別紙様式第２－１

医薬品　研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
一般的名称	－		研究報告の公表状況	http://www.fda.gov/cber/blood/fxivcjdqa.htm	公表国 米国	
販売名（企業名）	－					

研究報告の概要

変異型クロイツフェルトヤコブ病（vCJD）が血漿由来の血液凝固第 XI 因子製剤（pdFXI）投与により患者に伝播するリスクが問題となっている。米国では 1989 年から 2000 年にかけて約 50 名の患者に英国供血者血漿由来の pdFXI が投与された。
米国公衆衛生局（PHS）は、vCJD のリスクは小さいものだと考えている。リスク評価にコンピュータモデルを使用したが、多くの未知の要因があるため、正確なリスク評価は行えない。供血時に英国供血者が気付かずに vCJD を保持していた可能性があるため、この pdFXI 製剤を投与された患者には有意なリスクがあるかもしれない。
これまでのところ、英国供血者からの血漿分画製剤を長期にわたり投与された患者も含め、血友病患者や FXI 欠乏症などの血液凝固異常患者に vCJD が発症したという事例は世界的にも知られていない。
2003 年 12 月から 2007 年 4 月までの間に赤血球輸血を通じて vCJD 因子が伝播したとされる 4 例はすべて英国での報告であり、いずれも pdFXI などの血漿分画製剤は関与していなかった。
今のところ、健康な供血者や受血者の vCJD を検出するための検査はない。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
pdFXI の vCJD 伝播リスクは非常に小さいと考えられるとの情報である。 本情報にもあるとおり、現時点まで血漿分画製剤からの vCJD 伝播の報告はなく、血漿分画製剤の製造工程でプリオンが除去できるとの情報もある。 なお、本報告で問題とされている英国供血者血漿は弊社では使用していない。	今後とも vCJD に関する安全性情報等に留意していく。

Potential Variant Creutzfeldt-Jakob Disease (vCJD) Risk

From Investigational Factor Eleven (FXI) From Donors In The United Kingdom

Summary Information

Key Points:

- In recent years, questions have been raised concerning the risk from variant Creutzfeldt-Jakob disease (vCJD), a rare but fatal brain infection, in patients who received plasma-derived investigational Factor Eleven (pdFXI) made from plasma obtained in the United Kingdom (UK) where vCJD has occurred.
- Approximately 50 individuals in the US, between 1989 and 2000, received pdFXI made using plasma from donors in the UK. This product was used to prevent or treat bleeding due to a rare problem, a deficiency of FXI.
- The US Public Health Service (PHS) believes that the risk of vCJD is likely to be small based on a number of considerations. We used a computer model to help determine the risk but we recognize that many unknowns prevent us from accurately determining the risk. The model raised the possibility that those who received this pdFXI product could potentially be at significant risk due to the possibility that a UK blood donor unknowingly carried vCJD at the time of donation. However, we believe the risk is small based on additional considerations. ***To date we are not aware of any cases of vCJD having been reported worldwide in patients with hemophilia or other blood clotting disorders, including pdFXI deficiency, who have received large amounts of plasma-derived products manufactured from UK plasma. This includes patients who received these products over a long period of time.***
- Contacting a specialist in bleeding disorders, e.g. a healthcare provider specializing in hemophilia, and/or a Hemophilia Treatment Center is a good way to learn about any new information as it becomes available.

Additional Information:

- Between December 2003 and April 2007, there have been four reports of people, all in the UK, who probably acquired the vCJD agent through red blood cell transfusions. This has increased concern about the potential transmission of vCJD by blood products, particularly those made from UK blood donors. ***None of the reported cases involved any plasma-derived product, including pdFXI.***
- However, because of the finding that red blood cells can transmit vCJD, FDA used a computer model to conduct a risk assessment to try to estimate the possible risk that might occur from the UK investigational pdFXI.
- The actual risk of acquiring vCJD is unknown and is likely to be small. Because so much is unknown about vCJD and its prevalence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate the risk of vCJD in general, or the actual risk to individual FXI deficient patients. There is no test yet available to detect vCJD in healthy donors or recipients. The US Public Health Service believes the risk of vCJD is likely to be small. There have been no reports of vCJD in patients using any plasma-derived blood product in the UK or anywhere else in the world.
- At this time, PHS does not believe there is a need for UK pdFXI recipients to inform their surgeons or dentists about the recipient's potential exposure to vCJD. Also, there is no recommendation for surgeons and dentists to take any special precautions based on such potential exposures. This belief is based on the very large degree of uncertainty in the FDA risk assessment and the lack of known cases of vCJD transmitted by plasma-derived clotting factor products in the UK, where risk is considered greatest, or anywhere else in the world. Also, relatively few patients were exposed to the pdFXI product in the US compared to the number of recipients of plasma-derived clotting factors, of which pdFXI is only one of many, in the UK.
- vCJD originally came from a disease in cattle called "mad cow disease" or BSE (bovine spongiform encephalopathy). Transmission of the BSE agent to humans, leading to vCJD, is believed to occur primarily from eating beef and beef products contaminated with the BSE agent. Both BSE and vCJD are invariably fatal brain diseases with incubation periods typically measured in years.
- From 1995 through April 2007, 202 individuals with vCJD were reported worldwide, with 165 in the United Kingdom (UK), and three in the United States. Two of the individuals in the United States had lived in the UK from 1980-1996 during a key exposure period to the BSE agent. The third US individual with vCJD most likely acquired the infection in Saudi Arabia. The reported incidence of vCJD in the UK, based on disease onset, peaked in 1999 and has been declining thereafter. In the UK, where most cases of vCJD have occurred, the current risk of acquiring vCJD from eating beef and beef products appears to be negligible.
- More information about vCJD is available on these government websites:
  - FDA: Potential Risk of Variant Creutzfeldt-Jakob Disease (vCJD) From Plasma-Derived Products
  - Centers for Disease Control and Prevention: vCJD (Variant Creutzfeldt-Jakob Disease)
  - US Department of Agriculture
- Information also may be obtained from these non-government sources:
  - Committee of Ten Thousand
  - Hemophilia Federation of America
  - National Hemophilia Foundation and/or HANDI
  - World Federation of Hemophilia

Updated: May 30, 2007

Questions and Answers

Variant Cruetzfeldt-Jakob Disease (vCJD) and Factor XI (pdFXI)

Index

- What is vCJD and how is it spread?
- How does vCJD differ from Creutzfeldt-Jakob disease (CJD)?
- Is it known that pdFXI can transmit vCJD?
- What is the likelihood that a patient who received pdFXI could have become infected with vCJD?
- Why did FDA do a vCJD risk assessment for pdFXI made from UK plasma?
- Why is FDA informing patients, healthcare providers, and the public about vCJD and pdFXI now?
- Should patients inform their primary health care providers about a possible vCJD exposure from UK pdFXI?
- Do patients who received UK pdFXI need to do anything special when seeking dental or surgical care?
- What can recipients of pdFXI do with this information?
- What are Hemophilia Treatment Centers, and where can I find out about them?
- Where can I find more information about vCJD and pdFXI?

Q. What is vCJD and how is it spread?

A. Variant Creutzfeldt-Jakob disease, or vCJD, is a very rare, fatal disease that can infect a person for many years before making them sick by destroying brain cells. Eating beef and beef products contaminated with the infectious agent of bovine spongiform encephalopathy (BSE) is the main cause of vCJD.

Most cases of vCJD have occurred in the United Kingdom (UK). Individuals in the UK are at a greater risk for this rare disease than are individuals elsewhere because of the previous higher risk of potential exposure to contaminated beef in the UK diet. From 1995 through April 2007 there have been 202 individuals with vCJD reported worldwide, 165 of them in the UK. In the United States (US), there have been three reported cases of vCJD. Two of these individuals had lived in the UK during 1980-1996, a key exposure period to the BSE agent. The third US individual with vCJD probably acquired the infection in Saudi Arabia.

The reported incidence of vCJD in the UK, based on disease onset, peaked in 1999 and declined thereafter. In the UK, where most cases of vCJD have occurred, the current risk of acquiring vCJD from eating beef and beef products appears to be negligible.

Only three cases of BSE have been found in US cattle, and safeguards are in place to help prevent infected beef products from entering our food supply. These safeguards include restricting importation of cattle and beef products from almost all countries with BSE, a surveillance program to detect BSE in the US, prohibiting the use of high-risk animal-derived proteins in cattle feed, prohibiting meat from sick cattle to be used for human consumption, and requiring the removal of high-risk materials from carcasses of cattle over a certain age.

While vCJD is primarily due to eating infected beef and beef products, four people in the UK became infected with the vCJD agent after receiving red blood cells from three donors who later developed vCJD. Three of the red blood cell recipients developed typical vCJD and died from the disease. A fourth died of an unrelated illness but had evidence of infection. To date, there have been no reports of vCJD transmission by close personal contact (such as being in the same room with someone who has vCJD, hugging, kissing, or having sexual relations).

Q. How does vCJD differ from Creutzfeldt-Jakob disease (CJD)?

A. Both vCJD and CJD cause progressive degeneration of the brain leading to death. However, the variant form—never seen before 1994—usually affects persons much younger than other forms of CJD. Unlike CJD, vCJD has been acquired by food exposure and transmitted by blood transfusion. vCJD also has somewhat different clinical symptoms, a longer survival after onset of illness (the majority of illnesses lasting more than one year), and produces a characteristic abnormality in brain tissue called "florid plaques" rarely if ever seen in the other forms.

Q. Is it known that pdFXI can transmit vCJD?

A. No. However, pdFXI is made from plasma. Plasma is the liquid part of blood remaining after the cells are removed. Animal studies show that if blood carries the vCJD agent, so can the unprocessed plasma.

Manufacturing steps used in making pdFXI have been shown to help remove infectious agents, including agents similar to that causing vCJD. The manufacturing steps may reduce or eliminate most risk even if a vCJD-infected donor contributed plasma.

Q. What is the likelihood that a patient who received pdFXI could have become infected with vCJD?

A. The US PHS believes the risk of developing vCJD infection from pdFXI is likely to be small. Many unknowns prevent us from accurately determining the risk using a computer model, and we believe the risk is likely to be smaller than the modeling predicts. However, we do not know this with certainty. Right now, there is no test available to detect vCJD in blood donors or recipients. There is no way of knowing whether a person is infected if

they do not show symptoms of the disease.

At this time FDA, CDC, and NIH are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived clotting factors, including pdFXI. This includes patients who have received, over a long period of time, large amounts of clotting factor products manufactured from plasma donations from the UK, where the risk of vCJD is highest.

Q. Why did FDA do a vCJD risk assessment for pdFXI made from UK plasma?

A. We conducted a risk assessment on pdFXI because it was made from plasma obtained from donors in the UK. The UK population, including UK plasma donors, is at a considerably higher risk for vCJD than the US population due to eating food potentially contaminated with the BSE agent, although the estimates of risk vary widely. We believe that pdFXI is the only plasma product used in the US that was manufactured from UK donor plasma collected during the BSE epidemic. Note, however, that plasma pools used to manufacture the pdFXI product infused in the US did not contain donations from individuals known to have developed vCJD (that is, there were no known "implicated" lots).

Q. Why is FDA informing patients, healthcare providers, and the public about vCJD and pdFXI now?

A. The FDA has recently completed its risk assessment, and we think it is important that a person who received pdFXI be aware of the results of the risk assessment and have an opportunity to discuss any questions with a suitable health care provider.

The first case of probable vCJD infection transmitted by transfusion of red blood cells in the UK was reported in December 2003 and the second case in July 2004. These events prompted UK authorities in 2004, to communicate the potential risk of vCJD to recipients of clotting factors and some other plasma derived products. FDA initiated its risk assessment for pdFXI in 2004, and presented a draft to the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) in February 2005 (draft risk assessment, meeting transcript and slides). Since then FDA, with scientific advice from the TSEAC in October 2005, and other experts, has further refined the risk assessment and risk communication materials. Results of this extensive analysis are now available.

FDA, CDC, NIH, and the Office of Public Health and Science (OPHS) of the US Department of Health and Human Services, with advice from patient advocacy groups and communication experts, have now developed key message points and communication materials to accurately convey the possible risk to patients, health care providers, and others who may have an interest.

Q. Should patients inform their primary health care providers about a possible vCJD exposure from UK pdFXI?

A. Advising your primary health care provider (e.g., a family physician, internist, blood disease specialist, etc.) about your history of having received the pdFXI product might be beneficial in that your provider can keep you informed about new information as it becomes available, interpret its significance, and advise you about further appropriate actions in the future. However, sharing your personal health information is your choice.

Q. Do patients who received UK pdFXI need to do anything special when seeking dental or surgical care?

A. At this time, the US PHS does not believe that UK pdFXI recipients need to inform their surgeons or dentists about the potential exposure to vCJD. Also, the US PHS does not recommend that surgeons and dentists take any special precautions with patients who had such potential exposures. This belief is based on the very large degree of uncertainty in the FDA risk assessment, and the lack of known cases of vCJD transmitted by plasma-derived clotting factor products in the UK, where risk is considered greatest, or anywhere else in the world. Also, there were relatively few patients exposed to the pdFXI product in the US compared to the large number of recipients of plasma-derived clotting factors, of which pdFXI is only one of many, in the UK.

In the UK, public health authorities notified recipients of plasma-derived products, such as pdFXI, that they may have an increased risk of vCJD in addition to their risk from eating potentially contaminated UK beef products. The UK health authorities asked patients to inform their surgeons and dentists about their potential exposure as a public health precaution intended to prevent possible secondary spread of the disease from dental and surgical instruments. The US PHS, including the FDA, CDC, and NIH, does not believe that such notifications are necessary in the US. This belief is based on the very large degree of uncertainty in the FDA risk assessment, and on the lack of known cases of vCJD transmitted by plasma-derived clotting factor products in the UK or anywhere else in the world. Given this information, the PHS believes that there is no need to alter the standard current practices.

PHS agencies will continue to monitor and reevaluate the situation as new information becomes available.

Q. What can recipients of pdFXI do with this information?

A. While no new actions are recommended now, you can stay informed by keeping in contact with your primary physician and/or a specialist in bleeding disorders, such as a hemophilia specialist at a Hemophilia Treatment Center. Such contact will help you to learn about any new scientific advances in this field such as testing and diagnosis, and also to monitor your general health.

Q. What are Hemophilia Treatment Centers, and where can I find out about them?

A. Hemophilia Treatment Centers (HTC) are a network of federally funded comprehensive care clinics that promote the management, treatment, and prevention of complications experienced by persons with hemophilia

and other hereditary bleeding disorders.

You can find information about HTC's at:

1. CDC informational posting, containing information about the kinds of services provided by federally funded HTC's
2. CDC's directory of federally-funded HTC's
3. Regional HTC websites are also a good place for information

Q. Where can I find more information about vCJD and pdFXI?

A. You can find additional information at:

FDA

1. FDA informational posting, containing current pdFVIII risk assessment, fact sheet, and briefing materials
2. Blood Products Advisory Committee meeting – summary of recent TSEAC meeting and statement about pdFXI from the UK, on October 21, 2006
3. TSEAC meeting with discussion of first pdFXI draft risk assessment, on February 8, 2005, and discussion of UK risk communication for plasma derivatives
4. TSEAC Meeting with further discussion of the FDA risk assessment model, October 31, 2005
5. TSEAC Meeting with update on pdFXI risk assessment, September 18, 2006

CDC: vCJD (Variant Creutzfeldt-Jakob Disease)

Regional HTC websites

US Department of Agriculture: Bovine Spongiform Encephalopathy

Patient Organizations:

Committee of Ten Thousand
Hemophilia Federation of America
National Hemophilia Foundation and/or HANDI
World Federation of Hemophilia

Questions to FDA may be addressed through the Office of Communication, Training, and Manufacturers Assistance (OCTMA), at 1-800-835-4709, or octma@cber.fda.gov.

Updated: May 30, 2007