別紙様式第2-1
番号8

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2006年12月8日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①②③人血清アルブミン ④乾燥濃縮人血液凝固第Ⅷ因子 ⑤乾燥濃縮人血液凝固第Ⅸ因子	研究報告の公表状況	CDC/vCJD/ 20061129	公表国 アメリカ		
販売名 （企業名）	①献血アルブミン-Wf（ベネシス） ②献血アルブミン(5%)-Wf（ベネシス） ③アルブミン-Wf（ベネシス） ④コンコエイトーHT（ベネシス） ⑤クリスマシンーM（ベネシス）					

・研究報告の概要

バージニア州保健局とCDCは、米国住民におけるvCJD確定症例を公表した。これは米国の住民において確認された3番目のvCJD症例である。この米国の最新の症例は、サウジアラビアで生まれて育ち、2005年終りから米国に居住した青年に発生した。この患者は2001年以来、一時的に最長3ヶ月間米国に時折滞在しており、1989年には短期の滞在の経験がある。2006年11月の終りになって、カリフォルニアサンフランシスコ記憶・老齢センターの臨床プリオン研究チームが、扁桃と脳生検組織についての病理学検査からvCJDの臨床診断を下した。米国住民における先に報告された2つのvCJD症例は、各々患者は英国で生まれ育ち、その地で患者らはその疾患の原因病原体に感染したと考えられている。
サウジアラビアではウシのBSEは1件も報告されていないが、英国からの汚染されたウシ製品が英国でBSEが流行している期間に長年、サウジアラビアに輸出されていた可能性がある。
この患者は、輸血を受けたことも、過去に神経外科的手術をしたことも、又ヨーロッパに滞在或いは訪問したこともなかった。この患者の病歴、サウジアラビアでBSE汚染のウシ製品を摂取したことより発生したとされるvCJD症例報告、及び食物関連のvCJDの潜伏期間が7年を超えるとの予想に基づき、この米国の症例は、サウジアラビアに住んでいた子供の時代に摂取した汚染されたウシ製品から感染した可能性が極めて高い。この患者は、供血歴はなく、公衆衛生調査によりこの患者から米国住民に感染するリスクのないことが確認された。

報告企業の意見	今後の対応
米国で3例目のvCJD患者が確認されたが、生まれ育ったサウジアラビアで感染したものと推定され、米国民にvCJDを感染させるリスクもないことが確認されたとの報告である。 これまで血漿分画製剤によってvCJD、スクレイピー及びCWDを含むプリオン病が伝播したとの報告はない。しかしながら、万一vCJD感染者の血漿が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表として献血アルブミン-Wfの記載を示す。
2. 重要な基本的注意
(1)略
1)略
2)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。

vCJD (Variant Creutzfeldt-Jakob Disease)

Confirmed Case of Variant Creutzfeldt Jakob Disease (vCJD) in the United States in a Patient from the Middle East

The Virginia Department of Health and the Centers for Disease Control and Prevention announce the recent confirmation of a vCJD case in a U.S. resident. This is the third vCJD case identified in a U.S. resident. This latest U.S. case occurred in a young adult who was born and raised in Saudi Arabia and has lived in the United States since late 2005. The patient occasionally stayed in the United States for up to 3 months at a time since 2001 and there was a shorter visit in 1989. In late November 2006, the Clinical Prion Research Team at the University of California San Francisco Memory and Aging Center confirmed the vCJD clinical diagnosis by pathologic study of adenoid and brain biopsy tissues. The two previously reported vCJD case-patients in U.S. residents were each born and raised in the United Kingdom (U.K.), where they were believed to have been infected by the agent responsible for their disease. There is strong scientific evidence that the agent causing vCJD is the same agent that causes bovine spongiform encephalopathy (BSE, commonly known as mad cow disease).

Variant CJD is a rare, degenerative, fatal brain disorder that emerged in the United Kingdom in the mid-1990s. Although experience with this new disease is limited, evidence to date indicates that there has never been a case transmitted from person-to-person except through blood transfusion. Instead, the disease is thought to result primarily from consumption of cattle products contaminated with the BSE agent. Although no cases of BSE in cattle have been reported in Saudi Arabia, potentially contaminated cattle products from the United Kingdom may have been exported to Saudi Arabia for many years during the large U.K. BSE outbreak.

The current case-patient has no history of receipt of blood, a past neurosurgical procedure, or residing in or visiting countries of Europe. Based on the patient's history, the occurrence of a previously reported Saudi case of vCJD attributed to likely consumption of BSE-contaminated cattle products in Saudi Arabia, and the expected greater than 7 year incubation period for food-related vCJD, this U.S. case-patient was most likely infected from contaminated cattle products consumed as a child when living in Saudi Arabia (1). The current patient has no history of donating blood and the public health investigation has identified no risk of transmission to U.S. residents from this patient.

As of November 2006, 200 vCJD patients were reported world-wide, including 164 patients identified in the United Kingdom, 21 in France, 4 in the Republic of Ireland, 3 in the United States (including the present case-patient), 2 in the Netherlands and 1 each in Canada, Italy, Japan, Portugal, Saudi Arabia and Spain. Of the 200 reported vCJD patients, all except 10 of them (including the present case-patient) had resided either in the United Kingdom (170 cases) for over 6 months during the 1980-1996 period of the large UK BSE outbreak or alternatively in France (20 cases).

As reported in 2005 (1), the U.S. National Prion Disease Pathology Surveillance Center at Case Western Reserve University confirmed the diagnosis in the one previously identified case of vCJD in a Saudi resident. He was hospitalized in Saudi Arabia and his brain biopsy specimen was shipped to the United States for analysis. This earlier vCJD case-patient was believed to have contracted his fatal disease in Saudi Arabia (1).

1) Belay ED, Sejvar JJ, Shieh W-J, Wiersma ST, Zou W-Q, Gambetti P, Hunter S, Maddox RA, Crockett L, Zaki SR, Schonberger LB. Variant Creutzfeldt-Jakob disease death, United States. Emerg Infect Dis 2005, 11 (9):1351-1354.

Program Contents

- Topic Home
- Questions and Answer and vCJD
- Fact Sheet: vCJD
- Epidemiology
- Risk for Travelers
- Prevention
- Treatment
- News Archive
- References and Resou

Contact CDC

Centers for Disease Control and Prevention
National Center for Infec Diseases (NCID)

1 (800) CDC-INFO (232-
TTY: 1 (888) 232-6348

E-mail:
prion@cdc.gov

Centers for Disease Control and Prevention,1600 Clifton Rd, Atlanta, GA 30333, U.S.A
Tel: (404) 639-3311 / Public Inquiries: (404) 639-3534 / (800) 311-3435

医薬品　研究報告　調査報告書

報告番号・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	人血清アルブミン	研究報告の公表状況	http://www.fda.gov/cber/blood/vcjdrisk.htm	公　表　国	
販売名（企業名）	ブミネート 5% ブミネート 25% （バクスター株式会社）				

研究報告の概要	使用上の注意記載状況・その他参考事項等
合衆国で製造されたヒト血漿由来第 VIII 因子製剤を投与されたことのある重度血友病 A 患者及び重度疾患のあるフォン・ウィルブランド病患者が vCJD 病原因子に暴露される確率と程度、及び vCJD に感染するリスクについて数量的な見積りを行った。評価の結果、米国で製造される血漿由来 FVIII 経由の vCJD 感染リスクは非常に低いと推定されるが、しかしゼロではないということが示唆された。モデルによる推定の結果より、vCJD 病原因子への暴露の可能性があり、非常に低いとはいえ潜在的感染リスクがあることが示唆されたが、全般的 vCJD リスク又は患者個々の実際のリスクについては、モデルにより「正確に」見積もることは不可能である。実際のリスクがどの程度であるのかは極めて不確かであるが、リスクの度合いを左右する最も重要な要因は、製造工程を通しての vCJD クリアランス、各患者の製剤使用量、及び英国供血者母集団における vCJD 有病率であることをリスク評価モデルは示している。製造工程による削減レベルが 4～6 $\log_{10}$ であると仮定した場合、モデルを用いた推定では、血漿由来 FVIII を投与されている重度血友病 A 患者 1 人 1 年当たりの潜在的リスクは、15,000 回に 1 回（高いほうの vCJD 推定有病率かつ製剤使用量が多量のとき）から 940 万回に 1 回（低いほうの vCJD 推定有病率かつ製剤使用量が少量のとき）の範囲である。 リスク評価の結果を検討する上で留意すべき重要なこととして、英国での提供血漿より製造された血漿由来製剤を長期に渡り投与されている患者に vCJD が発症したと広く世界に報告された例はなく、このことからも、血漿由来 FVIII からの実際の vCJD 感染リスクは非常に低いであろうと考えられた。しかし発症例がないことは、将来いつか、発病を来たすような感染源に患者が暴露される可能性を否定するものではないともされた。 詳細は添付資料の通り。	2.重要な基本的注意 (1) 2) 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
リスク評価においても示されている通り、血漿分画製剤による vCJD 伝播が疑われる症例は報告されていないこと、並びに、血漿分画製剤では分画精製におけるウイルス不活化／除去工程により、プリオンが不活化あるいは除去できると考えられ、プリオン病感染のリスクが十分に低減されると考えられることより、血漿分画製剤による vCJD 伝播の可能性は極めて小さいと考えている。	当該感染症に関し、引き続き、情報の収集を行っていく。 また、同様に同一生物種等から人に感染すると認められる疾病に関する情報の収集に努める

感染症の用語は、MedDRA/J　version（10.0）を使用。

DRAFT

Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States (US) License From Plasma Collected in the US

November 27, 2006

Center for Biologics Evaluation and Research
US Food and Drug Administration

CONTRIBUTORS

Center for Biologics Evaluation and Research

Office of Biostatistics and Epidemiology
Steven Anderson
Hong Yang

Office of Blood Research and Review
Jay Epstein
Mark Weinstein
Jonathan Goldsmith
David Asher
Dorothy Scott

Office of the Center Director
Jesse L. Goodman
Karen Midthun
Diane Maloney

TABLE OF CONTENTS

TABLE OF TABLES

EXECUTIVE SUMMARY

RISK ASSESSMENT

TABLE OF FIGURES

EXECUTIVE SUMMARY

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disease attributed to human infection with the agent of bovine spongiform encephalopathy (BSE) and is most often transmitted by the consumption of beef products from infected cattle. Cases of vCJD were first reported in humans in the U.K. in 1996 – and as of August 2006, 195 cases have been reported worldwide, with 162 cases in the U.K. Since December 2003, there have also been three reports in the United Kingdom (U.K.) of probable variant Creutzfeldt-Jakob disease (vCJD) transmission by red blood cell transfusions. The donors were healthy at the time of donation, but later developed vCJD. Of the three red blood cell recipients who probably became infected with the vCJD agent after transfusion, two developed vCJD and died from the disease. The third died of an unrelated illness.

The probable transmission of vCJD via red blood cell transfusions raised the possibility that plasma derivatives might also pose a risk of vCJD transmission, although there have as of yet been no reported cases of vCJD in any recipients of plasma derivatives in the U.K., where the risk is considered greatest, or elsewhere in the world. U.K. authorities have notified physicians in the U.K. and their patients who received plasma derivatives made from plasma from U.K. donors about the potential for risk of vCJD from these products. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins.

This document "Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured Under United States (US) License From Plasma Collected in the US" quantitatively estimates the probability and level of exposure to the vCJD agent and the possible risk of vCJD infection in patients with severe hemophilia A (HA) and von Willebrand disease (vWD) patients with severe disease who have used human plasma-derived Factor VIII (pdFVIII) product manufactured in the US. Because BSE occurs at an extremely low level in US cattle (2 native born cows and 1 cow imported from Canada), the risk of plasma donors acquiring vCJD by consuming domestically produced beef is thought to be very low. Because of concerns about potential exposure to the BSE agent in US blood donors who traveled to or lived in the UK and other at risk European countries, FDA implemented donor deferral policies beginning in 1999. The policies are believed likely to reduce the possible risk from blood donors potentially exposed to BSE agent by ~ 90%. However, it is possible that a small number of non-deferred US donors may have been exposed to the BSE agent during extended travel or residence in the UK, France or other European countries and may be at risk for vCJD. Some of these donors may have been unknowingly infected with vCJD through eating beef from BSE-infected cattle and then contributed donations to plasma pools used to manufacture pdFVIII in the US.

The FDA risk assessment utilizes a computer-based simulation model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII starting with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various patient subpopulations. Risk for these products was estimated for the baseline year of 2002 but the results and conclusions also are likely to reflect the current vCJD risk for recipients of pdFVIII. A few major elements of the model greatly influence vCJD risk. The most influential of these are manufacturing processes, which may reduce or eliminate the amount of vCJD agent in the final product. The amount of product used by patients in different clinical scenarios also has a significant impact on risk. Additionally, the risk estimate is significantly affected by the prevalence

of vCJD in the United Kingdom population, which is used to estimate vCJD prevalence in US donors who resided in or traveled to the UK and other countries of Europe. The risk assessment model estimates the potential for vCJD exposure and the potential risk of vCJD infection for patients receiving pdFVIII from plasma collected in the US and the accompanying uncertainty of these estimates. Because scientific data on the level of exposure to vCJD agent and the likelihood of certain human health outcomes, such as infection and illness, are lacking, the estimates generated may not be accurate. As a result of these and other large uncertainties, it is not possible to provide a precise estimate of the vCJD risk to patients potentially exposed to the agent through plasma-derived products.

Patients with hemophilia A (HA) have an inherited, recessive, sex-linked bleeding disorder that affects approximately 14,000 individuals in the United States (Soucie et al 1998). FDA estimated that there are approximately 1,800 patients in the US with severe disease who use plasma-derived products. The blood of affected individuals contains functionally abnormal or abnormally low concentrations of FVIII. FVIII is a glycoprotein circulating in blood plasma that is part of the blood coagulation pathway and is critical for the normal clotting of blood. In the case of severe disease, FVIII is <1% of normal. Among severely affected persons, spontaneous bleeding or bleeding at the site of an injury or within a joint is common and can lead to severe disability or death without treatment. The complications of HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

Patients with vWD (Type 3) have an inherited, non-sex linked bleeding disorder associated with abnormal platelet adhesion caused by deficiency in von Willebrand Factor (vWF) activity. FDA estimated that there are approximately 250 patients in the US with severe vWD who use plasma-derived products. Mucosal bleeding is common in patients with vWD due to the platelet adhesion disorder. In some cases there may be a deficiency in FVIII coagulant activity (anti-hemophilic factor) as well. Patients with severe vWD can experience persistent bleeding into joints resulting in pain, degeneration of joints, swelling and loss of range of motion similar to patients with HA. Mild forms of vWD are often treated successfully with desmopressin but more severe forms of the disease usually require treatment with coagulation factor concentrates that contain both vWF and FVIII. Patients who need vWF must use plasma-derived sources of FVIII which contain vWF. No recombinant vWF is currently available.

Results from the Model

An important, yet also highly uncertain parameter in driving the risk assessment results is the estimate used for vCJD prevalence in the UK. The prevalence of vCJD in the UK population was estimated in the model using two different approaches. The first approach to estimating vCJD prevalence in the UK was from a study based on epidemiological modeling that was derived using actual reported vCJD cases in the UK combined with an estimate of future vCJD cases (Clarke and Ghani, 2005). Several factors used in epidemiologic modeling approaches are difficult to quantify and add uncertainty to the final estimated number of future vCJD cases. These factors include: the intensity of human exposure to the BSE agent, incubation period, time of infection, and whether illness will develop in individuals who are not homozygous for methionine at codon 129 of PrP. All cases of vCJD to date have occurred in individuals who are homozygous for methionine at this location. Our calculations, based on the Clarke and Ghani study (2005) and diagnosed cases in 2002 and 2003, yielded a prevalence estimate of approximately 1.8 vCJD cases per million in the UK.

Running the model with this vCJD case prevalence estimate (~1.8 per million) produces an estimate suggesting that, on average, there was a 0.027% likelihood that a plasma pool, which then undergoes manufacturing, will contain at least one donation from an individual whose blood contains the vCJD agent. Therefore, on average, more than 99% of the time the model predicts the product as administered will contain no vCJD agent and this is reflected in the (0 – 0) values for the 5th and 95th percentiles shown for the lower prevalence estimate results in Table I.A. (below).

However, it is possible that the prevalence of vCJD in the UK is higher than that estimated above. This could happen if there are people infected who never develop the disease (but can still spread the infection) or if some individuals take extremely long to become ill. Therefore, a second approach to estimating vCJD infection prevalence was used based on a relatively small tissue surveillance study by Hilton, *et al* (2004), which tested stored tonsil and appendix tissues from the UK for accumulation of abnormal prion protein. It yielded a much higher prevalence estimate of 1 in 4,225 (237 infections per million). This study was not controlled using tissues from a non-BSE exposed population and false positive findings cannot be ruled out. It is also not known whether this staining of appendiceal tissues is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation. However, while unconfirmed, the findings from this study provide a higher prevalence estimate that may be relevant to transfusion risk and therefore should also be considered. Use of these data as the basis for a vCJD infection prevalence estimate which is then used in the model produces a significantly higher estimate suggesting that, on average, if it were correct, there could be a 2.41% likelihood that a plasma pool, which then undergoes manufacturing, may contain at least one donation from an individual whose blood contains the vCJD agent.

Estimated annual potential vCJD risk associated with human pdFVIII used to treat severe Hemophilia A

Results from the model indicate that it is possible that a donor unknowingly infected with vCJD may have donated plasma used in the manufacture of pdFVIII in the US. Output from the model using the lower UK vCJD prevalence estimate (~1.8 in 1 million) indicated that, on average, there is a 0.027% (95% CI: 0 % - 0 %) likelihood that a plasma pool may contain at least one donation from an individual with the vCJD agent in their blood. Readers may notice that the 5th and 95th percentile intervals for all of the model outputs are from 0 to 0, meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. This means that at least ninety five percent of the time the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. Again, actual model predictions indicated that, at the lower prevalence, 0.027% of the time the exposure to vCJD may be greater than zero. When the model was run using the higher UK vCJD prevalence estimate (1 in 4,225) to derive an estimate for vCJD prevalence in US plasma donors, the FDA model predicted that, on average, there is an approximately 2.41% (95% CI: 0 % - 10 %) likelihood that a plasma pool will contain at least one donation from an individual with the vCJD agent in their blood. For either set of results, the model assumes that if vCJD agent were present, the amount in a plasma pool would likely be reduced or possibly eliminated by processing steps used during the manufacture of pdFVIII product.

Individuals with HA vary in their degree of FVIII deficiency. For simplicity, the model results and this executive summary specifically address potential vCJD exposure and risk for persons with severe HA. FDA estimates that among the total population of 14,000 HA patients in the United States, approximately 1,800 (Table I.A.) have severe disease and use pdFVIII products. FDA obtained data

on FVIII utilization from the Centers for Disease Control (CDC). The data were generated as part of a collaborative effort between CDC and six states in a study conducted from 1993 –1998. Treatment regimens for HA are administered either as prophylaxis to prevent the occurrence of bleeding episodes or on an episodic basis to control bleeding when it occurs. Additionally, inhibitors may be treated with very high doses of pdFVIII to induce immune tolerance. Assuming these patients are treated with a pdFVIII product that has a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent, Table I.A. displays model outcomes for patients treated using either prophylaxis or episodic treatment, and with respect to their inhibitor status.

Table I.A. Model Results for all Severe Hemophilia A Patients who use a Hypothetical Plasma-derived FVIII Product with 4-6 $\log_{10}$ Manufacture Process Reduction of vCJD Agent: *Predicted mean potential per person annual vCJD risk using two different UK vCJD prevalence estimates.*

				4 - 6 $\log_{10}$ Reduction	
				Model Output for LOWER vCJD Case Prevalence estimate of ~1.8 in 1,000,000 based on Clark and Ghani (2005)	***Model Output for HIGHER vCJD Infection Prevalence based on estimate of 1 in 4,225*** *by Hilton, et al (2004)*
Treatment Regimen	**Inhibitor Status**	**Est. Total Number patients in US**	**Mean quantity FVIII used per person per year (5th - 95th perc)[b]**	**Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]**	**Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]**
Prophylaxis	No Inhibitor	**578**	**157949 IU[c]** (21242 , 382316)	1 in 4.0 million (0-0)[d]	1 in 54,000 (0 - 1 in 12,000)
	With Inhibitor – No Immune Tolerance	**63**	**190523 IU[c]** (26956 , 447639)	1 in 4.8 million (0-0)[d]	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor – With Immune Tolerance	**62**	**558700 IU[c]** (33235, 1592943)	1 in 1.3 million (0-0)[d]	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	**946**	**85270 IU[c]** (4633, 244656)	1 in 9.4 million (0-0)[d]	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	**151**	**160458 IU[c]** (5314 , 488906)	1 in 8.0 million (0-0)[d]	1 in 48,000 (0 - 1 in 12,000)

[a] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.