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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Safety Concerns Regarding C1 Esterase Inhibitors (Human) for Treatment of Hereditary Angioedema

CITIZEN PETITION

The undersigned submits this petition pursuant to the Federal Food, Drug, and Cosmetic Act ("FDC Act") and the Food and Drug Administration's ("FDA's") implementing regulations at 21 C.F.R. § 10.30 to request that FDA take the actions listed in Section I, below, in connection with CINRYZE[1] and BERINERT,[2] C1 Esterase Inhibitor (Human) ("C1-INH") products for the treatment of hereditary angioedema ("HAE").

Executive Summary

Two recent studies show that the incidence of thrombosis in patients prescribed C1-INH products presents an unacceptable risk, far greater than FDA has previously considered. The studies highlight the association between on-label use of C1-INH products and serious thromboembolic events, such as deep vein thrombosis, myocardial infarction, and embolic stroke. Despite these studies, current marketing materials for C1-INH products have begun encouraging off-label use of higher doses for HAE patients with inadequate responses to on-label doses. This is alarming given that FDA has long

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[1] CINRYZE (C1 Esterase Inhibitor (Human)) is approved under Biologics License Application ("BLA") No. 125267 (Oct. 10, 2008).

[2] BERINERT (C1 Esterase Inhibitor (Human)) is approved under BLA No. 125287 (Oct. 9, 2009).

recognized the direct relationship between C1-INH exposure and risk of thrombosis. Moreover, the studies that the sponsors of C1-INH products use to support the use of higher, off-label doses contain data that, themselves, link C1-INH products to the risk of thrombosis. In addition, current data also suggest a link between C1-INH products, infection, and sepsis in patients using permanent venous access ports and catheters.

Current C1-INH product labeling is inadequate, and these adverse events continue to occur despite existing warnings. Patients at increased risk of thromboembolic complications and infection should not be needlessly exposed to C1-INH products. Thus, FDA should first evaluate current data in its Adverse Event Reporting System ("AERS") database for additional evidence of the risk of thromboembolic complications, infections, and device-related injury. Then, the Agency should use its authority to require boxed warnings, a risk evaluation and mitigation strategy ("REMS"), a contraindication in patients at risk for thrombosis, and postmarketing studies to address these unacceptable risks.

I. ACTIONS REQUESTED

We request that FDA:

1) Add a boxed warning to the labeling for C1-INH products alerting of the risks of systemic venous and arterial thromboembolic complications associated with exposure to these agents;

2) Add a boxed warning to the labeling for C1-INH products alerting of the enhanced risk of thromboembolic and septic complications associated with administration of these products through a permanent venous access port or catheter;

3) Require a REMS program that ensures health care providers understand the risk of systemic venous and arterial thromboembolic complications associated with exposure to these agents and are able to identify and exclude from treatment any patient with pre-existing risk for thromboembolic complications;

4) Modify labeling to contraindicate C1-INH products in patients with underlying risk factors for thromboembolic complications;

5) Modify labeling to require direct medical supervision of administration of any of these agents through a permanently placed venous access port or catheter by a health care provider trained in the safe use of permanent venous access ports or catheters; and

6) Require Sponsors of C1-INH products to conduct studies to better define the true incidence of thromboembolic and septic complications associated with the use of these agents.

II. STATEMENT OF GROUNDS

Continued use of C1-INH products without effective boxed warnings, an effective REMS program, or contraindications in patients with underlying risk factors for thrombosis poses a significant public health concern. Recent reports of serious adverse events following exposure to C1-INH products warrant urgent action by the Commissioner in the interest of public safety.

A. Factual Background

Although HAE is a rare disease,[3] there are multiple approved drugs for HAE. Doctors and patients must be clearly informed of the benefits and risks of each HAE treatment so that, together, they can make informed decisions about each individual's treatment plan. To this end, data that describe serious, potentially life-threatening risks associated with these products should be clearly described in Package Inserts and Patient Medication Guides. For this reason and because evidence suggests that medical literature and current C1-INH product marketing materials do not fully present information related to the risk of serious thromboembolic complications and sepsis associated with exposure to C1-INH products, boxed warnings should be included in the labeling for both CINRYZE and BERINERT.

HAE is a life-threatening and debilitating disease. Before 2008, the need for HAE-treatment options in the United States was dire. Given the dramatic unmet need at the time, FDA acted quickly to approve first therapies for both prophylaxis and treatment of acute attacks.[4] Undeniably, FDA was correct in ushering through this new class of

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[3] HAE effects approximately 1 in 10,000 to 1 in 50,000 people worldwide (equivalent to about 6,000 – 10,000 patients in the US). Bruce L. Zuraw, Hereditary Angioedema, 359 New Eng. J. Med. 1027 (2008).

[4] CINRYZE was granted Fast Track designation on October 30, 2005, and on August 15, 2007 CINRYZE was granted priority review designation ensuring a decision within six months of its original BLA filing. CINRYZE

products. Acknowledging, however, that the pivotal studies were small (*e.g.*, the CINRYZE pivotal study enrolled a mere 24 subjects with only 22 subjects completing the study), FDA rightly noted that the small size of the studies was insufficient to detect the possible spectrum of serious, life-threatening adverse events. For example, during the CINRYZE Advisory Committee meeting on May 2, 2008, an Advisory Committee member emphasized the inability of such small sample sizes to identify risks that might emerge during repeated, long-term use. Specifically, Dr. Thomas Fleming, a professor of Biostatistics at the University of Washington stated that:

> [he would] encourage the FDA to work with the sponsor to provide greater clarification about the nature of the benefit-to-risk profile . . . .
>
> The safety data to date seem encouraging but 22 patients basically are enough to rule out events that would occur more than 15 percent of the time. So if there are serious events, the sample sizes still are inadequate to reliably detect those. So doing surveillance and possibly randomized trials to understand the rare events, the longer term safety and efficacy events . . . would all be important to benefit the patient population.[5]

Although current labeling of these products acknowledges the possible risk of thrombotic complications, inadequate emphasis is placed on this always-serious adverse event. In fact, current labeling does little to highlight the incidence of these events in C1-INH treated patients as documented by a recent report from Gandhi et al.[6] and an additional study of the AERS database (*see infra*). Furthermore, the current package inserts do not inform health care providers to evaluate patients for existing risk of thrombosis prior to prescribing C1-INH products or to exclude such patients from treatment with C1-INH products.

Final Clinical Review, at 17, *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm094092.pdf.

[5] Fleming, Thomas R., Ph.D., Professor, Department of Biostatistics, University of Washington, Blood Products Advisory Committee (May 2, 2008).

[6] Pranav K. Gandhi et al., *Thrombotic Events Associated with C1 Esterase Inhibitor Products in Patients with Hereditary Angioedema: Investigation from the United States Food and Drug Administration Adverse Event Reporting System Database,* 32 Pharmacotherapy 902 (2012) (attached in **Appendix A**).

In some patients, chronic intermittent infusion of C1-INH products through a peripheral vein results in the loss of available venous injection sites. In response to loss of venous injection sites, permanent indwelling venous access devices have historically been placed into patients. This is alarming because data show that the risk of thrombosis associated with the use of C1-INH products may substantially increase when administered through permanent indwelling venous catheters and ports. Moreover, supervising physicians, usually allergists,[7] are not sufficiently familiar with risks associated with these devices and are therefore not able to adequately supervise patients in the proper use of such devices.

There are currently four non-hormonal HAE-specific treatment options: CINRYZE, BERINERT, Kalbitor,[8] and Firazyr.[9] FDA should therefore revisit the approval of CINRYZE and BERINERT against the current regulatory backdrop. Moreover, the post-approval studies and adverse reporting case forms available to FDA should be reanalyzed by the Agency and a determination should be made to re-label and add warnings against the use of C1-INH products based on newly established and emerging safety data related to serious thromboembolic complications. In addition, the Agency should examine data describing serious thromboembolic and septic complications associated with the use of permanent indwelling venous access devices for chronic administration of C1-INH products.

1. Risk of thromboembolic complications and new safety signals related to infection, sepsis and device-related risks

Several recent studies raise serious concerns regarding the safety of C1-INH products and indicate that FDA may not have required adequate warnings regarding the risk of thromboembolic complications when it adopted revised labeling for CINRYZE and BERINERT in 2010 and 2011.[10] Moreover, these studies show the emergence of new, critical safety signals with regard to infection, sepsis, and device-related risks.

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[7] Ugochukwu C. Nzeako, *Diagnosis and Management of Angioedema with Abdominal Involvement: A Gastroenterology Perspective*, 16 World J. Gastroenterol. 4913 (2010); Ugochukwu C. Nzeako, Hilary J. Longhurst, *Many Faces of Angioedema: Focus on the Diagnosis and Management of Abdominal Manifestations of Hereditary Angioedema*, 24 Eur. J. Gastroenterol. Hepatol. 353 (2012).

[8] Kalbitor (Ecallantide) is approved under BLA No. 125277 (Nov. 27, 2009).

[9] Firazyr (Icatibant Acetate) is approved under New Drug Application ("NDA") No. 22-150 (Aug. 25, 2011).

[10] In the first quarter of 2010, FDA required revised labeling for CINRYZE and BERINERT based on potential signals discovered in the AERS database between January and March 2010. The label change added a warning that "Thrombotic events have been reported in patients receiving CINRYZE for routine prophylaxis" and

a. Gandhi Paper

Recently, in 2012, Gandhi et al. published results of an independent analysis of thrombotic events associated with the use of C1-INH in US patients.[11] The authors extracted cases from AERS database.

A Bayesian statistical methodology, Bayesian Confidence Propagation Neural Network Methodology ("BCPNN"), was used to identify potential signals of drug-associated adverse events.[12] The thromboembolic events identified in the AERS database by the authors' search included: deep vein thrombosis (n=2), transient ischemic attack (n=2), myocardial infarction (n=1), jugular vein thrombosis (n=2), pulmonary embolism (n=1), and embolic stroke (n=1). The authors stated that:

- The BCPNN analysis "highlighted an association between the use of Cinryze and the reports of thrombotic events in the AERS database;"[13]
- ". . . the thrombotic events identified in our study were associated with Cinryze administered at . . . the dosage recommended in their product's labeling;"[14] and
- "Our study findings merit attention, as thrombotic events were reported in patients using Cinryze at normal doses."[15]

"Thrombotic events have been reported at the recommended does of C1 Esterase Inhibitor (Human) products, including BERINERT, following treatment of HAE." AERS January – March 2010 report *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm216272.htm.

[11] *See* Gandhi at 2.

[12] "With BCPNN methodology, the association between the drug and adverse event is estimated using a measure of disproportionality called the information component (IC). The estimation of the IC value is dependent on parameters such as the number of unique drug reports, the specific adverse event, the listing of the specific drug-adverse event combination case reports, and the total number of reports in the database." *Id.* at 4.

[13] *Id.* at 6.

[14] *Id.*

[15] *Id.*

In their conclusion, the authors stated that "[t]he extracted reports from the AERS database indicated continuing cases of thrombotic events associated with the use of Cinryze for HAE."[16, 17]

b. AERS Study

An additional study ("AERS Study") was carried out and shows an alarming rate of thrombotic events and highlights the risk of infections.

The AERS database was queried cumulatively[18] through the second quarter of 2012 for all events that referred to "CINRYZE," "BERINERT," "BERINERT P,"[19] and "C1-Esterase Inhibitors."

The AERS Study sought to determine:

1. The overall volume of reports for each product;
2. The number of thromboembolic or thromboembolic-related events for each product;
3. The number of device-related infections for each product; and
4. The number of non-device-related infections for each product.

The results are listed below (in **Tables 1** and **2**) and in **Appendix B**, and indicate that the number of adverse events associated with C1-INH products is substantial and while the study cannot be used to calculate incidence estimates for these events because

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[16] *Id.* at 7.

[17] While the rationale for why Gandhi did not report any thrombotic events that involved BERINERT is unclear from the paper, it is useful to mention that BERINERT was approved nearly a full year after CINRYZE and therefore there may have been substantially less patient exposure to the relatively new BERINERT product during the study period (the study included data up to the second quarter of 2011). Also, because FDA and the medical literature have noted the similarity between CINRYZE and BERINERT, including the similar class effects regarding safety, adverse event data for CINRYZE used in the Gandhi paper can be logically applied to BERINERT.

[18] Using a list of specialized MedDra search terms listed in List A of **Appendix B**.

[19] Berinert P is not marketed in the US but did account for one (1) of the sixty-seven (67) AERS in the study.

adverse event reporting is incomplete, the number of adverse events may be considerably larger than FDA considered in the 2008 and 2009 initial approvals of CINRYZE and BERINERT, the 2010 Potential signals of serious risks/new safety information identified by the AERS between January – March 2010 and subsequent relabeling,[20] and the 2011 supplemental approvals of both C1-INH products.[21]

The results of the AERS Study are consistent with those of Gandhi et al. described above but also add a significant number of BERINERT-related serious adverse events. The study therefore shows that the use of CINRYZE and BERINERT is associated with a significant and unappreciated risk of serious thromboembolic events. Such events can occur in all exposed patients, but may occur at higher frequencies in patients with underlying risks for thrombosis (*e.g.*, diabetes, obesity, history of thrombosis, cigarette smoking, use of birth control pills) or in patients with chronic indwelling catheters and venous access ports.

Comparing the Gandhi paper to the AERS Study highlights the important need for FDA to assess the risk of thrombosis for C1-INH products because FDA's last analysis of the data was in 2010 for CINRYZE and 2011 for BERINERT and did not include a sufficiently developed dataset. Gandhi et al. did not include any reports of BERINERT-related thrombosis, likely because its dataset only extended into the second quarter of 2011. In comparison, the AERS Study included a dataset with events that occurred up to the second quarter of 2012 and found a significant number of BERINERT-related thrombotic events. This comparison shows that the dataset FDA analyzed may not have been sufficiently developed and that the seriousness of the risk from BERINERT-related thrombosis may be substantially underappreciated.

The AERS Study also highlights the significant and unappreciated risk of infections and sepsis in HAE patients, with and without permanent indwelling catheters and ports, treated with C1-INH products. (*See* **Appendix B**).

It is important to note that: 1) these events are serious and many were likely life-threatening; 2) additional events may have occurred and were not reported or recognized

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[20] U.S. Food and Drug Administration. Potential signals of serious risks/new safety information identified by the Adverse Event Reporting System (AERS) between January – March 2010 *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm216272.htm.

[21] The AERS database contains voluntary reporting that may represent only a small fraction of the actual adverse events that have occurred in this patient population.

as potentially C1-INH related; and 3) the lack of recognition of the association between C1-INH administration and risk of thrombosis and infection may result in patients being re-exposed to C1-INH products after suffering a thrombotic complication or serious infection. In addition, the rate of C1-INH product catheter- and port-related complications may be quite high because only a subset of patients receiving C1-INH therapy use catheters and ports.[22]

c. Lack of evidence refuting the risk of thromboembolic complications, infections, and device-related risks

Against the backdrop of mounting evidence of SAEs related to thromboembolic complications, infections (including sepsis), and device-related risks, there is a lack of evidence refuting these risks.

We know of one paper in the medical literature that deemphasizes these risks, entitled "Safety and Efficacy of Prophylactic Nanofiltered C1-inhibitor in Hereditary Angioedema." In 2012, Zuraw and Kalfus published the paper and described an open-label study of 146 subjects with HAE who received C1-INH product for up to 2.6 years and received 1000 units every 3 to 7 days.

In the safety section of this report, the authors wrote that:

> a total of 99 of the 101 serious adverse events reported were considered not related to [C1-INH], and 2 serious adverse events were of unknown relationship. Five subjects (all with underlying risk factors for thrombotic events) experienced serious adverse events of a thromboembolic nature (myocardial infarction, deep vein thrombosis, cerebrovascular accidents and pulmonary embolism), *but none were considered study drug related.*[23]

However, no evidence was presented in the paper to support the conclusion that the five thrombotic events in the open-label study were not study-drug related.[24] In fact, the adverse events dismissed in the Zuraw and Kalfus paper were of the same nature as those

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[22] For example, if 100 patients used C1-INH products, it is possible that only 25 use indwelling catheters and ports. So if there are 5 catheter- and port-related SAEs, the incidence of catheter- and port-related SAEs would actually be 20%, rather than 5%.

[23] Bruce L. Zuraw, Ira Kalfus, *Safety and Efficacy of Prophylactic Nanofiltered C1-inhibitor in Hereditary Angioedema* Am. J. of Medicine, at 5 (2012) (emphasis added) (attached in **Appendix C**).

[24] The results of this analysis may actually indicate that the risk of thrombotic complications is 5/146 = 3.42%.

that appeared in the AERS database review conducted by Gandhi et al. in which the authors concluded that "the thrombotic events identified in our study were associated with Cinryze administered at . . . the dosage recommended in their product's labeling"[25] and the medical reviewer for Cinryze's 2011 postapproval study ("PAS") labeling supplement who stated that the "possible contribution of Cinryze to the TE events in 4 of these 5 subjects cannot be excluded at this time."[26]

It is even more disconcerting that Zuraw and Kalfus suggest "further dose adjustment on the basis of response to therapy," implying that doctors should consider increasing the dose given to patients whose HAE is "not well controlled even at twice-weekly dosing"[27] despite evidence that the risk for thromboembolic complications increases with higher doses.[28]

Therefore, the combination of medical literature and inadequate product labeling in the current Package Insert may result in patients and health care providers incorrectly concluding that the risk of serious thromboembolic complications from C1-INH therapy are minimal, even at doses higher than approved in labeling.

d. Conclusion: There is mounting evidence of thromboembolic complications infections, and device-related risk and that the current warnings are inadequate

Evidence presented in the Gandhi paper and AERS Study raises serious concerns regarding the safety of C1-INH products and their associated risks of thromboembolic complications, infections (including sepsis), and device-related risks.

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[25] Gandhi at 6.

[26] CINRYZE Summary Basis for Regulatory Action, at 17 (Jan. 2011).

[27] Zuraw & Kalfus at 6.

[28] *See e.g.*, CINRYZE Summary Basis for Regulatory Action, at 59 ("If HAE patients who do not receive an adequate clinical benefit (reduction in HAE attack frequency) from the labeled routine prophylaxis dose schedule choose to intensify the routine prophylaxis dose schedule, there may be a thrombotic risk."); CINRYZE Package Insert at 4-5; CINRYZE Pharmacology/Toxicology Review Memorandum, at 12-13 (Dec. 28, 2007), (explaining that evidence from animal models suggests that "[e]xceeding recommended doses of C1-INH (>20 U/kg max of two doses) can have thrombogenic risk) *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm229783.pdf

2. Regulatory history of CINRYZE relevant to the risk of thromboembolic complications

During the initial review of CINRYZE, FDA identified the potential for thrombotic events but did not observe any such events in the single pivotal trial's 24 subjects. Despite this lack of events, FDA required CINRYZE's package insert to include a warning of thrombotic events when used off-label at higher than approved doses.

Then, when FDA reviewed labeling in 2010 after observing postmarketing signals of thrombosis, the Agency modified the CINRYZE package insert to include a warning about the risk of thrombogenicity at levels used on-label for prophylaxis.

Now, we urge FDA to consider the additional data relating to the risk of thrombotic events and analysis contained in this Citizen Petition. The evidence used to evaluate the risk of thromboembolic events in 2010 was incomplete and therefore may have underestimated the true risk. Risk data that have emerged since 2010 indicate that the trend in thrombotic-event-related adverse reactions continues in spite of the new, more explicit warnings following FDA's 2010 review.

a. Initial approval

CINRYZE's initial approval letter states that "available data indicates the potential for a serious risk, i.e. thrombosis, with the use of the product when administered at higher than labeled dose schedules."[29] The Summary Basis memo also noted that "In vitro and in vivo thrombogenicity studies indicate a potential for clot formation when CINRYZE is administered other than for replacement therapy."[30]

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[29] CINRYZE Approval Letter, at 3 (Oct. 10, 2008), *available at* http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm093602.htm.

[30] CINRYZE Summary Basis for Regulatory Action, at 9 (Oct. 10, 2008).

b. 2009 Untitled Letter

On June 9, 2009, before there was substantial evidence of an *actual* risk of thrombotic events at on-label doses, FDA issued an Untitled Letter regarding, *inter alia*, the Sponsor's failure to warn about thrombotic events and highlighted the Sponsor's history of inadequate labeling with regard to promotional materials and omission and minimization of risk information.[31] FDA also noted that the Sponsor "fail[ed] to provide any information pertaining to the potential risk of thrombotic events with the use of CINRYZE."[32]

c. Potential signals of serious risks and new safety information identified by the Adverse Event Reporting System (AERS) between January – March 2010

FDA identified "[t]hromboembolic events in patients with certain thrombogenic risk factors" as a potential risk factor for C1-INH products based on information identified by the AERS between January – March 2010.[33] Notably, FDA found that these signals were sufficient to update labeling after less than a year and a half after CINRYZE's approval. Based on the limited number of AERS signals at the time, FDA required CINRYZE to include the following expanded warning: "Thrombotic events have been reported in patients receiving CINRYZE for routine prophylaxis."

d. Supplemental approval

In 2011, FDA approved the Sponsor's PAS labeling supplement to incorporate additional safety data from an open-label uncontrolled trial into labeling. FDA noted that from the data presented from the open-label extension study:

> there were a total of 5 thrombotic/thromboembolic (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 thrombosis of the subclavian and internal jugular veins

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31 CINRYZE Untitled Letter (June 9, 2009).

32 *Id.*

33 Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between January – March 2010 *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm216272.htm.

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.[34]

Because the data used in this study were the same as were used in the 2010 AERS monitoring, the Agency stated it would not add additional warnings based on duplicate data.[35]

e. Current marketing material

Current marketing material for CINRYZE do not adequately present risk information. For instance, a piece entitled "Taking the next step – Path to Independence" provides only minimal thromboembolic complication warnings and states only to "Tell your healthcare provider about all of your medical conditions, including if you . . . Have a history of blood clotting problems. Very high doses of C1 esterase inhibitor could increase the risk of blood clots."[36]

Also, a piece entitled "Power of prevention" states "Allergic reactions may occur with CINRYZE. Call your healthcare provider or get emergency room support services right away if you have any of the following symptoms . . . ."[37] Importantly, none of the unique symptoms of thrombosis are included in the labeling such as slurred speech or loss of consciousness. An additional statement mentions "Important Risk Information . . . 'Tell your healthcare provider about all of your medical conditions, including if you . . . Have a history of blood clotting problems. Very high doses of C1 esterase inhibitor could increase the risk of blood clots.'" However, marketing materials such as these do not adequately explain the serious risk of thromboembolic complications at normal doses.

A ViroPharma press release from November 13, 2012 further highlights the inappropriate minimization of the risk of thrombosis in current marketing materials.[38]

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[34] CINRYZE Summary Basis for Regulatory Action, at 16 (Jan. 2011).

[35] *Id.* at 15.

[36] "Taking the next step – Path to Independence," at 3 (Dec. 2010) (attached in **Appendix D**).

[37] "Power of prevention," at 4 (Feb. 2011) (attached in **Appendix D**).

[38] ViroPharma Press Release, "ViroPharma's Cinryze® (C1 Esterase Inhibitor [Human]) Prophylaxis Study Showed Safety Data of Escalating Doses in Patients with Hereditary Angioedemia" (Nov. 2012) (attached in **Appendix D**).

The press release reported on a presentation entitled "Safety and Efficacy of Escalating Doses of C1 Esterase Inhibitor [Human] (Cinryze) as Prophylaxis in Patients with Hereditary Angioedema (HAE)" and stated that "higher doses of Cinryze do not result in systemic thrombotic events, and may be considered for patients with HAE who do not respond to lower doses."[39] This statement is alarming for at least two reasons. First, it minimizes the warnings in FDA-approved labeling related to thrombotic events. Second, it ignores the fact that a blood clot *did in fact* occur in the 20-patient study which suggests that the study only further confirmed the risk of thrombosis.

3. Regulatory history of BERINERT relevant to the risk of thromboembolic complications

As with CINRYZE, FDA identified the potential for thromboembolic complications related to the use of BERINERT during the product's initial review and included a warning about higher-than-recommended doses in the original package insert. The BERINERT package insert was also subsequently amended as a result of a signal raised by the AERS between January – March 2010.[40]

a. Initial approval

In BERINERT's initial approval letter FDA noted that "Use of [BERINERT] at higher than recommended doses has been associated with fatal thrombotic events in a clinical trial of pediatric subjects where the product was administered for an indication other than hereditary angioedema. The minimum dose of your product associated with thrombotic events is unknown."[41]

The Review for Pharmacovigilance Planning[42] noted that "[s]ince 1985 a total of 15 spontaneous reports of thrombosis were received by the sponsor. The outcome was fatal in 11 cases (10 off-label use), recovered in one case and unknown in three cases. 14/15 reports were in off label use in cardiac surgery (12 newborns, one 6 year old, one

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39 *Id.*

40 Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between January – March 2010 *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm216272.htm.

41 BERINERT Initial Approval Letter (Oct. 9, 2009).

42 BERINERT Review for Pharmacovigilance Planning (October 22, 2008).

72 year old). One report was in a 52 year old, for which causality was excluded after autopsy." The Pharmacology/Toxicology Review Memo also noted that "[i]t is known that doses in children and neonates administered BERINERT® P do exhibit thrombogenicity at 90 U/kg (4.5 fold the recommended clinical dose)."[43]

It is important to note that the pivotal study for BERINERT only observed the safety profile of the biologic from a single exposure during a 12-week period in 124 patients. This single exposure to BERINERT over such an extended length of time is a poor comparison to real-world conditions and actual use. For many patients, HAE attacks occur at a rate of approximately one to more than five times per month during their lifetimes and therefore exposure to BERINERT is repeated, frequent, and long term unlike the single exposure in BERINERT's pivotal trial.

b. Potential signals of serious risks and new safety information identified by FDA's AERS between January – March 2010

FDA also required relabeling of BERINERT on the basis of potential signals of serious risks/new safety information identified by FDA's AERS between January – March 2010 (*see supra*). The following expanded warning was added in 2011: "Thrombotic events have been reported at the recommended dose of C1 Esterase Inhibitor (Human) products, including BERINERT, following treatment of HAE."

c. Supplemental approval

On December 22, 2011, FDA approved an additional indication for the treatment of laryngeal attacks of HAE.[44] FDA also commented on the issue of safety during postmarketing and stated:

> Postmarketing adverse events in the FDA AERs database were recently reviewed for approved Berinert labeling supplement 117, which strengthened statements in the package insert concerning thrombotic and thromboembolic events to indicate that such events [in very small numbers] have been observed after administration of Berinert at the recommended dose for the treatment of acute HAE attacks.

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[43] BERINERT Pharm/Tox Review Memo, at 5 (Sept. 10, 2009).

[44] BERINERT Approval Letter, at 1 (Dec. 22, 2011).

> FDA concluded that recently examined postmarketing AERs database for Berinert does not change the favorable risk: benefit balance for the two existing indications or the new indication, treatment of acute laryngeal HAE attacks, for any age group.[45]

These statements indicate that based on the data available at the time, FDA was not aware of the full risk of thromboembolic complications for BERINERT reported in the 2012 Gandhi paper and AERS Study because it was relying on the same, limited data available from the January – March 2010 timeframe.

d. Current marketing material

Current BERINERT marketing material insufficiently describes the risk of thromboembolic complications. For example, the marketing piece: "BERINERT Helps You Take Control of Your HAE Attacks" only states that patients should "report signs and symptoms of thrombosis that occur after infusing: including swelling and pain in the limbs, or abdomen, chest pain, shortness of breath, loss of sensation, or motor power, or altered consciousness or speech."[46] This risk information is not presented until page 8 of the 18-page document and does not include a warning that patients should discuss their history or thrombotic events.[47]

4. REMS, Contraindications, Self-Administration Warnings

Despite the risks associated with C1-INH products, there are currently no REMS, contraindications, or self-administration warnings for these products.

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[45] BERINERT Summary Basis for Regulatory Action, at 24-25 (Dec 11, 2011).

[46] "BERINERT Helps You Take Control of Your HAE Attacks," at 8-9 (Jan. 2011) (attached in **Appendix D**).

[47] It also does not include a statement "you should have epinephrine with you" to deal with shock.

5. Device-related issues

Risks associated with indwelling catheters and venous access ports are well-known.[48] In the AERS Study, there were five (5) unique device-related infection events. Infections and thrombotic events are highly associated with the use of these devices in administering C1-INH products. While the numbers included from the AERS Study are not intended to be the sole basis for regulatory action by FDA, they underscore the need for action by FDA to use its resources to investigate the alarming safety concerns associated with the use of devices in conjunction with C1-INH products, particularly the enhanced risk of thromboembolic and septic complications associated with the administration of C1-INH products.[49]

a. Device-related infections and sepsis are high risk events

Risk of infection and sepsis is particularly dangerous. The AERS Study indicates that there have been at least five (5) C1-INH-related infections associated with device usage reported in the AERS.

b. Allergists are ill-equipped to implant, manage, and remove indwelling catheters and ports

HAE patients are generally managed by allergists.[50] However, most allergists lack adequate training in the use of indwelling catheters and ports. Given the high risk associated with these devices, including the risk of thromboembolic events and infections, this lack of training presents an opportunity to improve the risk-benefit profile for patients with permanent indwelling venous catheters and ports by ensuring adequately

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[48] *See e.g.*, Naomi P. O'Grady, et al. *CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011* at 8-9 (2011) (discussing the risk of infection associated with intravascular catheters) *available at* http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf, Robert W. Taylor, Ashok V. Palagiri, Central venous catheterization, 35 Critical Care Medicine 1390, 1390 (2007) (describing amongst other risks, the serious risk of thrombosis associated with central venous catheters).

[49] There is no way of knowing how accurate the AERS database is. It is well-recognized that this voluntary reporting system captures only a fraction of all adverse drug experiences. Nevertheless, information in the AERS database is useful in identifying problems that FDA should further investigate.

[50] Ugochukwu C. Nzeako, Hilary J. Longhurst, *Many Faces of Angioedema: Focus on the Diagnosis and Management of Abdominal Manifestations of Hereditary Angioedema*, 24 Eur. J. Gastroenterol. Hepatol. 353 (2012); Ugochukwu C. Nzeako, *Diagnosis and Management of Angioedema with Abdominal Involvement: A Gastroenterology Perspective*, 16 World J. Gastroenterol. 4913 (2010).

trained individuals oversee: (1) the administration of these drugs for patients using these devices; (2) the implantation and removal of the devices; and (3) their maintenance.

In addition, permanent indwelling venous catheters and ports are known to suffer from patency issues such as blockages that potentially prevent adequate administration of C1-INH product. Patency is particularly concerning with BERINERT because it is used to treat acute HAE attacks, including laryngeal attacks. This concern arises because a delay in treatment due to occlusion could increase the chance of asphyxiation, especially in the home-administration setting.

B. Legal Background

The "primary objective of prescription drug labeling is to provide the essential information the practitioner needs to use the drug safely and effectively in the care of patients"[51] such as "the directions for use and cautionary statements, if any."[52] Thus, the manufacturer of a prescription drug is required to provide adequate labeling for practitioners to be able to administer or dispense the drug safely and for the purposes for which it is intended.[53] Therefore, the manufacturer must provide adequate information to the health professional, whose burden it is to decide whether to prescribe the medicine for a particular patient, knowing the risks and benefits associated with the drug.[54]

FDA may determine that a drug is misbranded if the Agency finds the labeling to be false or misleading[55] for failing to reveal certain facts material to the customary or usual conditions for use of the drug.[56] FDA asserts that the FDC Act requires that "[a]n adequate warning of possible danger must appear on all [drug] labeling . . . or the product is misbranded."[57]

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[51] 40 Fed. Reg. 15,392 (Apr. 7, 1975).

[52] 21 U.S.C. § 353(b)(2) (FDC Act § 503(b)(2)).

[53] 21 C.F.R. § 201.100.

[54] *United States v. Evers*, 643 F.2d 1043, 1052 (5th Cir. 1981).

[55] 21 U.S.C. § 352(a) (FDC Act § 502(a)).

[56] 21 U.S.C. § 321(n) (FDC Act § 201(n)).

[57] 39 Fed. Reg. 33,229 (Sept. 16, 1974).

Thus, in the labeling for any prescription drug, FDA requires that cautionary information be categorized according to the relative severity of the hazard and the degree to which the risk has been substantiated. Accordingly, drug package inserts contain many detailed paragraphs of information about side effects to assist physicians in making prescription decisions. Depending on the relative severity of the hazard, topic headings in prescription drug labeling are set forth in descending order of importance as "Contraindications," "Warnings," "Precautions," and "Adverse Reactions."[58] Therefore, "as known adverse side effects increase in intensity and severity, the manufacturer's warning in respect to the drug's potential for harm should accordingly ascend to a higher category." [59]

FDC Act § 505(o)(4) gives FDA authority to compel labeling changes when it becomes aware of "new safety information" at any time after a drug is approved. Such information can come from a clinical trial, adverse events reports, or other scientific data; it can also include new analysis of previously existing data.

1. Boxed warnings

Under 21 C.F.R. § 201.57(c)(1), a boxed warning may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury. Two key considerations for boxed warnings are: (1) the severity of the hazard, and (2) the degree to which the risk is substantiated.[60]

FDA considers certain contraindications or serious warnings, particularly those that may lead to death or serious injury, to potentially require a boxed warning.[61] The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.[62]

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58 21 C.F.R. §§ 201.56, 201.57.

59 *McFadden v. Haritatos*, 448 N.Y.S.2d 79, 81 (N.Y. App. Div. 1982).

60 Judith E. Beach, et al., *Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs*, 53 Food and Drug Law J. 403, 404 (1998).

61 21 C.F.R. § 201.57(c)(1).

62 *Id.*

A boxed warning is ordinarily used to highlight whether:

> There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug; ***OR***
>
> There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); ***OR***
>
> FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act [] "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).[63]

"Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS section should therefore be evaluated to determine whether it warrants inclusion in a boxed warning."[64]

2. Contraindications

If, in any situation, a drug "should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefits," the drug should be contraindicated in that situation.[65] These situations must be known, not theoretical.[66]

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[63] FDA, Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, at 11 (Oct. 2011) *available at* http://www.fda.gov/downloads/Drugs/.../Guidances/ucm075096.pdf.

[64] Warnings and Precautions Guidance at 11.

[65] 21 C.F.R. § 201.57(c)(5).

[66] *Id.*

3. Warnings

The Warnings "section must describe clinically significant adverse reactions (including *any* that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification)."[67] A summary of the most clinically significant warnings and precautions information must be included in the Highlights of Prescribing Information section of labeling for the drug product.[68]

"In accordance with 314.70 and 601.12 of [the Food and Drug regulations], the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[69]

4. REMS

Under FDC Act §505-1(a)(2)(A), "[i]f the Secretary has approved a covered application (including an application approved before the effective data of this section) and did not when approving the application require a risk evaluation and mitigation strategy. . . the Secretary. . . may subsequently require such a strategy for the drug involved (including when acting on a supplemental application seeking approval of a new indication for use of the drug) if the Secretary becomes aware of *new safety information* and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risk of the drug."[70]

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67 21 C.F.R. § 201.57(c)(6) (emphasis added).

68 21 C.F.R. § 201.57(a)(10).

69 21 C.F.R. § 201.57(c)(6).

70 (Emphasis added).

5. Postapproval clinical trial

Under FDC Act §505(o), FDA may require a postapproval study or clinical trial of a drug product in an approved NDA or BLA if the Agency becomes aware of new safety information. Under section 505(o)(3)(A) through (B) of the FDC Act, the requirement must be based on scientific data and for one or more of the following purposes:

- To assess a known risk related to the use of the drug involved;
- To assess signals of serious risk related to the use of the drug; or
- To identify an unexpected serious risk when available data indicate the potential for a serious risk.[71]

6. New safety information

"New safety information" is derived from a clinical trial, an adverse event report, a postapproval study (including a study under FDC Act § 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under FDC Act § 505(k); or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the product that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.[72]

C. Analysis

In 2010, FDA conducted a review of C1-INH product postmarketing data. The review demonstrated that there is a real risk of thrombosis that may lead to serious injury. Despite the 2010 CINRYZE and 2011 BERINERT labeling changes that strengthened warnings related to risks of thrombotic events, current C1-INH product marketing materials insufficiently convey these risks, medical literature inadequately presents these risks, and serious thrombotic events continue to occur.

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[71] Furthermore, before requiring a postapproval study, FDA must make a determination that adverse event reporting under section 505(k)(1) and the active postmarket risk identification and analysis system under section 505(k)(3) of the FDC Act are not sufficient to meet the purposes outlined above (section 505(o)(3)(D)(i)). Before requiring a firm to conduct a postapproval clinical trial, FDA must make a determination that a postapproval study will not be sufficient to meet the purpose outlined above (section 505(o)(3)(D)(ii)).

[72] 21 U.S.C. § 355-1(b)(3) (FDC Act § 505-1(b)(3)).

Based on the evidence presented in this Citizen Petition, the current labeling of C1-INH products does not adequately warn health care providers and patients about the serious risk of thromboembolic and septic complications. In particular, taking steps to ensure that health care providers and their patients are better informed about the risks of C1-INH-associated thrombosis and sepsis may help to decrease the number of the adverse events. The significance of the risk of C1-INH-associated thrombosis and sepsis and the benefits of increased awareness by health care professionals justify the need for a boxed warning under 21 C.F.R. § 201.57(c)(1), a REMS under FDC Act § 505-1, and a contraindication under 21 C.F.R. §201.57(c)(5).

1. Thromboembolic complications

Thromboembolic complications represent serious, life-threatening risks. FDA has reviewed evidence of at least five (5) thrombotic events in postmarketing studies[73] and has noted that these events occurred in "subjects [that] had underlying risk factors for thrombotic events."[74] However, the current labeling only warns health care providers to "Monitor closely patients with known risk factors for thrombotic events."[75] This warning: (1) is too weak; (2) does not give adequate prominence to the risk of thromboembolic complications; and (3) does not adequately ensure that patients at risk for thromboembolic complications are excluded from this treatment option.

As mentioned above, "as known adverse side effects increase in intensity and severity, the manufacturer's warning in respect to the drug's potential for harm should accordingly ascend to a higher category."[76] Therefore, based on the mounting evidence presented in this Citizen Petition, the risk of thromboembolic complications should be included in a boxed warning and REMS.

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[73] CINRYZE Package Insert, at 5; CINRYZE Summary Basis for Regulatory Action, at 17.

[74] CINRYZE Package Insert, at 5.

[75] *Id.*

[76] *McFadden v. Haritatos*, 448 N.Y.S.2d at 81.

a. Boxed warning

The incidence and serious nature of thrombotic events are inadequately described in the package insert and labeling and should be included in a boxed warning. Ongoing reports of thromboembolic complications warrant reconsideration of the risks and benefits to public health in continuing to allow C1-INH products to be marketed without a boxed warning against thrombotic events and corresponding REMS, especially considering that four (4) non-hormonal HAE-specific treatments are available and C1-INH products no longer fill the unmet need they did in 2009 and 2010.

Although the Gandhi paper and AERS Study cannot provide incidence estimates for these events because adverse event reporting is incomplete, both provide evidence that these thrombotic events are occurring at a rate that warrants a boxed warning. According to the AERS Study, there have been multiple unique reported cases of thrombotic events. (*See* **Table 1**).

Table 1: Reports of Thrombotic Events

Thrombotic Events	
BERINERT and BERINERT P	9
CINRYZE	16
C1-INH products	19

As mentioned above, key considerations for boxed warnings include whether the inclusion of risk information in a boxed would help:

- To ensure that the prescribing doctor has the necessary information to perform risk/benefit analyses for the specific patient in particular circumstances;
- To ensure safe and effective dosing of the drug;
- To secure crucial methods and settings for administration of the drug; and
- To promote the monitoring of patients for serious, but possible reversible, adverse reactions.[77]

[77] Beach at 410.

By adding a boxed warning that indicates there is a serious risk of thrombotic events during the course of normal treatment with C1-INH products, and that the risk increases with increased doses of C1-INH, doctors and patients will be more likely to discuss the benefits and risks of C1-INH therapies, the risk of associated thrombotic events, and whether the patient has known risk factors for thrombotic events. Doctors will also be better able and more likely to identify patients with favorable risk-benefit ratios. Patients that are at an increased risk of thrombotic events can, therefore, be advised to use one of the alternative HAE therapies and avoid further increasing their risk of thrombotic events.

The addition of a boxed warning is also important because the added prominence of the warning will create greater awareness of thromboembolic risk and facilitate early detection of side effects related to thromboembolic complications. This early detection by physicians, patients, and caregivers may result in more rapid intervention during a thrombotic event, thereby reducing the risk of long-term and serious injury.

The boxed warning should also indicate that increased doses are associated with increased risk of thrombosis. Therefore, if the normal treatment dose is ineffective, a physician aware of the increased risk of thrombosis associated with increased dosages would consider using a different treatment rather than increasing the dose, especially in patients with pre-existing risks for thromboembolic complications.

(1) Proposed boxed warning

The following boxed warning should be incorporated into each C1-INH product package insert:

> Thrombotic and thromboembolic events have been reported during post-marketing surveillance following routine administration of CINRYZE/BERINERT. Evidence also indicates that the risk of thromboembolic complications increases with dose.
>
> CINRYZE/BERINERT is CONTRAINDICATED in patients with underlying risk factors for thrombosis. Physicians should consider patients' risk of thromboembolic complications before prescribing CINRYZE/BERINERT and evaluate other available treatment options for these patients.
>
> Administration of CINRYZE/BERINERT through permanent venous access ports and catheters has also been reported to increase the risk thromboembolic and septic complications. [78]
>
> (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

[78] This paragraph of the proposed boxed warning is discussed below.

(2) Precedent for boxed warning for thromboembolic events

There is strong precedent for requiring boxed warnings for thromboembolic events, including other fractionated plasma products that are administered as both prophylaxis and acute treatment. For example, FEIBA NF, an infusion drug for hemophilia, also made from human plasma, includes the following boxed warning:

> Thrombotic and thromboembolic events have been reported during post-marketing surveillance following infusion of FEIBA VH and FEIBA NF, particularly following the administration of high doses and/or in patients with thrombotic risk factors (See WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

This example is particularly applicable because like CINRYZE and BERINERT, FEIBA NF is indicated for a serious condition (the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and hemophilia B patients with inhibitors), and yet medical literature indicates that the rate of thrombosis is relatively low with only 8.24 incidents per 10^5 infusions (CI, 4.71-13.4 per 10^5 infusions).[79]

FDA has also included boxed warnings related to increased risk of thromboembolic complications on a wide range of other drugs that treat both non-serious diseases and serious, life-threatening diseases, including Caldolor (ibuprofen), Ortho Evra (ethinyl estradiol and norelgestromin), NuvaRing (etonogestrel/ethinyl estradiol), Zortress (everolimus), and Evista (ralovifene HCl).

(3) Current marketing materials

Current marketing materials have failed to adequately convey the risk of thromboembolic complications and current labeling insufficiently addresses these risks. (*See supra.*)

Adding a boxed warning to the package inserts will better ensure that risk is appropriately presented in marketing materials. Also, the presence of a boxed warning, per 21 C.F.R. § 202.1(e)(2)(ii), will prohibit reminder advertisements for C1-INH

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[79] Louis M. Aledort, *Comparative Thrombotic Event Incidence After Infusion of Recombinant Factor VIIa Versus Factor VIII Inhibitor Bypass Activity*, 2 J. Thromb. Haemost. 1700, 1700 (2004).

products. Removing reminder advertisements for C1-INH products is important so that doctors do not disassociate serious risks from C1-INH products.

A boxed warning also will improve the reporting of thromboembolic complications because doctors, patients, and caretakers will be better able to identify symptoms of thrombosis and recognize the need to both take medical action to reduce the risk of thrombosis and report the adverse events to FDA.

(4) Conclusion

A boxed warning is appropriate because thromboembolic complications are adverse reactions so serious in proportion to the potential benefit of using C1-INH products over other available HAE therapies that it is essential that the risk be assessed by health care professionals before the products are prescribed. In addition, a boxed warning could alert the prescribing physician that thromboembolic complications could be prevented or the risk could be reduced by screening for pre-existing risk for thromboembolic complications (*e.g.*, diabetes, obesity, history of thrombosis, cigarette smoking, use of birth control pills) and patients requiring chronic indwelling catheters and venous access ports for administration of C1-INH products.

b. REMS

A REMS is appropriate given the seriousness of the risk of thromboembolic complications, the lack of awareness of the risks among health care providers regarding the risks, and the need to communicate risk to patients and physicians. The Gandhi paper and AERS Study present important new safety data and provide evidence of a serious signal. Additionally, a review of current marketing materials and medical literature suggests that doctors have not been adequately informed of the risks associated with thromboembolic complications.[80] Therefore, the risks associated with thromboembolic complications should be addressed in a REMS Communication Plan.

A Communication Plan that includes a "Dear Health Care Provider" letter and a Medication Guide would aid health care professionals in informing patients of the risks associated with C1-INH products and better enable patients to be matched with the most appropriate HAE therapy.

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[80] *See e.g.*, Untitled Letter to CINRYZE, 6/9/2009.

Ample precedent exists with regard to the risk of thrombosis and the requirement of a REMS. For example, FDA required a REMS for, *inter alia*, the risk of thrombosis associated with OMONTYS (an erythropoiesis-stimulating agent indicated for the treatment of anemia due to chronic kidney disease in adult ("ESA") on dialysis only).[81, 82] Additionally, the HAE treatment space already has a REMS for a similar product, Kalbitor. The Kalbitor REMS was implemented to address the risk of anaphylaxis, which is labeled at a rate of 3.9%.[83] For the C1-INH products, the incidence of an equally serious condition (thrombosis) was nearly the same with a 3.4% rate of thrombosis in the open-label extension study.[84]

Gandhi's peer-reviewed medical literature presented in this Citizen Petition along with the data extracted from the AERS Study meet the definition of "new safety information" in FDC Act §505-1(b)(13) because this information regarding the serious risk associated with the use of C1-INH products is derived from adverse event reports, postapproval studies, and peer-reviewed biomedical literature that were developed only after both CINRYZE and BERINERT were approved.

2. Boxed warning addressing device-related risks

C1-INH product labeling does not warn against the risk of thrombosis or infection associated with the use of permanent venous access ports or catheters.[85] The AERS Study highlights that there have been multiple unique incidents of device-related infections. (*See* **Table 2**). Additionally, the potential for increased incidence of thrombosis associated with permanent venous access ports and catheters was noted in FDA's 2011 approval of CINRYZE's PAS labeling supplement. Therefore, FDA should

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81 The boxed warning states that ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.

82 Another example of a product with a REMS that addresses thrombotic events is XARELTO.

83 Kalbitor's REMS includes a communication plan. REMS for Kalbitor *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM261985.pdf.

84 The incidence of risk even "exceeded 5% when indwelling-central venous catheter-associated thromboses of the subclavian and internal jugular veins were included." CINRYZE Summary Basis for Regulatory Action, at 17 (Jan. 3, 2011).

85 These risks are of particular concern for CINRYZE because it is used for prophylaxis and requires frequent administration.

work to determine the incidence of these serious, life-threatening device-related events and add the following text to a boxed warning: "Administration of CINRYZE/BERINERT through permanent venous access ports and catheters has also been reported to increase the risk thromboembolic and septic complications."

Table 2: Reports of Device-Related Infections

Infections	
BERINERT and BERINERT P	1
CINRYZE	2
C1-INH products	2

3. Contraindication

Based on the data presented in this Citizen Petition, there is compelling evidence that C1-INH products should be contraindicated in individuals with underlying risk factors for thrombosis. For these individuals, the use of C1-INH may present an unacceptable risk of life-threatening thromboembolic complications that clearly outweighs any possible benefit, especially because there are three (3) other, non-C1-INH products that are available to treat HAE. FDA should, therefore, fully explore the relationship between the predisposition to thromboembolic complications and the risk of thrombosis due to C1-INH product use, and it should carefully consider an appropriate related contraindication.

4. Postapproval studies

FDA both has the authority to require postapproval studies under FDC Act § 505(o)(3) and should exercise this authority in order to determine the seriousness of these risks. These postapproval studies are crucial for reassessing the risk-benefit profile for C1-INH products given the new safety information presented in this Citizen Petition and the fact that these products no longer meet an unmet medical need.

a. FDA's authority to require postapproval studies

FDA has the authority to require postapproval studies to, *inter alia*, assess known risks or signals of serious risk related to the use of a drug and to assess signals of serious risk related to the use of a drug.[86] These signals must be based on scientific data.[87] If FDA determines that postapproval studies are insufficient to assess these risks, FDA may also require the C1-INH product Sponsors to conduct postapproval clinical trials.[88]

Here, the scientific data presented in this Citizen Petition indicate that the incidence of thrombotic events may be substantially higher than FDA expected in 2010, based on then available data. Additionally, C1-INH products now show a signal of serious risk related to device-related infections and sepsis. Five (5) cases of device-related infection including two (2) cases of sepsis were found for C1-INH products. Therefore, because C1-INH products have a known risk of thromboembolic events and a new signal of serious risks associated with infections and device-related injuries, FDA has the authority to require postapproval studies and clinical trials.

b. Passive surveillance has insufficiently characterized risk and postapproval studies are necessary

As discussed at the 2008 Advisory Committee for CINRYZE, an analysis of spontaneous postapproval adverse events reported under section 505(k)(1) of the FDC Act will not be sufficient to assess the known serious risk of thromboembolic complications, sepsis, and device-related injury following treatment with a C1-INH product, especially with regard to the relationship between dose and risk.[89] Only postapproval studies or clinical trials (rather than nonclinical or observational studies) would be sufficient to assess this known serious risk in patients who are taking C1-INH products for HAE and to better define what risk factors may predispose patients to such injury.

Therefore, C1-INH product Sponsors should be required to conduct prospective, randomized clinical trials to study the risk of thromboembolic complications, sepsis, and

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[86] 21 U.S.C. § 355(o)(3) (FDC Act § 505(o)(3)).

[87] *Id.*

[88] *Id.*

[89] Fleming, Thomas R., Ph.D., CINRYZE Advisory Committee.

device-related injury to better define what risk factors may predispose patients to such injuries. Additionally, prospective, randomized clinical trials would be able to better identify the subset of patients that have a positive risk-benefit ratio related to treatment with devices. Both the Gandhi paper and AERS Study encourage "[f]uture research [to] investigate the mechanism of CINRYZE-associated thrombotic events that may occur due to use of *catheters*, off-label doses, or other plausible explanations."[90]

5. Requirement for adequate medical supervision of patients with permanent indwelling catheters and ports

The risks associated with self-administration must be viewed in light of the benefits of self-administration, including faster access to treatment; however, there are a number of harms that can be reduced by labeling against self-administration for patients with indwelling catheters and ports.

For example, the risk of receiving too much or too little product due to patency issues would be decreased if patients with indwelling catheters and ports were overseen by health care professionals that were adequately trained to maintain and monitor such devices, including the use of saline flushes to maintain patency and anticoagulants to decrease the risk of thrombi forming in the devices. These health care professionals would also be better able to monitor signs of infection and sepsis thereby decreasing the associated harm from these risks by initiating early treatment.

6. Additional studies are needed to assess additional device-related risks

The increased risk associated with indwelling catheters and venous access ports supports the need for evaluating the true, additional risk associated with the use of these devices in conjunction with C1-INH products.

Substantial precedent exists to limit the use of a drug to a certain route of administration or device.[91] Therefore, FDA should use its available resources to

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[90] Gandhi at 6 (emphasis added).

[91] For example, INFUMORPH, a preservative-free morphine sulfate sterile solution, is "indicated only for intrathecal or epidural infusion" and has a highlighted warning against "single-dose intravenous, intramuscular or subcutaneous administration due to the very large amount of morphine in the ampul and the associated risk of overdosage." INFUMORPH Package Insert, at 3 (May 27, 2004) *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/018565s012lbl.pdf.

determine the risks associated with the use of implantable devices in conjunction with C1-INH products, and exercise its authority to require additional postmarketing studies to determine if there is an increased risk of thrombotic or septic complications from the use of indwelling catheters and venous access ports in conjunction with C1-INH products.

III. Environmental Impact

The requested relief does not require an environmental assessment or environmental impact statement under 21 C.F.R. § 25.31.

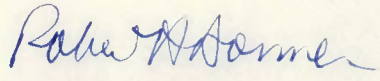
IV. Economic Impact

Information on the economic impact of the action request by this Citizen Petition will be submitted if requested by FDA.

V. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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