Management of notifications of donors with Creutzfeldt-Jakob disease (post-donation information)

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Introduction

Recent notifications of blood and plasma donors who have developed Creutzfeldt-Jakob disease (CJD), whose donations collected during the pre-clinical phase of the disease have entered into industrial pools for the manufacturing of plasma-derived medicinal products, highlighted the institutional need for a position paper on the preventive measures, management and communication regarding these cases. As a consequence a document was jointly produced and agreed by the Italian Medicine Agency (AIFA), the Italian National Blood Centre (CNS) and the National Institute of Health (ISS). At its meeting on September 25th, 2012 the National Council of Health unanimously expressed a positive opinion on this document, resulting in its full approval also by the Ministry of Health (MoH). On the basis of the most recent scientific evidence and international guidelines and recommendations, the position paper is intended to define the procedures to be followed in order to manage a possible precautionary quarantine (ban of use) or a possible recall of plasma-derived medicinal products. It is also intended to define the method and content of risk communications to healthcare professionals, patients and general population.

Current legislations and international recommendations do not provide for the adoption of restrictive measures in the case of sporadic, genetic or iatrogenic CJD, whereas they do recommend precautionary lots recall in case of a diagnosis of variant CJD. Reference must be made to the following legislation and guidance documents:

1- "Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components"[1], transposed with Decree of the Ministry of Health of March 3rd, 2005 "Protocols for determining the suitability of donors of blood and blood components"[2].

2- Committee for Medicinal Products for Human Use (CHMP) Position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. European Medicines Agency (EMA). London, 23 June 2011[3].

3- Guidance for Industry. Revised preventive measures to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) by Blood and Blood Products, May 2010 Food and Drug Administration (FDA)[4].

This position paper was prepared on the basis of current scientific knowledge, taking into account the above-mentioned legislation and guidelines, and shall be subject to review if new scientific evidence becomes available.

Classification of human transmissible spongiform encephalopathies

Transmissible spongiform encephalopathies (TSE) or prion diseases are degenerative disorders of the central nervous system caused by an infective agent called prion. The central event in the pathogenesis of TSE is the accumulation of abnormal prion protein (PrP^{Sc}) starting from its normal cellular precursor (PrP^{C})[5].

The TSE that occurs in humans are sporadic, iatrogenic and variant CJD. The genetic TSE includes genetic CJD, Gerstamnn-Sträussler-Scheinker syndrome and fatal familial insomnia[6]. For each of these forms, diagnostic certainty can only be achieved after the death of the subject through neuropathological and/or immunohistochemical (search for PrP^{Sc}) analysis of autopsy material.

Sporadic Creutzfeldt-Jakob disease

Sporadic Creutzfeldt-Jakob disease accounts for about 80% of the cases of CJD. It has a peak incidence in the seventh decade of life; the median duration of the disease is about 6 months[7].

There are various subtypes of sporadic CJD[8] and for some of the rarest of these, it is not always possible to reach a reliable clinical diagnosis using clinical and instrumental diagnostic criteria. In these cases, a neuropathological diagnosis is particularly important to either exclude or confirm the suspected diagnosis.

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Genetic transmissible spongiform encephalopathies

Genetic transmissible spongiform encephalopathies account for about 10-20% of the TSE and are associated with mutations in the *PRNP* gene[9]. The diagnosis of genetic TSE is based on a positive family history or identification, through sequencing, of mutations in the *PRNP* gene[10].

Iatrogenic Creutzfeldt-Jakob disease

Iatrogenic Creutzfeldt-Jakob disease occurs consequently to accidental exposure to the aetiological agent during medical and/or surgical procedures (administration of cadaver-derived pituitary hormones, transplanted dura mater or cornea from donors with sporadic CJD, exposure to neurosurgical instruments used previously in a patient with definite or probable CJD). The incubation time ranges from 1 to 38 years[11].

Variant Creutzfeldt-Jakob disease

Variant Creutzfeldt-Jakob disease is related to the consumption of food products contaminated by the infective agent responsible for bovine spongiform encephalopathy (BSE). The definite diagnosis of variant CJD is based on neuropathological and/or immunohistochemical studies[12].

A probable diagnosis of variant CJD can be made from clinical symptoms, magnetic resonance images of the brain and the possible presence of PrP^{Sc} in biopsy samples of tonsil tissue.

Two autochthonous cases of variant CJD have been described in Italy. Neither of these subjects had stayed in the United Kingdom or in other countries at risk (e.g. France) and neither had given or received blood or blood components. They were, therefore, exposed to the infective agent of BSE in Italy.

Scientific evidence

1- Experimental transmission studies to evaluate the infectivity of blood/plasma from patients with sporadic, iatrogenic or variant CJD have been substantially negative. The few studies that have shown infectiveness of blood from these patients have not been widely accepted by the scientific community[13]. However, in various experimental models of TSE in animals, blood and plasma have been demonstrated to be infected[14].

2- The experimental evidence of infectivity in peripheral tissues of subjects with sporadic CJD is scarce[15]. Some data show the presence of infectivity in various tissues, including lymphoid tissues (spleen, lymph nodes)[15].

3- It cannot be excluded that patients with sporadic CJD have very low levels of infectivity in blood/plasma. These levels cannot be measured by currently available techniques.

4- Epidemiological studies have provided strong evidence regarding the transmissibility of variant CJD through labile blood components. In the case of plasma derivatives, the transmission of variant CJD is considered possible on the basis of a single case reported in the literature of a patient with haemophilia A, who died of non-neurological causes[16].

5- Observational studies have not identified any cases of transmission of sporadic CJD in recipients of whole blood or labile blood components from donors with preclinical sporadic CJD, during an observation period of more than 15 years in some cases. Nevertheless, these results must be interpreted taking into consideration that 60% of patients receiving a transfusion are over 65 years old and that about 50% die within 5 years of causes related to the problem necessitating the transfusion[14].

6- Retrospective epidemiological studies do not have yet sufficient statistical power to formally exclude the risk of transmission by blood. However, these studies have shown that the transmission of sporadic CJD is either an improbable or rare event related to a long incubation period[17,18].

7- An observational (case-control) study carried out in Italy suggests that there is a higher risk of developing sporadic CJD after a transfusion of labile blood components occurred more than 10 years ago[19]. However, it is not possible to exclude that the results of these studies could have been influenced by both data collection and subjects recruitment methodologies. One British study, carried out with a similar although not identical method, did not find any association between transfusions and sporadic CJD[20], confirming the difficulty in drawing definitive conclusions[21].

8- In the context of specific surveillance programmes, which include a collaborative study set up in 1993 within the European Union, no case of sporadic CJD has ever been confirmed in subjects with coagulation disorders or who have been treated with plasma derivatives[14].

9- There are no experimental or clinical epidemiological data on the presence or absence of infectivity in the blood of subjects with iatrogenic or genetic CJD or other forms of genetic TSE. For the purposes of evaluating the risk of plasma derivatives, it has been hypothesised that these forms behave like sporadic CJD. Furthermore, there are currently no "validated" diagnostic tests that enable the detection of subjects who are infected, but clinically healthy at the time of blood donation. The lack of knowledge on the risk factors for sporadic CJD and the absence of tests to screen donated blood/plasma do not prevent the accidental use of blood/

plasma for transfusions or for the manufacturing of plasma-derived medicinal products from donors in a preclinical phase of CJD[14].

10- The manufacturing process of various plasma-derived medicinal products is able, when adequately validated and correctly applied, to remove or inactivate significant fractions of prion infectivity potentially contained in the plasma. Biological and biochemical assays have detected levels of infectivity, in decreasing order, in: cryoprecipitate (intermediate product of factor VIII), fraction I+II+III (intermediate product of immunoglobulin) and fraction V (intermediate product of albumin). Validation studies involve the use of external sources of infectivity (spikes) to try to mimic the natural infectivity potentially present in the blood and to quantify the theoretical reduction achieved by the whole manufacturing process or by its single steps. The molecular size and form of the infective agent potentially present in blood/plasma are unknown and the choice of both the type and the method of preparing the spike used in the validation study are fundamental in order to estimate the real capacity of a given procedure to remove infectivity[22]. Moreover, the variability in both manufacturing processes and validation studies carried out by manufacturers of blood derivatives hampers comparisons and often makes it impossible to generalise the estimates made[14].

International recommendations and legislation in force

1- For the purposes of prevention, the only valid approach is an evaluation of the prospective donor's history and general health status, as set out in the legislation actually in force. In order to protect the health of the recipient, the Decree of March 3rd, 2005 of the Ministry of Health "Protocols for determining the suitability of a donor to give blood and blood components"[2], which transposes Directive 2004/33/EC[1] of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and Council relative to some technical requirements of blood and blood components, provides for the permanent deferral from donation of blood or blood components those subjects recognised as being at risk of developing CJD. These subjects include:
   a- people with a past medical or family history of a risk of TSE;
   b- donors who have received a corneal and/or dura mater transplant and/or who have been treated in the past with products derived from the human pituitary glands;
   c- prospective donors who lived for a cumulative period of more than 6 months in the United Kingdom in the period from 1980 to 1996;
   d- prospective donors who received allogeneic blood transfusions in the United Kingdom after 1980.

2- The criteria for excluding donors considered at risk of developing variant CJD, iatrogenic CJD and genetic TSE are well defined by both Italian and European legislation, whereas it is still not possible to establish which subjects are at risk of sporadic CJD.

3- The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommends the recall of plasma derivatives from the market only in case the plasma pool is found to contain a donation from a subject with a diagnosis of variant CJD, whereas "on the basis of the current epidemiological evidence, the CHMP recommendation that the recall of plasma-derived medicinal products is not justified when a donor is later confirmed as having sporadic, genetic or iatrogenic CJD or if the CJD risk factors are maintained"[3]. Furthermore, the EMA document emphasises the importance of reaching a precise diagnosis in cases of suspected CJD in order to decide actions to be taken and mentions the potential for diagnostic confusion between sporadic CJD and variant CJD, prior to post-mortem findings, particularly in younger age groups.

4- This potential diagnostic confusion between sporadic CJD and variant CJD led the Food and Drug Administration (FDA) of the USA to recommend case-by-case evaluation, in particular for donors under the age of 55 years in whom it is not possible to exclude variant CJD definitively[4].

Precautionary measures to be adopted in Italy

Introduction

With regards to the cases of sporadic, genetic or iatrogenic CJD, the recommendations of EMA, reported in point 3 of the section on "international recommendations and legislation in force" of this paper, have been widely implemented. In the event that recall of plasma-derivatives following the identification of a donor with one of the above-mentioned forms of CJD involves national plasma, patients in our country would be exposed to a high risk of shortage, given that Italy is not self-sufficient in the production of many plasma-derived medicinal products[23-25], including life-saving medical products or medicines indicated as essential by the World Health Organisation[26]. The importation of any similar products from abroad with the purpose of overcoming shortages would not offer more guarantees of biosafety to plasma-derived medicinal products used in Italy, since there is no disposition to recall such products in other countries that have decided to follow the EMA recommendations.

It follows that the benefit-risk assessment is in favour of maintaining on the market the plasma-derived medicinal products obtained from plasma pool containing donations from donors who only at a later stage developed sporadic, genetic or iatrogenic CJD, since the benefit of the availability of a life-saving treatment greatly exceeds that of the risk of transmission, which, on the basis of current scientific evidence, is only hypothetical and since more restrictive measures would be of dubious efficacy, given the above-described issues in the importation from abroad.

However, in order to safeguard patients, in all cases of donors notified as having a suspected diagnosis of CJD, the national health authorities have decided to adopt interim precautionary measures (quarantine/ban of use), waiting for the finalisation of the investigations needed for any diagnostic confirmation.

The following precautionary operational measures can, therefore, be defined (Table I): in the event that a donation from a subject with a diagnosis of variant CJD is found *a posteriori* in a plasma pool, it is recommended that the related plasma-derived medicinal products are recalled, in line with the recommendation in the EMA document; in the event that a donation from a subject with a TSE is *a posteriori* found in a plasma pool and in whom a diagnosis of variant CJD cannot be excluded, it is recommended, as a precautionary measure, to quarantine (ban the use) the related plasma-derived medicinal products until the diagnostic procedure has been completed by further investigations; in the event that a donation from a subject with "classical" TSE is *a posteriori* found in a plasma pool and in whom a diagnosis of variant CJD has been excluded, no precautionary measures are recommended regarding the related plasma-derived medicinal products.

Table I - Precautionary operational measures to be adopted.

Case	Plasma-derived medicinal products[a]	Communication
1. Variant CJD	Recall from the market	Yes
2. "Classical TSE"[b] in which the clinical picture does not yet enable a diagnosis of variant CJD to be excluded	Quarantine (Ban of use)	Yes
3. "Classical TSE" in which the diagnosis of variant CJD cannot be definitively excluded[c]	Continuation of the quarantine (ban of use)	No
4. "Classical TSE" in which the diagnosis of variant CJD has been excluded	Lifting the quarantine	Yes

Legend

[a]Given its production process, albumin is considered one of the plasma derivatives with the lowest risk. In the event of albumin used as an excipient, its possible recall should be carefully evaluated case by case because a single lot of albumin can be used to produce various lots of medicinal products and efforts should be made to avoid an automatic quarantine/recall from having repercussions on entire stocks of a product and creating major shortages on the market. In this regard, it is worth noting that, as a precautionary measure, albumin used as an excipient should not come from countries in which cases of variant CJD have been reported.; [b]The simplified term "classical" TSE indicates the sporadic, iatrogenic and genetic forms of CJD and other genetic TSE; [c]It would be useful that donors with a diagnosis of "classical" TSE in whom the diagnosis of variant CJD could not be excluded undergo post-mortem studies (i.e., neuropathological and/or immunochemical analyses).

Algorithm for the management of notifications

1- If there is a suspected case of TSE in a blood donor, the Regional Blood Coordinating Centres, the Blood Service or the foreign Blood Collection Centre shall directly notify to the manufacturer as soon as the Centre or Service becomes aware of the case.
2- The manufacturer shall notify to AIFA and to CNS of both the suspected case and the related lots of plasma-derived medicinal products.
3- AIFA shall ask the National CJD Registry at the ISS for the diagnostic classification of the case. In order to comply with current legislation on the protection of personal data, the CJD Registry shall communicate the classification of the cases to AIFA and CNS using the simplified term "classical" TSE to indicate any of the sporadic, genetic or iatrogenic forms of CJD or the other genetic TSE.
4- The CJD Registry at the ISS shall inform AIFA of the diagnostic classification of the case and send the same information to CNS.
5- When the notification concerns donation of blood/plasma not collected in Italy, AIFA shall contact directly the relative foreign authorities and structures, if necessary.
6- The AIFA shall adopt precautionary measures for the medicinal product involved, as summarised in Table I and shall communicate the decision to the company manufacturing the medicinal products.
7- In the case that specific measures are taken, AIFA shall inform the public through its official website, in accordance with appendix 1.
8- The CJD Registry of the ISS shall promptly inform AIFA of any changes in the initially communicated diagnostic classification of cases.
9- If the suspicion of TSE is excluded or a definite diagnosis of "classical" CJD is made, so that the diagnosis of variant CJD can be excluded, AIFA shall lift the precautionary quarantine (ban of the use) of the lots involved.

Keywords: Creutzfeldt-Jakob disease, blood donors, transmissible spongiform encephalopathy, medicinal blood products.

The Authors declare no conflicts of interest.

References

1) Official Journal of the European Union L91, March 30th, 2004. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:091:0025:0039:EN:PDF. Accessed on 28/02/2013.
2) Official Journal of Italian Republic no. 85, April 13th, 2005. Decreto del Ministro della Salute 3 marzo 2005: "Protocolli per l'accertamento della idoneità del donatore di sangue e di emocomponenti". Available at: http://www.centronazionalesangue.it/content/decreto-3-marzo-2005-0. Accessed on 10/03/2013.
3) CHMP Position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. EMA/CHMP/BWP/303353/2010. European Medicines Agency (EMA). London, 23 June 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2011/06/WC500108071.pdf. Accessed on 18/02/2011.
4) Guidance for Industry. Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products, May 2010. Food and Drug Administration (FDA). Available at: http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm213415.pdf. Accessed on 10/03/2013.
5) Vetrugno V, Cardinale A, Filesi I, et al. KDEL-tagged anti-prion intrabodies impair PrP lysosomal degradation and inhibit scrapie infectivity. Biochem Biophys Res Commun 2005; **338**: 1791-7.
6) Head MW, Ironside JW. Creutzfeldt-Jakob disease: prion protein type, disease phenotype and agent strain. Neuropathol Appl Neurobiol 2012; **38**: 296-310.
7) Pocchiari M, Puopolo M, Croes EA, et al. Predictors of survival in sporadic Creutzfeldt-Jakob disease and other human transmissible spongiform encephalopathies. Brain 2004; **127**: 2348-59.
8) Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999; **46**: 224-33.
9) Ladogana A, Puopolo M, Poleggi A, et al. High incidence of genetic human transmissible spongiform encephalopathies in Italy. Neurology 2005; **64**: 1592-7.
10) Kovacs GG, Puopolo M, Ladogana A, et al. Genetic prion disease: the EUROCJD experience. Human Genet 2005; **118**: 166-174.
11) Brown P, Brandel JP, Sato T, et al. Iatrogenic Creutzfeldt-Jakob disease, final assessment. Emerg Infect Dis 2012; **18**: 901-7.
12) Heath CA, Cooper SA, Murray K, et al. Validation of diagnostic criteria for variant Creutzfeldt-Jakob disease. Ann Neurol 2010; **67**: 761-70.
13) Brown P. Can Creutzfeldt-Jakob disease be transmitted by transfusion? Curr Opin Hematol. 1995; **2**: 472-7.
14) Vetrugno V, Puopolo M, Giampaolo A, et al. Risk analysis of Creutzfeldt-Jakob disease transmission through plasma-derived medicinal products in humans (Italian). Roma: Istituto Superiore di Sanità (2011). (Rapporti ISTISAN 11/8). Available at: http://www.iss.it/binary/publ/cont/undici8web.pdf. Accessed on 28/02/2013.
15) Brown P, Gibbs CJ, Johnson PR, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. Ann Neurol 1994; **35**: 513-29.
16) Peden A, McCardle L, Head MW, et al. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia 2010; **16**: 296-304.
17) Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. Vox Sang 2006; **91**: 221-30.
18) Dorsey K, Zou S, Schonberger LB, et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion 2009; **49**: 977-84.
19) Puopolo M, Ladogana A, Vetrugno V, Pocchiari M. Transmission of sporadic Creutzfeldt-Jakob disease by blood transfusion: risk factor or possible bias. Transfusion 2011; **51**: 1556-66.
20) Molesworth AM, Mackenzie J, Everington D, et al. Sporadic Creutzfeldt-Jakob disease and risk of blood transfusion in the United Kingdom. Transfusion 2011; **51**: 1872-3.
21) Puopolo M, Ladogana A, Vetrugno V, Pocchiari M. (Author reply to: Molesworth et al., (2011). Sporadic Creutzfeldt-Jakob disease and risk of blood transfusion in the United Kingdom). Transfusion 2011; **51**: 1873-4.
22) Cardone F, Simoneau S, Arzel A, et al. Comparison of nanofiltration efficacy in reducing infectivity of centrifuged versus ultracentrifuged 263K scrapie-infected brain homogenates in "spiked" albumin solutions. Transfusion 2012; **52**: 953-62.
23) Official Journal of Italian Republic no. 82 April 9th, 2011. Decreto del Ministero della Salute 20 gennaio 2011: "Programma di autosufficienza nazionale del sangue e dei suoi prodotti per l'anno 2010". Available at: http://www.centronazionalesangue.it/sites/default/files/dm_20.01.2011_programma_nazionale_autosufficienza_2010.pdf. Accessed on 28/02/2013.
24) Official Journal of Italian Republic no. 271 November 21st, 2011. Decreto del Ministero della Salute 7 ottobre 2011: "Programma di autosufficienza nazionale del sangue e dei suoi prodotti, per l'anno 2011". Available at: http://www.centronazionalesangue.it/sites/default/files/d.m._7.10.11_programma_nazionale_autosufficienza_2011_gu_22.11.11.pdf. Accessed on 28/02/2013.
25) Official Journal of Italian Republic no. 241 October 15th, 2012. Decreto del Ministero della Salute 4 settembre 2012: "Programma di autosufficienza nazionale del sangue e dei suoi prodotti per l'anno 2012". Available at: http://www.centronazionalesangue.it/sites/default/files/programmazione_autosuff_2012_0.pdf. Accessed on 28/02/2013.
26) 17th WHO Essential Medicines List and the 3rd WHO Essential Medicines List for Children updated in March 2011. World Health Organization (WHO). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed on 24/01/2013.

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Appendix 1

Communication for professionals and patients concerning a ‹recall from the market› ‹quarantine (ban of use)› of plasma-derived medicinal products.

The AIFA has ordered, for purely precautionary reasons, a ‹recall from the market› ‹quarantine (ban of use)› of some lots of plasma-derived medicinal products made from a pool of plasma containing donations from a blood donor suspected as suffering from transmissible spongiform encephalopathy (e.g. Creutzfeldt-Jakob disease).

‹Any details of the specific case› ……

This is a precautionary measure, issued pending the results of ongoing analysis and controls, adopted following consolidated monitoring procedures aimed at reducing any health risk for patients, even if only hypothetical.

‹The packages of plasma-derived medicinal products from the lots covered by the quarantine must be set aside, waiting for the results of further investigations, which could lead to the quarantine lifting if it is established that the donor does not suffer from variant Creutzfeldt-Jakob disease. In this case the products could still be used within the expiry date reported on the label.›

According to current knowledge, it has never been clinically proven that variant Creutzfeldt-Jakob disease can be transmitted through the use of plasma-derived medicinal products, but it cannot be absolutely excluded. In Italy, only two autochthonous cases of variant Creutzfeldt-Jakob disease have been described; nobody of the two subjects had ever donated or received blood components. In the case of sporadic Creutzfeldt-Jakob disease there is no evidence of transmission through plasma-derived medicinal products and, therefore, the international guidelines, such as those published by the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA), do not suggest any precautionary actions. Furthermore, during more than 30 years of use of plasma-derived medicinal products, no case of transmission of sporadic Creutzfeldt-Jakob disease associated with their use has ever been reported, although occasional donors with sporadic Creutzfeldt-Jakob disease have been found in the past.

The European Medicines Agency (EMA) recommends to recall plasma-derived medicinal products from the market only in the case that it is ascertained that the plasma has been donated by a subject suffering from variant Creutzfeldt-Jakob disease, while, on the basis of the current epidemiological evidence, EMA considers that recall of plasma-derived medicinal products is not justified when a donor is later diagnosed as having sporadic or genetic Creutzfeldt-Jakob disease.

Since there is no validated test available to identify the presence of the infectious agents responsible for Creutzfeldt-Jakob disease and other human transmissible encephalopathies (prion diseases) in the blood, it is scientifically incorrect to state that there is "zero-risk" of prions transmission. However, it is worth noting that the current manufacturing methods of plasma-derived medicinal products use chemical and/or physical mechanisms to inactivate and remove pathogens, enabling significant levels of biological safety to be reached.

For this reason the ‹recall from the market› ‹quarantine› of plasma-derived medicinal products has to be considered as a precautionary measure that should not raise fear in patients but should strengthen their confidence that all the necessary measures are taken to guarantee and monitor the safety of medicinal products.

Patients are invited to contact their own ‹general practitioner/paediatrician› ‹specialist› who will have no difficulty in prescribing other packages of the product ‹or other corresponding medicinal products› to replace ‹those› covered by the precautionary measure adopted by AIFA.

A list of lots subject to this provision is attached.

Appendix 2

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