TRANSFUSION TRANSMITTED DISEASES

Position paper

Revision and update of the position paper on the management of notifications of donors with Creutzfeldt-Jakob disease in Italy

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INTRODUCTION

Notifications of blood and plasma donors who have developed Creutzfeldt-Jakob disease (CJD) and whose donations, collected in the pre-clinical phase of the disease, have entered industrial pools for the production of plasma-derived medicinal products (PDMP), have highlighted the need to develop a technical-scientific document (position paper). This document outlines the prevention, management and communication measures to be adopted in such cases and will be shared among the institutions involved: the Italian Medicines Agency (AIFA), the National Blood Center (CNS), the National Institute of Health (*Istituto Superiore di Sanità*, ISS) and the Ministry of Health.

The position paper, "Management of notifications of donors with Creutzfeldt-Jakob disease (post-donation information)" was initially adopted by AIFA in December 2012 and then published in 2014[1]. The current revision (10 years later) of the former position paper is to update available scientific evidence and, by so doing, redefine the procedures to be followed to manage a possible precautionary quarantine (ban of use) or a possible recall of PDMP. In particular, the document aims to define the procedures to be followed to manage a possible precautionary ban on use or a possible withdrawal of PDMP based on the most recent scientific evidence and international guidelines/recommendations. The goal is to minimize the potential shortage of life-saving PDMP. Additionally, it outlines the methods and contents of the risk communication to professionals, patients, and the general public.

This document will be updated in the light of new and significant scientific evidence and/or regulatory requirements.

CLASSIFICATION OF HUMAN TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

Transmissible spongiform encephalopathies (TSE), or prion diseases, are rare degenerative diseases of the central nervous system, invariably fatal, caused by an infectious agent called prion[2]. The central event in the pathogenesis of TSE is the accumulation of the pathological prion protein (PrP^{TSE}) starting from its cellular precursor (PrP^{C}). PrP^{TSE} tends to form fibrillar aggregates that damage central nervous system tissues. This pathogenic mechanism of TSE is shared with other neurodegenerative diseases, called protein misfolding diseases, such as Alzheimer's disease, in which beta-amyloid peptides and the tau protein are involved, and Parkinson's disease with alpha-synuclein. What differentiates TSE from other neurodegenerative diseases is their intra- and

Arrived: 3 June 2024
Revision accepted: 23 July 2024
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Blood Transfus. 2025; 23(2): 158-167 doi: 10.2450/BloodTransfus.829

inter-species transmissibility, raising important public health challenges. TSE are mandatory notifiable diseases. Based on etiology, human TSE are classified into three categories: sporadic, genetic and acquired[3]. Sporadic forms include sporadic CJD (sCJD), the most frequent human TSE, sporadic fatal insomnia and variably protease-sensitive prionopathy. Genetic forms are genetic CJD, Gerstmann-Sträussler-Scheinker (GSS) syndrome, fatal familial insomnia (FFI), and prion protein systemic amyloidosis[4], formerly known as chronic diarrhea and hereditary sensory and autonomic neuropathy. Acquired forms include kuru, now virtually extinct, iatrogenic CJD (iCJD) and variant CJD (vCJD). Suspected cases of human TSE are classified according to published criteria and subject to periodic review[5].

Three levels of diagnostic accuracy are recognized for human cases of TSE: possible, probable and definite. The certainty of the diagnosis for each of the described forms is only obtained *post-mortem*, through neuropathological and/or immunochemical analysis (PrP^{TSE} detection) at autopsy. The diagnostic criteria for CJD and related syndromes, revised in 2017, now include, among laboratory investigations, the real-time quaking induced conversion (RT-QuIC) assay, an *in vitro* PrP^{TSE} amplification test in biological fluids, such as cerebrospinal fluid (CSF), or tissues, such as the olfactory mucosa[6], and more recently, micro-biopsies of skin tissue[7]. It is a highly reproducible, rapid and safe assay that requires limited manipulation, thus resulting in a low risk of contamination of biological samples. Importantly, the RT-QuIC test is highly sensitive for sporadic and genetic forms, but not for acquired forms[8]. The RT-QuIC test has also improved the detection of pathological prion protein in several peripheral tissues, possibly even before the clinical onset of the disease[9]. This test has, therefore, significantly improved the diagnostic process *in vitam*, with sensitivity values of around 96% and specificity close to 100% for the CSF and olfactory mucosa. It is important to underline that the product of the amplification during the CSF assay is not infectious, as demonstrated by experimental inoculation in transgenic mice[10].

Recently, an optimization of a protein amplification technique, known as protein misfolding cyclic amplification (PMCA), has allowed the quantification of pathological prion protein in olfactory mucosa samples from patients affected by sporadic CJD with a sensitivity of 79.3% and a specificity of 100%[11]. However, further experimentation and optimization will be necessary for its effective diagnostic use. It is important to note that the amplification product in PMCA, unlike that in the RT-QuIC assay, has been demonstrated to be infectious, posing potential contamination risks for both the operator and the environment.

Unfortunately, to date, there is no laboratory technique that allows us to identify donors at risk of prion transmission (except, of course, the very rare cases of prion protein gene [*PRNP*] mutation carriers). Therefore, the biosafety of plasma derivatives regarding prion risk is currently based on the implementation of prion removal techniques (primarily leukodepletion and nanofiltration for blood-derived proteins) and precautionary measures, where possible, to limit the number of donors in plasma pooling.

Sporadic Creutzfeldt-Jakob disease

The sporadic form of CJD comprises approximately 80% of CJD cases, with a peak incidence in the seventh decade of life and a median disease duration of approximately 6 months[11]. There are multiple molecular subtypes of sCJD[13,14]. The RT-QuIC assay is a very reliable methodology for the *ante-mortem* diagnosis of sCJD, with excellent diagnostic accuracy, having a high sensitivity and a specificity close to 100%[15-17].

Genetic transmissible spongiform encephalopathies

Genetic TSE (genetic CJD, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia) represent approximately 10-20% of TSE. They are associated with mutations in the human prion protein gene (*PRNP*), located on the short arm of chromosome 20 in position 13, with an autosomal dominant transmission. The *PRNP* gene may contain pathogenic variants/mutations that determine genetic forms of prion diseases, which differ in penetrance, clinical phenotype, age at onset, disease duration, and diagnostic test results[18]. The diagnosis of genetic TSE is based on a positive family history or on the identification, by sequencing, of mutations of the *PRNP* gene[19].

Iatrogenic Creutzfeldt-Jakob disease

This subtype of CJD is secondary to accidental exposure to the etiological agent during medical and/or surgical

procedures, such as administration of pituitary hormones extracted from cadaveric pituitary glands, transplantation of dura mater and cornea from donors affected by sporadic CJD, and exposure to neurosurgical instruments previously used in a CJD case classified as definite or probable. The incubation time varies from 1 to 38 years[20-22].

Variant Creutzfeldt-Jakob disease

The variant form of CJD is linked to the consumption of food products contaminated by the infectious agent responsible for bovine spongiform encephalopathy (BSE). In contrast to sCJD, vCJD typically affects younger individuals (i.e., onset or death in individuals younger than 55 years), presents with symptoms at the onset of the illness and/or persistent painful sensory symptoms, and the illness lasts more than 6 months. The definitive diagnosis of vCJD is based on neuropathological and/or immunochemical examination[23]. The diagnosis of probable vCJD is based on clinical symptoms, brain magnetic resonance imaging and possibly the presence of PrP^{TSE} in tonsillar biopsy samples.

In the United Kingdom (UK), four cases of iatrogenic transmission of vCJD associated with blood transfusions from donors who subsequently developed the disease have been described. Three recipient patients, in turn, developed vCJD. The fourth case involved a patient who died from causes other than vCJD, in whom the infectious agent was discovered only *post-mortem*[24]. All the cases described received non-leukodepleted erythrocyte concentrates. After the introduction of leukodepletion procedures for red blood cell concentrates, no more blood-related cases of vCJD have been observed. It has been experimentally demonstrated that the leukodepletion procedure is able to remove significant fractions of prion infectivity[25]. In Italy, pre-storage leukodepletion (immediately after collection) became mandatory with the Health Ministerial Decree of 2 November, 2015 entitled "*Provisions relating to the quality and safety requirements of blood and blood components*"[26].

The incidence of vCJD has declined dramatically since the global epidemic of this disease peaked in the year 2000. As of July 5, 2022, 233 cases of vCJD had been recorded of which 178 were in the UK, 29 in France, and 26 in the rest of the world[27]. The last published case of vCJD was in France and involved a 33-year-old female patient, a laboratory technician, who for occupational reasons (i.e., pricking a finger with infected scissors) had been exposed to the BSE infectious agent, 7.5 years earlier[28]. A search for pathological prion protein in this patient's CSF by RT-QuIC gave a negative result; in contrast, with the PMCA technique, plasma and CSF were positive. A definite diagnosis of vCJD was obtained *post-mortem* by neuropathological examination.

This latest report raised strong concerns about the peripheral transmission mode of the infectious agent and the repercussions on the prevention and management of "prion risk" in professional practice, as a consequence of the large number of potentially infected biological samples processed for research and diagnostic purposes by medical and laboratory personnel[29,30].

In Italy, the last patient affected by vCJD, who died in 2016, had been exposed for occupational reasons to BSE- and vCJD-infected brain tissues. Internal epidemiological investigations did not find any laboratory incident, although it cannot be definitively ruled out that the infection occurred during routine laboratory activities[17,28]. In total, in Italy, three cases of vCJD have been described in subjects who did not stay in the UK or in other countries at risk (France), and who were, therefore, likely exposed to the BSE infectious agent in Italy. The three Italian cases did not donate or receive blood components.

SCIENTIFIC EVIDENCE OF THE RISK OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY INFECTIVITY IN BLOOD AND BLOOD DERIVATIVES

1. In several experimental animal models of TSE, blood and plasma have been shown to be infected. The first experimental transmission studies to evaluate the presence of infectivity in the blood/plasma of patients affected by sporadic, iatrogenic and variant CJD were substantially negative[25]. However, more recent studies, both *in vitro* (using a protein amplification technique called PMCA)[31] and *in vivo* (in transgenic mouse models that overexpress the human prion protein) have demonstrated the presence of infectivity in the blood and plasma of patients affected by vCJD, both in the pre-symptomatic and symptomatic stages[32], and in the bone marrow[33,34] and plasma (2/4 tested)[35] of sCJD patients.
2. In subjects affected by sCJD, infectivity was demonstrated not only in the central nervous system

but also in a few peripheral tissues, including lymphoid ones (i.e., spleen, lymph nodes)[36]. Recent experimental studies have detected the presence of infectivity in numerous other tissues (e.g., skin, kidney, lung, adrenal gland)[34,37].

3. Epidemiological studies have provided strong evidence regarding the transmissibility of vCJD via labile blood components[25]. In the case of plasma derivatives, the transmission of vCJD is considered possible on the basis of a single case, reported in the literature, of a patient with hemophilia A who died of non-neurological causes and was discovered to be infected only *post-mortem*[38].
4. Repeated observational studies, during an observation period exceeding 20 years, have not highlighted cases of sCJD transmission in subjects who had received whole blood or labile blood components from donors affected by sCJD in the preclinical phase. The interpretation of these studies must, however, take into consideration that 60% of patients undergoing transfusion are over the age of 65 years and that approximately 50% die within 5 years of the transfusion from causes related to their pathology[25,39].
5. An observational (case-control) study conducted in Italy suggested an increased risk of developing sCJD following transfusion of labile blood components more than 10 years earlier[40]. However, in this type of study, it cannot be excluded that the results are conditioned by the methods of data collection and subject recruitment. A British study, performed with a similar, although not identical method, had not highlighted any association between transfusion and sCJD[41], confirming the difficulty of drawing definitive conclusions from this type of study[42].
6. Epidemiological look-back studies do not yet have sufficient statistical power to formally exclude the risk of possible blood-related transmission. These studies do, however, clearly show that the transmission of sCJD via blood is either unlikely (theoretical) or is a very rare event with long incubation times[39,43,44].
7. In 2017, as part of specific surveillance actions, including a collaborative study within the European Union (EU) that started in 1993, two cases of sCJD, confirmed *post-mortem*, were identified in the UK. The subjects had coagulopathies and had extensively used plasma derivatives produced from plasma collected and fractionated in the UK[45]. This observation raised concerns. However, a definite causal link between exposure to potentially contaminated plasma derivatives and the disease has not been established. The authors of the publication do not exclude that the occurrence of such cases may simply be a stochastic event in the context of systematic surveillance of CJD in large populations.
8. On the basis of epidemiological data that have not detected cases of TSE transmission linked to blood from a donor affected by iatrogenic CJD or genetic CJD[43], it is hypothesized that in assessing the risk of plasma derivatives, iatrogenic CJD, genetic CJD and other forms of genetic TSE behave like sCJD.
9. To date, there are no "validated" diagnostic tests that enable the identification of infected subjects who were clinically healthy at the time of donation. Therefore, the lack of knowledge of the risk factors for sCJD, as well as the absence of validated, safe and reliable screening tests for donated blood/plasma, makes it impossible to prevent the accidental use of blood/plasma from donors in the preclinical phase of CJD for transfusion purposes or to produce plasma-derived medicines[6].
10. The production processes of the various PDMP are able to remove/inactivate significant fractions of prion infectivity, potentially contained in plasma. Biological and biochemical assays have shown decreasing levels of infectivity in the following order: cryoprecipitate (factor VIII intermediate), fraction I+II+III (immunoglobulin intermediates) and fraction V (albumin intermediate). The validation studies involve the use of experimental sources of infectivity (spikes) that aim to mimic natural infectivity possibly present in the blood and quantify a theoretical reduction factor for the entire production process or for individual steps. Since little is known about the shape and molecular size of prions present in blood/plasma (although an average size between 17 and 27 nm is assumed)[46], the choice of experimental infectivity models (spikes) for testing nanofiltration procedures on blood products is crucial for estimating the actual capacity of a given

procedure to remove prions. In fact, it was shown that adopting ultracentrifuged preparations as the spike (i.e., containing poorly aggregated prion infectious particles), nanofilters, with pore sizes between 20 and 15 nm, remove approximately two orders of magnitude less infectivity than previously found with a "standard" spike (i.e., low-speed supernatant)[47]. The variability present within different production processes and among different validation studies carried out by blood product manufacturers prevents easy comparisons, often making it impossible to generalize the estimates obtained[25,47,48].

11. The scientific uncertainties, revealed so far, justify the maintenance and implementation of active global TSE surveillance programs for public health reasons[17].

LEGISLATION IN FORCE IN ITALY AND INTERNATIONAL RECOMMENDATIONS

1. For the purposes of prevention, the only valid approach is evaluation of the medical history and general health conditions of a candidate donor, as required by current Italian legislation. To this aim, the Decree of 2 November 2015 of the Ministry of Health "*Provisions relating to the quality and safety requirements of blood and blood components*" establishes the permanent exclusion from donating blood or blood components of subjects recognized as at risk of developing CJD, in order to protect the health of the recipient[26]. These subjects include: (i) donors who have received corneal, sclera or dura mater transplants, or who have been treated with pituitary gland extracts; (ii) people with a medical or family history of a risk of contracting TSE (rapidly progressive dementia, degenerative neurological diseases including pathologies of unknown origin); (iii) prospective donors who lived in the UK in the period from 1980 to 1996 for more than 6 cumulative months; (iv) prospective donors who underwent surgery or received allogeneic blood transfusion or blood products in the UK from 1980 to 1996.
2. The exclusion criteria for donors considered at risk of developing vCJD, iatrogenic CJD and genetic TSE are well established by European and Italian legislation, while it is not yet possible to establish which subjects are at risk of sCJD.
3. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommends the withdrawal of plasma derivatives from the market only if a donation of plasma from a subject diagnosed with vCJD is identified in the plasma pool. Based on current, accumulated epidemiological evidence, the CHMP considers that "a recall of plasma-derived medicinal products is not justified, where a donor is later confirmed as having sporadic, genetic or iatrogenic CJD or risk factors (. . .) in cases where a post-mortem differentiation between vCJD and other types of CJD is not possible or not yet available, it can be justified not to recall affected batches or product intermediates upon risk assessment including the epidemiology, clinical data from the donor, and prion reduction capacity of the manufacturing process"[49]. Furthermore, the EMA document underlines the importance of obtaining an accurate diagnosis in suspected cases of CJD in order to decide actions to be taken. It also mentions the potential for diagnostic confusion between sCJD and vCJD, before the *post-mortem* findings, particularly in younger age groups.
4. This potential diagnostic confusion between sCJD and vCJD led the Food and Drug Administration (FDA) of the USA to recommend case-by-case evaluation, in particular for donors under investigation for vCJD (i.e., with a suspected CJD diagnosis and aged less than 55 years)[50].
5. The UK lifted the ban (originally implemented in 1999) on the use of UK-sourced plasma for the manufacture of immunoglobulins and albumin medicinal products in 2021 and 2023, respectively. Following the UK reviews, the risk of transfusion-transmitted vCJD due to geographic and transfusion exposure has so far been reassessed by the following countries: Ireland, USA, Australia, Canada, Hong Kong, Israel and New Zealand. Both the US FDA and the Australian Therapeutic Goods Administration (TGA) removed the restrictions on blood donors who had previously spent time in the UK, based on quantitative probabilistic risk analyses. Mathematical modeling estimated the increased risk of transfusion-transmitted vCJD after the removal of restrictions as very low or negligible, with no or

a very low increase in the projected number of vCJD cases. Recently, the European Blood Alliance (EBA) published a useful position paper on assessing the risk of transfusion-transmitted vCJD, aimed to support the discussion on risk assessment and preventive measures[51].

In January 2023, the European Center for Disease Prevention and Control (ECDC) published its technical report, "vCJD in donors of blood and plasma having temporarily resided in or visited the United Kingdom", focusing on blood and plasma for transfusion (i.e., excluding plasma-derived medicinal products). In this guidance, the ECDC agrees with the conclusions of modeling studies regarding a very low risk of transmission of vCJD through blood transfusion and recommends that each country assesses the local risk of transmission of vCJD via transfusion, considering country-specific differences in populations (e.g., demography, genetic susceptibility to infection), and balances the risk against supply needs in the country[52].

On May 31, 2024, the EMA published the "CHMP reflection paper on Creutzfeldt-Jakob disease (CJD) and plasma-derived and urine-derived medicinal products"[49]. It replaces the former "CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. 16 November 2018 (EMA/CHMP/BWP/303353/2010 Rev.3)". In this 2024 reflection paper, the recommendation that donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 should be excluded from donating plasma for fractionation due to the risk of vCJD is no longer made. This decision is based on the decline of vCJD cases and the absence of a new wave of cases as well as on the risk-reducing factors specific to PDMP, such as prion reduction during manufacture[49].

PRECAUTIONARY MEASURES TO BE ADOPTED IN ITALY

Background

Given that scientific evidence, reported above, cannot exclude with absolute certainty a possible risk associated with the use of PDMP manufactured with plasma pools including a donation from a subject later discovered to be affected by "classical" CJD, the regulatory framework offered by the leading international public health organizations must be considered. These organizations allow the use of these donations to protect citizens who could suffer life-saving drug shortage.

In EU countries, in the case of sporadic, genetic, or iatrogenic CJD, there is widespread application of the EMA recommendations, as reported in point 3 of the section on "Legislation in force in Italy and international recommendations".

In the event that the recall of plasma derivatives following the identification of a donor affected by the aforementioned forms of CJD involves nationally produced plasma, the recall or ban on use of medicines derived from it would result in the use of imported products prepared from commercial plasma that are not subject to recall.

Any more restrictive or precautionary measures by the national authorities would be of dubious efficacy, since there is no disposition to recall PDMP deriving from plasma pools of donors affected by sporadic, genetic or iatrogenic CJD, nor to block the importation of the aforementioned medicines from abroad, since this might cause serious risks of shortage, given Italy's non-self-sufficiency for many of the PDMP, including life-saving products or those indicated by the World Health Organization as essential drugs[53,54].

To the best of our knowledge, with regards to classical CJD, where a donor is later confirmed as having sporadic, genetic or iatrogenic CJD, only France, where national self-sufficiency in blood products was guaranteed, had imposed batch recall measures until December 2015 but adopted the EMA recommendation thereafter[55].

Precautionary operational measures

As a consequence of the foregoing, the following precautionary operational measures can be defined (**Table I**):

1. In the event that a donation from a subject diagnosed with vCJD is retrospectively identified in a plasma pool, it is recommended that the relevant PDMP are recalled, in line with the recommendation in the EMA document.
2. In the event that a donation from a subject with TSE is retrospectively identified in a plasma pool and the diagnosis of vCJD cannot yet be excluded,

Table I - *Precautionary operational measures to be adopted in the case of suspected transmissible spongiform encephalopathy in a blood donor*

Case	PDMP*	Communication
1. Variant CJD	Recall from the market	Yes
2. "Classical" TSE[§] in which the clinical diagnosis cannot yet exclude the diagnosis of variant CJD	Quarantine (ban of use)	Yes
3. "Classical" TSE classified as definite or probable[^,#]	Lifting the quarantine	Yes

*Albumin, due to its production process, is considered the product with the lowest risk among plasma-derived medicinal products. In the case of albumin used as an excipient, a possible withdrawal must be carefully evaluated on a case-by-case basis since a single batch of albumin can be used to produce several batches of medicines because of the small amounts that are typically used as an excipient. Consequently, a recall could affect complete stocks of a product and create severe shortages.
[§]The simplified term "classical" TSE case refers to the overall forms of sporadic, iatrogenic, genetic CJD or other genetic TSE.
[^]It would be appropriate that donors with a diagnosis of "classical" TSE undergo a post-mortem examination (i.e., neuropathological, immunochemical or biochemical analysis).
[#] With a positive RT-QuIC assay performed on cerebrospinal fluid or other tissue. It is important to note that RT-QuIC efficiently amplifies "classical" CJD prions but not variant CJD prions.
PDMP: plasma-derived medicinal products; CJD: Creutzfeldt-Jakob disease; TSE: transmissible spongiform encephalopathy; RT-QuIC: real-time quaking induced conversion assay.

it is recommended, as a precautionary measure, to quarantine (ban the use) of the related PDMP, until the diagnostic procedures are completed by further investigations.

3. In the event that a plasma donation from a subject with a diagnosis of "classical" TSE, classified as definite or probable[5], is retrospectively identified in a plasma pool, no precautionary measures are recommended for the related PDMP.

Algorithm for the management of notifications

1. If there is a suspected case of TSE in a blood donor, the Regional Blood Coordination Center, the Blood Establishment or the foreign Blood Collection Center shall directly notify the plasma-product manufacturer as soon as they become aware of the case.
2. The manufacturer shall notify the Italian Medicines Agency (AIFA) and the Italian National Blood Center (CNS) of both the suspected case and the related lots of PDMP.
3. AIFA shall ask the National CJD Registry at the Italian National Health Institute (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 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 the CNS.
5. When the notification concerns donation of blood/plasma not collected in Italy, AIFA shall contact the relative foreign authorities and structures directly, if necessary.
6. AIFA shall adopt precautionary measures for the medicinal product involved, as summarized 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 at 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 or probable diagnosis of "classical" CJD is made, AIFA shall lift the precautionary quarantine (ban of use) of the lots involved.

ACKNOWLEDGMENTS

We thank all the people in the different institutions involved in the critical reading and approval process of the manuscript: "Transmissible Spongiform Encephalopathies Group - National Institute of Health" (GESTISS, Rome): *Vito Vetrugno, Anna Ladogana, Romolo Nonno, Letizia Lombardini, Giuseppe Marano*; "Italian National Blood Centre" (CNS,

Rome): *Vincenzo De Angelis, Simonetta Pupella, Ilaria Pati*; the "Italian Medicines Agency" (AIFA, Rome): *Domenico Di Giorgio, Sara Ferrucci, Concettina Oliva;* "National Health Council (CSS)" (Section II and V Working Group): *Franco Locatelli, Giuseppe Curigliano, Giuseppe Remuzzi, Silvia Giordano, Renato Bernardini, Maria Del Zompo, Andrea Laghi, Giulia Veronesi, Marco Ferrari, Filippo Crea, Paola Di Giulio, Cristina Mecucci, Maria Rosaria Capobianchi, Paolo Antonio Grossi, Vito Martella, Anna Odone, Enrico Alleva, Adriano Aguzzi;* and the "Ministry of Health" (Rome): *Gianni Rezza, Mauro Dionisio.*

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

The Authors declare no conflicts of interest.

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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 Italian Medicines Agency (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 of having a 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 being lifting if it is established that the donor does not have “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 three autochthonous cases of variant Creutzfeldt-Jakob disease have been described; none of the three 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 EMA recommends recalling 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, the EMA considers that recall of plasma-derived medicinal products is not justified when a donor is later diagnosed as having sporadic, genetic or iatrogenic 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 spongiform encephalopathies (prion diseases) in the blood, it is scientifically incorrect to state that there is “zero-risk” of prion transmission. However, it is worth noting that the current methods of manufacturing plasma-derived medicinal products use chemical and/or physical mechanisms to inactivate and remove pathogens, enabling significant biological safety.

For this reason, the ‹recall from the market› ‹quarantine› of plasma-derived medicinal products must 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/pediatrician› ‹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.