Summary Basis for Regulatory Action - CINRYZE

Date: Thursday, October 09, 2008
From: Felice D'Agnillo
Subject: Summary Basis for Regulatory Action
BLA #/Supplement#: 125267/0
Applicant: Lev Pharmaceuticals
Date of Submission: July 31, 2007
PDUFA Goal Date: October 14, 2008
Proprietary Name / Established (USAN) names: CINRYZE / C1 inhibitor (Human)
Dosage forms: 500 Units (U) per glass vial, Lyophilized
Proposed Indication(s): Prophylactic treatment of patients with Hereditary Angioedema (HAE)
Recommended Action: *Approval*
Signatory Authority(ies) Action: *Offices Signatory Authority:* **Basil Golding**
X□ *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*

Material Reviewed/ Consulted - List of specific documentation used in compiling SBRA

Clinical Review: Charles Maplethorpe
Statistical Review: Boris Zaslavsky
Clinical Pharmacology: Iftekhar Mahmood
Pharmacology/ Toxicology Review: Paul Buehler
CMC Review/Facilities: Felice D'Agnillo, Elena Karnaukhova, Omer I. Butt, Mahmood Farshid, and J. David Doleski
Establishment Inspection Report: J. David Doleski and Felice D'Agnillo
Biomonitoring Review: Robert Wesley
Labeling: Jean Makie
Advisory Committee Transcript: May 2, 2008

1. **Introduction**

   CINRYZE is a sterile, nanofiltered, lyophilized preparation of human plasma-derived C1 esterase inhibitor. CINRYZE is manufactured from U.S. Source Plasma by a process that includes ---(b)(4)-------, precipitation, filtration and chromatography steps. CINRYZE is supplied as a lyophilized powder in single-use glass vials. CINRYZE is administered by intravenous injection after reconstitution with the appropriate volume of Sterile Water for Injection (USP). CINRYZE is

indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

2. **Background**

The Biologics License Application (BLA) from Lev Pharmaceuticals (New York, New York) for C1 inhibitor (human) or CINRYZE was received by CBER on July 31, 2007 and qualified for priority review with an Action Due Date of January 31, 2008. Orphan drug designation was granted on July 16, 2004. The clinical studies were conducted under IND --(b)(4)--.

The Biologics Licensing Application (BLA) contains data from one phase 3 trial for routine prophylaxis (LEVP2005-1/B) and data from three supportive trials conducted in Europe with an earlier version of the product. Data from an investigational study to study the use of the product to treat HAE attacks was included in the submission, but was withdrawn by the sponsor during the review. Open-label studies are ongoing.

This application was presented at the Blood Products Advisory Committee (BPAC) meeting on May 2, 2008. The committee concurred with FDA's assessment that there is sufficient safety and efficacy data to approve the prophylaxis indication. The committee also concurred with FDA’s assessment regarding the need for post marketing studies. The sponsor submitted the complete response to the CR letter on April 14, 2008. The submission was classified as Class II with a review deadline of October 14, 2008.

CINRYZE is manufactured under contract to the Sanquin Blood Supply Foundation in Amsterdam, Netherlands for Lev Pharmaceuticals. Sanquin has manufactured and marketed C1 inhibitor products for over 35 years. Sanquin’s currently marketed C1 inhibitor, Cetor ®, was approved in the Netherlands in 1997. The main differences between Cetor ® and CINRYZE include; the requirement that CINRYZE be manufactured solely from US Source Plasma, the manufacturing process for CINRYZE includes a nanofiltration step, and CINRYZE does not contain added hepatitis B immunoglobulin.

3. **Chemistry, Manufacturing and Controls (CMC)**

General Manufacturing Summary:

C1 inhibitor (human) or CINRYZE is manufactured from US Source Plasma by a series of ----(b)(4)----------, precipitation, chromatography and filtration steps. CINRYZE is available in single-use vials that nominally contain 500 Units (U) C1 inhibitor (human) and is reconstituted with 5 mL of Sterile Water for Injection (USP). Two vials of reconstituted CINRYZE are combined to provide a single dose of CINRYZE at a concentration of 100 U/mL. CINRYZE, when reconstituted with the appropriate volume of diluent, contains the following excipients: 4.1 mg/ml sodium

chloride, 21 mg/ml sucrose, 2.6 mg/ml trisodium citrate, 2.0 mg/ml L-Valine, 1.2 mg/ml L-Alanine, and 4.5 mg/ml L-Threonine.

Manufacturing Overview

C1-inhibitor finished product (Drug Product)

Manufacturing Notes:

The manufacturing process submitted in the original BLA and in place at the start of the preapproval inspection allowed for manufacturing of ----------(b)(4)------ at both -(b)(4)------ and Sanquin. However, the manufacturing plans have now been modified partly in response to issues raised during FDA's pre-approval inspection regarding process validation. The proposed plan submitted by the sponsor in response to FDA Form 483 and the CR letter is for **---(b)(4)--- to manufacture only ---(b)(4)------.** This intermediate would then be shipped to Sanquin to resume manufacturing of ---(b)(4)-- followed by the rest of the manufacturing for final product (CINRYZE).

-- ---
-- --

--------- ---------------------------(b)(4)---
-- ---------------------------------------

----------------- ---
--- -------------------------------

------------------------ ---
---.

Drug Product Composition

Ingredient	Amount per ml (w/v), Reconstituted in 5 ml	Function of ingredient
C1-inhibitor (U/ml)	100	Active ingredient
Trisodium citrate (mg/ml)	2.58	Buffer
Sodium Chloride (mg/ml)	4.09	Tonicity
Sucrose (mg/ml)	20.54	---(b)(4)----
Valine (mg/ml)	1.99	---(b)(4)----
Alanine (mg/ml)	1.16	---(b)(4)----
Threonine (mg/ml)	4.53	---(b)(4)----

Drug Product Release Specifications

Test	Specification
C1-inhibitor (U/ml)	---(b)(4)----
Total protein (g/l)	---(b)(4)---
Specific C1-inhibitor activity (U/mg)	--(b)(4)---
Sterilty	Sterile
---(b)(4)----	---(b)(4)----

Test	Specification
---------(b)(4)-------	-(b)(4)-
pH (measured directly in the solution)	6.6 - 7.4
----------(b)(4)----------	---(b)(4)---------
---(b)(4)---	--(b)(4)--
----------(b)(4)----------	--(b)(4)--
Stability (3 hours at room temperature after reconstitution)	---(b)(4)---- ----------
Moisture (---(b)(4)---) (g/g)	--(b)(4)--
Sodium (mmol/l)	--(b)(4)--
Sucrose (mmol/l)	--(b)(4)---
Citrate (mmol/l)	---(b)(4)--
----------(b)(4)----------	---(b)(4)---
Valine (mmol/l)	--(b)(4)--
Alanine (mmol/l)	-(b)(4)--

Test	Specification
Threonine (mmol/l)	-(b)(4)--

Viral Inactivation Studies

The manufacturing process for CINRYZE includes steps designed to reduce the risk of viral transmission. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and plasma preparation. Each individual plasma donation used in the manufacture of Cinryze is collected only at FDA-approved blood establishments and is tested by FDA licensed serological tests for Hepatitis B Surface Antigen (HBsAg), and for antibodies to Human Immunodeficiency Virus (HIV-1/HIV-2) and Hepatitis C Virus (HCV). All plasma is tested by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1 and found to be nonreactive (negative). In addition, the plasma has been tested by NAT for parvovirus B19 and found to be nonreactive (negative).

Two dedicated, independent and effective viral reduction steps are employed in the manufacture of CINRYZE: pasteurization at 60°C for 10 hours in solution with stabilizers, and nanofiltration through two sequential 15 nm Planova filters. These viral reduction steps, along with a step in the manufacturing process, PEG precipitation, have been validated in a series of in vitro experiments for their capacity to inactivate/remove a wide range of viruses of diverse physicochemical characteristics including: Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), and the following model viruses: Bovine Viral Diarrhea Virus (BVDV) as a model virus for HCV, Canine Parvovirus (CPV) as a model virus for Parvovirus B19, and Pseudorabies Virus (PRV) as a model for large enveloped DNA viruses (e.g., herpes virus). Total mean $\log_{10}$ reductions achieved by the relevant manufacturing steps are shown in the table below.

	Enveloped Viruses			Non-Enveloped Viruses	
Process Step	**HIV**	**BVDV**	**PRV**	**HAV**	**CPV**
PEG precipitation	5.1 ± 0.2	4.5 ± 0.3	6.0 ± 0.3	2.8 ± 0.2	4.2 ± 0.2
Pasteurization	> 6.1 ± 0.2	> 6.7 ± 0.3	> 6.7 ± 0.2	2.8 ± 0.3	0.1 ± 0.3
Nanofiltration	> 5.6 ± 0.2	> 5.5 ± 0.2	> 6.4 ± 0.3	> 4.9 ± 0.2	> 4.5 ± 0.3

	Enveloped Viruses			Non-Enveloped Viruses	
Process Step					
	HIV	**BVDV**	**PRV**	**HAV**	**CPV**
Total reduction	**> 16.8**	**> 16.7**	**> 19.1**	**> 10.5**	**> 8.7**

Stability Testing

The -------(b)(4)-------intermediates and Pasteurized Planova filtrate (drug substance) have a shelf life of (b)(4) months when stored at --(b)(4)-. Appropriate stability studies in which intermediate and drug substance lots were stored up to ----------(b)(4)----------to support storage for this period without any impact to product. Stability testing is ongoing for the ---(b)(4)----batches manufactured at ----(b)(4)--- as well as---(b)(4)-------and drug substance lots derived from these ---(b)(4)---- batches and used to manufacture the ----------(b)(4)----------.

The proposed shelf-life for CINRYZE is --- months at 2-25 °C. The sponsor completed the manufacture of ----------(b)(4)---------- manufactured with ---(b)(4)--- batches produced at ---(b)(4)--- and completed at Sanquin using the ----------(b)(4)---------- ----------(b)(4)----------. FDA indicated that the stability data from the original conformance and clinical lots would factor into the determination of the approved shelf-life for the product. Stability testing at 2-8°C and 25-27 °C was provided for the three original conformance lots up to 12 months and three clinical lots up to -- months. Accelerated stability data at --(b)(4)-- for 6 months was also provided. Based on the totality of the stability data submitted to FDA, the decision was made to approve a dating period of 12 months when stored at 2-8°C and/or 25-27 °C. ----------(b)(4)---------- (see Section 12).

Lev Pharmaceuticals requested an exemption to the general safety test (GST) on final product in a letter dated October 3, 2008. This request was granted on October 10, 2008.

The CMC review team finds that sufficient data and information has been provided on the chemistry, manufacture and controls to support licensure of CINRYZE.

CBER Lot Release

CBER will release lots of CINRYZE based upon review of results of in process and final release tests performed by the manufacturer and submitted in the Lot Release

Protocols. During the review of the BLA, the sponsor agreed to include final release testing for . --(b)(4)-- Lot Release Protocols were reviewed and approved by CBER.

Facilities

CINRYZE is manufactured under contract to the Sanquin Blood Supply Foundation in Amsterdam, Netherlands for Lev Pharmaceuticals. The manufacturing facilities and their respective roles are listed below:

1. Sanquin Plasma Products, Plesmanlaan 125, P.O. Box 9190, 1006 X Amsterdam, Netherlands

   ----------(b)(4)----------.

2. ----------(b)(4)----------
3. ----------(b)(4)----------

Lev Pharmaceuticals does not possess a manufacturing facility. However, Lev Pharmaceuticals does have the following responsibilities: quality of the US source plasma; look back and notifications; US distribution; complaints; recalls; returned products; change control; pharmacovigilance; and reporting to FDA. Lev Pharmaceuticals also releases the lots within the US and has overall quality oversight over the manufacturing of this product. Lev was not inspected by FDA.

CBER conducted pre-approval inspections of ----------(b)(4)---------- from ----------(b)(4)---------- and SBSF from November 30 to December 7, 2007. These were the first FDA inspections of these facilities for plasma manufacturing, although Sanquin was inspected once before in 1988 by FDA for blood banking. During these inspections, -(b)(4)-- was cited for eight FDA 483 items related to manufacturing and quality issues. SPP was cited for twelve FDA 483 items related to manufacturing and quality issues. The responses to the FDA 483 items were received, reviewed and found to be acceptable.

There are no ongoing or pending investigations or compliance actions with respect to the above facilities or their products. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission.

The facilities reviewer (J. David Doleski) considers this submission approvable on the basis of the facilities information provided.

4. **Nonclinical Pharmacology/Toxicology**

Toxicology

CINRYZE (C1-INH) was found to be safe in GLP toxicology studies at doses ranging from the maximum clinical dose to 10 fold the maximum clinical dose. Both rodent (rat) and non-rodent (rabbit) species were included in the CINRYZE pre-clinical safety assessment. The totality of pre-clinical safety studies included both acute and repeated dose exposures of animals to CINRYZE. In repeat dosing studies neutralizing antibodies were found to significantly influence the outcome of toxicological assessment beyond seven days of dosing. This finding is not atypical with human proteins dosed repeatedly in animals. In vitro and in vivo thrombogenicity studies indicate a potential for clot formation when CINRYZE is administered other than for replacement therapy.

Carcinogenesis, mutagenesis and impairment of fertility

In vitro and in vivo mutagenesis and carcinogenesis studies have not been performed with CINRYZE. Both embryo and fetal development studies conducted in pregnant rats were inconclusive due to the development of neutralizing antibodies to CINRYZE.

5. Clinical Pharmacology

Pharmacokinetics of CINRYZE in HAE subjects

This was a randomized, parallel group, open label study to compare the PK of a single dose of CINRYZE to that of 2 doses (1 dose followed by a second dose 60 minutes later). There were 27 subjects with hereditary angioedema in the study (1 to 46 years of age). Of the 27 subjects, 13 received single dose (1000 U CINRYZE) and 14 received double dose (1 dose of 1000 U followed by a second dose 60 minutes later). PK parameters were estimated by non-compartmental analysis.

The clearance and half-life of antigenic C1INH in single-dose subjects were 0.65 ± 0.60 mL/min and 45 ± 12 hours, respectively. The clearance and half-life of antigenic C1INH in double-dose subjects were 0.70 ± 0.36 mL/min and 47 ± 22 hours, respectively. The clearance and half-life of functional C1INH in single-dose subjects were 0.85 ± 1.07 mL/min and 56 ± 36 hours, respectively. The clearance and half-life of functional C1INH in double-dose subjects were 1.17 ± 0.78 mL/min and 62 ± 38 hours, respectively. Both Cmax and AUC(0-∞) values were higher with the double dose than the single dose for both antigenic and functional C1INH.

The PK of CINRYZE in subjects with hereditary angioedema indicates that in terms of antigenic and functional C1INH, the drug has a long half-life and slow clearance. Administration of the second dose of CINRYZE 60 minutes after the first dose did not follow the linear kinetics (Cmax and AUC were not dose proportional).

6. Clinical/Statistical-Efficacy

Routine Prophylaxis Trial LEVP2005-1/B

The Biologics Licensing Application (BLA) contains data from one phase 3 trial for routine prophylaxis (LEVP2005-1/B) and data from three supportive trials conducted in Europe with an earlier version of the product. Data from an investigational study to study the use of the product to treat HAE attacks was included in the submission, but was withdrawn by the sponsor during the review. Open-label studies are ongoing.

Efficacy

The routine prophylaxis trial LEVP2005-1/B is pivotal to the efficacy claims in this BLA. The primary objective of LEVP2005-1/B was to assess safety and efficacy of twice weekly dosing of CINRYZE (1000 Units by intravenous injection) to prevent HAE attacks over a 3 month period. The study was conducted at clinical centers (not at home) and had a prospective, randomized, double-blinded, placebo-controlled crossover study design. In the study, the According to Protocol (ATP) efficacy cohort was used for the primary efficacy analysis, and consisted of 22 HAE subjects greater than 6 years of age who experienced 3 months of routine prophylaxis with CINRYZE and placebo according to the crossover study design. The reduction of HAE attack frequency from placebo phase to active treatment phase was calculated for each subject.

In LEVP2005-1/B, an HAE attack was defined as the subject reported indication of swelling at any location following a report of no swelling on the previous day. HAE attacks were graded as mild, moderate or severe by the following definitions:

- Mild – Events that were usually transient, required no special treatment, and did not interfere with the subject's daily activities.
- Moderate – Events that introduced some level of inconvenience or concern to the subject, and may have somewhat interfered with daily activities, but were usually ameliorated by simple therapeutic measures (may have included drug therapy).
- Severe – Events that were unacceptable or intolerable, significantly interrupted the subject's usual daily activity, and required systemic drug therapy or other treatment.

The applicant demonstrated that CINRYZE, at 1000 Units per dose every 3 or 4 days, was effective in reducing the frequency of HAE attacks in patients with hereditary angioedema. The mean number of HAE attacks was reduced from 12.7 attacks on placebo to 6.1 attacks on CINRYZE routine prophylaxis for the three month period.

Safety

In LEVP200-1/B, there were 24 subjects treated with randomized study medication. Of these, 23 subjects were treated with CINRYZE and 23 subjects were treated with Placebo. All subjects received open-label treatment with CINRYZE during their

Placebo treatment phase, which confounds true attribution of adverse events to CINRYZE or placebo. There were 20 subjects (87.0%) who had a treatment-emergent adverse event (TEAE) after exposure to open-label or double-blind randomized CINRYZE. In 9 subjects, the TEAEs were categorized as related to study medication. The most common related TEAEs were viral upper respiratory infections (3 subjects) and rash (3 subjects). There were 3 subjects with 1 or more treatment-emergent SAEs and 1 subject with an SAE reported prior to randomization with study medication. None of these events were reported as related to study medication. There were no deaths or withdrawals due to AEs. There were no meaningful changes in clinical laboratory results or in evaluation of vital signs. Immunogenicity studies were flawed by technical problems with assays. Subsequent analysis using data from other testing facilities resulted in the conclusion that the product is not immunogenic, however this conclusion is being tested in a phase 4 study.

Serious adverse events - deaths

None.

Serious adverse events

In LEVP2005-1/B there were 3 subjects with a treatment-emergent SAE.

All of these subjects had an HAE attacks that required hospitalization. In addition, one subject had surgery for a cyst and the placement of a subcutaneous port put in place to improve IV access. None of these SAEs were considered related to study medication.

Solicited adverse events

Of the 24 subjects in the safety population, 21 (87.5%) had 1 or more treatment-emergent adverse events (TEAEs). There was only 1 subject who had a TEAE (sinusitis) during treatment with Placebo and prior to exposure to open-label or randomized CINRYZE. The remaining 20 subjects (87.0%) had at least 1 TEAE that followed exposure to *open-label* or randomized double-blind CINRYZE. In subjects treated with CINRYZE, the most common TEAEs were those that coded to the Infections and Infestations system organ class (14 subjects, 60.9%). Within this system organ class, the most common individual TEAEs were sinusitis (5 subjects, 21.7%), upper respiratory tract infection (4 subjects, 17.4%) and viral upper respiratory tract infection (3 subjects, 13.0%). Gastrointestinal Disorders were experienced by 8 subjects (34.8%). The most common TEAEs in this system organ class were gastro-esophageal reflux disease (2 subjects, 8.7%) and vomiting (2 subjects, 8.7%). Treatment-emergent AEs that coded to the Skin and Subcutaneous Tissue Disorder system organ class were reported by 6 subjects (26.1%). TEAEs within this system organ class included rash (5 subjects, 21.7%), pruritus (2 subjects, 8.7%), dermatitis contact (1 subject, (4.3 %) and erythema (1

subject, 4.3 %). In other system organ classes, headache was reported by 4 subjects (17.4%).

No other individual TEAE was reported by more than 2 subjects.

Conclusion

CINRYZE at a potency of 1000 Units per dose every 3 or 4 days by intravenous injection was effective in preventing or reducing the HAE attack frequency in patients with hereditary angioedema.

The effectiveness of C1 inhibitor prophylaxis in reducing the number of HAE attacks was variable among the subjects as shown in the following table:

LEVP2005-1/B Prevention of HAE Attacks Clinical Trial Results by Subject

Subject	Attacks on C1INH	C1INH Attack Frequency (Attacks/Day	Attacks on Placebo	Placebo Attack Frequency (Attacks/Day	Percent Reduction in Number of Attacks	Percent Reduction in Attack Frequency
1	0	0.00	6	0.07	100%	100%
2	0	0.00	7	0.07	100%	100%
3	0	0.00	14	0.17	100%	100%
4	0	0.00	14	0.18	100%	100%
5	2	0.02	22	0.23	91%	90%
6	1	0.01	9	0.10	89%	88%
7	2	0.02	13	0.16	85%	84%
8	2	0.02	12	0.14	83%	83%
9	2	0.02	9	0.11	78%	78%
10	2	0.02	8	0.10	75%	76%
11	8	0.10	20	0.24	60%	60%
12	10	0.12	19	0.22	47%	47%
13	7	0.09	14	0.15	50%	43%
14	7	0.09	10	0.15	30%	43%
15	11	0.14	17	0.20	35%	32%
16	13	0.16	19	0.23	32%	31%
17	6	0.08	8	0.10	25%	25%
18	12	0.15	15	0.19	20%	21%
19	12	0.15	14	0.16	14%	10%
20	6	0.07	6	0.07	0%	1%
21	17	0.21	16	0.20	-6%	-8%
22	15	0.17	8	0.09	-88%	-85%

Summary Statistics on Number of HAE Attacks in LEVP2005-1/B

	CINRYZE	Placebo
N	22	
Mean	6.3	12.7
Difference	6.5	
95% CI on Difference	4.2 - 8.7	
Treatment Effect	[a]p < 0.0001	

[a]p-value based a test of the null hypothesis of no difference in attack frequency between prophylaxis periods. It was calculated using the Generalized Estimating Equation (GEE) method applied to the Poisson distribution.

Patients treated with CINRYZE had a 66% reduction in days of swelling (p<0.0001), and decreases in the average severity of attacks (p=0.0008) and the average duration of attacks (p=0.0004), as shown in the following table:

LEVP2005-1/B Clinical Trial Secondary Efficacy Outcomes

	CINRYZE N=22	Placebo N=22	Treatment Effect p-value
Mean Severity of HAE Attacks (Score from 1 to 3) (SD)	1.3(0.85)	1.9 (0.35)	0.0008
Mean Duration of HAE Attacks	2.1 (1.13)	3.4 (1.39)	0.0004

	CINRYZE N=22	Placebo N=22	Treatment Effect p-value
(Days) (SD) Days of Swelling (SD)	10.1 (10.73)	29.6 (16.9)	<0.0001

1. **Safety**

Safety analyses were assessed using the following measures: extent of exposure, AEs, vital signs, physical examinations, and laboratory tests. All summary safety analyses were carried out using subjects included in the safety dataset.

Twenty-two subjects were evaluated in study LEVP2005-1/B for routine prophylaxis.

There were no treatment-emergent serious adverse reactions related to CINRYZE in study LEVP2005-1/B.

Adverse reactions in trial LEVP2005-1/B that occurred in at least two subjects during CINRYZE prophylaxis, irrespective of the causality assessment, are given in the following table:

Table: Adverse Reactions in Routine Prophylaxis Study LEVP1005-1/B

Adverse Event	Number of Adverse Events	Number of Subjects (N = 24)
Sinusitis	8	5
Rash	7	5
Headache	4	4
Upper respiratory tract infection	3	3
Viral upper respiratory tract infection	5	3
Bronchitis	2	2
Limb injury	2	2
Back pain	2	2
Pain in extremity	2	2
Pruritus	2	2

Serious Adverse Events

There were no deaths during the pivotal study. There were 4 serious adverse events (SAEs) in study 2005-1 Part B. The SAEs were categorized as moderate in intensity and not related to study medication

Safety Conclusion

The adverse events appear to be related to intercurrent illnesses and the underlying disease rather than being due to treatment with CINRYZE. The small number of skin, hypotensive and pulmonary events, suggest that immune responses to the product, if they occurred, were not associated with typical hypersensitivity reactions. Therefore, CINRYZE appears to have an acceptable safety profile for prophylaxis of HAE attacks when administered according to the labeled dose schedule. However, since prophylaxis involves repeated and long-term treatment, a post marketing clinical study to evaluate safety and immunogenicity will be required.

2. **Advisory Committee Meeting**

The Blood Products Advisory Committee meeting convened on May 2, 2008 to discuss Lev Pharmaceuticals' clinical trial for the use of CINRYZE for the prophylaxis of Hereditary Angioedema attacks.

The Committee addressed two specific questions:

1. Is the safety and efficacy evidence sufficient for approval of CINRYZE for prophylactic treatment of HAE?

   The Committee unanimously agreed that the safety and efficacy evidence is sufficient for approval of CINRYZE for prophylactic treatment of HAE.

2. If the answer to Question #1 is yes, should post-marketing studies be performed to further evaluate the following:

- the optimal dose for prophylaxis in males and females
- immunogenicity
- long-term safety

The Committee agreed that post-marketing studies should be performed to address these issues and provided comments as to how these studies could be conducted.

1. **Pediatrics**

CINRYZE was granted orphan drug status on July 16, 2004. Pediatric Research Equity Act (PREA) does not apply to orphan indications.

2. **Other Relevant Regulatory Issues**

No other relevant regulatory issue to disclose

3. **Labeling**

The sponsor's proprietary name, CINRYZE, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective during the first and second review cycles and was found to be acceptable upon initial review on October 25, re-evaluation on December 13, 2007 and re-evaluation on August 5, 2008. OBBR concurred.

Full Prescribing Information (FPI): APLB reviewed the original FPI submitted by the applicant. Comments from a promotional and comprehension perspective were provided to OBRR on September 18 and November 26, 2007. Comments regarding the FPI were conveyed to the applicant on January 30, 2008. The applicant subsequently submitted a revised FPI. APLB reviewed the revised FPI on July 8, 2008 and provided additional comments to OBBR for discussion with the applicant. FDA's comments were conveyed to the applicant on September 22, 2008. The applicant accepted all of FDA's remaining comments and recommendations. All FPI issues have been adequately resolved to proceed with final approved labeling.

Carton and immediate container labels submitted in the original application were reviewed by APLB. Comments on them from a promotional and comprehension perspective were provided on November 26, 2007 (for original submission) and June 27, 2008 (for revised submission). The applicant submitted revised carton and container labeling that APLB reviewed on August 28, 2008. The applicant accepted all outstanding recommendations. All carton/container labeling issues were adequately resolved.

Patient labeling/Medication guide: Patient Information was included in all reviews of the FPI under Section 17 of the FPI. All issues were adequately resolved.

4. **Post-Marketing Studies**

Rationale for requiring a post-marketing study:

Only a single dose schedule was studied in the pivotal study LEVP2005-1/B for routine prophylaxis of angioedema attacks in patients with Hereditary Angioedema. Some subjects experienced little or no clinical benefit, as evidenced by no decrease in the angioedema attack frequency. It is reasonable to assume that the labeled dose schedule for routine prophylaxis will give similar results during the post-licensure period. Patients who experience little clinical benefit from the labeled dose schedule may decide to increase the intensity of the routine prophylaxis dose schedule by increasing the dose or by dosing more frequently. Published reports of nonclinical and clinical studies have shown there may be a risk of thrombosis from high doses of C1 inhibitor. There are no submitted data on the safety profile of an intensified dose schedule of CINRYZE for routine prophylaxis. This post-marketing

requirement (PMR) will provide the needed safety profile for a more intensified dose schedule for the routine prophylaxis indication.

A meeting was held on September 30, 2008, between members of the review team and Lydia Falk (CBER Senior Regulatory Affairs Advisor). The purpose of the meeting was to decide whether the phase 4 clinical study to evaluate the safety profile of an intensified dose schedule of CINRYZE for routine prophylaxis would be a post-marketing commitment (PMC) or a post-marketing requirement (PMR). At this meeting, Lydia Falk made the following points:

- The first and only-to-date example of a PMR in CBER is the required post-marketing study of the Rotarix vaccine. There was a concern about the rate of the serious adverse event intestinal intussusception, which the sponsor had agreed to study as a post-marketing commitment (PMC). CBER changed this PMC to a PMR under title IX of FDAAA even though the sponsor had already agreed to conduct a clinical trial to measure the rate of this serious adverse event.
- At the present time, the CBER Safety Working Group intends to make all post-marketing studies that are motivated by a safety concern about a serious adverse event that satisfies one of the three criteria stated in Subparagraph B of Title IX Section 901 of FDAAA as PMRs, not as PMCs, even if sponsors agree to conduct such studies (clinical trials) as PMCs.

Therefore, the request for this post-marketing study must be a PMR.

Post Marketing Requirement:

3. Lev Pharmaceuticals, Inc. is required to conduct a clinical trial designed to evaluate higher than labeled dose schedules of CINRYZE for routine prophylaxis of angioedema attacks in patients with Hereditary Angioedema (HAE). The objective of the clinical trial will be to define the safety profile of intensified dose schedules that may be used by patients who do not obtain an acceptable clinical benefit (reduction of HAE attack frequency) from the labeled dose schedule of CINRYZE for routine prophylaxis of HAE attacks. The clinical trial will include the following features:
   - ♋ Gender-balanced enrollment of subjects with HAE who are receiving CINRYZE for routine prophylaxis of HAE attacks at the labeled dose schedule, and who still have an unacceptable HAE attack frequency,
   - ♌ Procedures for establishing a baseline HAE attack frequency for each subject,
   - ♍ A dose escalation algorithm that is based on a conclusion of lack of acceptable clinical benefit (reduction of HAE attack frequency) for each subject,
   - ♎ Scheduled monitoring of adverse events, with emphasis on signs and symptoms of thrombotic adverse events, and
   - ♏ Scheduled monitoring for immunogenicity using a validated assay that can detect neutralizing antibodies to CINRYZE.

The following timetable gives the required milestones for the above post-marketing requirement:

Protocol Submission: within 3 months of the date of licensure

Trial/Study Start Date: within 9 months of the date of licensure

Final Report Submission: within 48 months of the date of licensure

Post Marketing Commitment:

----------(b)(4)----------:

4. ---------- ---(b)(4)---------- ----------.
5. ---------- ---(b)(4)---------- ----------.
6. ---------- ---(b)(4)----------(b)(4)----------.

1. **Recommendation**

   Approval