to the sponsor. The sponsor

subsequently submitted a revised package insert. This was an iterative process. The sponsor ultimately accepted all of FDA's comments and recommendations regarding the draft PI with only occasional minor modification.

Carton and immediate container labels: no changes to previously approved versions.

Patient labeling: Patient information is appropriately provided following the Package Insert's Full Prescribing Information.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends the approval of this supplement.

b) Risk/ Benefit Assessment

Efficacy and safety data were found adequate to favor potential benefits over risks. Results from the Change 3 clinical trial, together with safety data from the prior pivotal IND study reviewed in the original BLA and a prior FDA review of postmarketing data, support maintaining the current indication for routine prophylaxis to prevent acute HAE attacks in adults and adolescents.

c) Recommendation for Post-Marketing Activities

Pharmacovigilance will continue through passive reporting. FDA will continue to monitor reports of thrombotic and thromboembolic events and other potential safety signals. FDA will maintain the option of requesting additional active surveillance via a postmarketing Registry.

d) Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments related to this new indication.