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Evaluation of Medicines for Human Use

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CPMP POSITION STATEMENT ON NEW VARIANT CJD and PLASMA-DERIVED MEDICINAL PRODUCTS

This Position Statement is superseded by the CPMP Position Statement on "Creutzfeldt-Jakob Disease and plasma-derived and urine-derived medicinal products" dated 20 February 2003

SUMMARY

A workshop of international experts on transmissible spongiform encephalopathies (TSEs), convened under the auspices of CPMP, was held on 15 January 1998 to consider the available information on new variant Creutzfeldt-Jakob disease (nvCJD) and relevant TSEs. In the light of the emerging information, the CPMP has reached the following conclusions:

There is no evidence that sporadic, familial or iatrogenic Creutzfeldt-Jakob disease (CJD) are transmitted via blood transfusion or via plasma-derived medicinal products. Therefore, the CPMP reaffirms its recommendation that recall of plasma-derived products is not justified where a donor is later confirmed as having CJD.

It is now recognised that nvCJD has different characteristics to sporadic, familial and iatrogenic CJD. Knowledge of other TSE agents suggests that transmission of nvCJD by medicinal products derived from human blood or plasma is very unlikely. Nevertheless, since there is a lack of specific information on nvCJD, the CPMP considers that, as a precautionary measure, it would be prudent to withdraw batches of plasma-derived medicinal products from the market if a donor to a plasma pool is subsequently strongly suspected, by a recognised reference centre, of having nvCJD. However, consequences for essential medicinal products where alternatives are not available will need careful consideration by national authorities.

Since a recall involving albumin used as an excipient has the potential to cause major supply difficulties for essential products, manufacturers should avoid using, as an excipient, albumin derived from countries where a number of cases of nvCJD have occurred.

1. Introduction

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease affecting approximately one person per million population per year. Cases can arise spontaneously (sporadic), may arise at higher frequency in families with certain genetic mutations (familial) or can result from exposure to infectious material (iatrogenic).

The CPMP has considered the risk of transmission of CJD via plasma-derived medicinal products on a number of occasions. The CPMP position adopted in December 1995[1] was based on both the epidemiological and experimental data available on CJD (sporadic, familial and iatrogenic) and concluded that recall of batches was not justified where a donor subsequently developed CJD.

In 1996, a few cases of a new variant (nv) form of CJD were identified[2]. Recent published studies provide strong evidence that nvCJD is distinct from sporadic CJD and is caused by the agent responsible for BSE in cattle[3,4.] The CPMP, therefore, considered that there was a need to review all available information (including unpublished/preliminary data) on nvCJD and on relevant transmissible spongiform encephalopathies (TSEs)[5]. A workshop of international experts, convened under the auspices of the CPMP, was held on 15 January 1998. This was followed, on 16 January, by a CPMP expert working group meeting to advise, in the light of the emerging information, on any

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implications for plasma-derived medicinal products. This CPMP position statement is based on the outcome of these meetings.

2. Sporadic, Familial and Iatrogenic CJD

Investigations with sporadic CJD have failed to show any transmissibility by intravenous transfusion. Experimental infectivity studies with TSEs in animal models have only irregularly found evidence of low levels of infectivity in blood or its components. Many studies did not detect infectivity[6, 7, 8, 9] Such experimental studies are complex and can be difficult to interpret but these results infer that transmission by transfusion is highly unlikely.

Epidemiological studies have also been carried out, including the investigation of recipients of blood from donors who later developed CJD. There are no cases of CJD that have been causally linked to transfusion of blood or plasma-derived products. Case control studies and cohort studies have shown no association with transfusion of blood, its components, plasma fractions or plasma-derived medicinal products[9].

In conclusion, there is no evidence that CJD is transmitted via blood or plasma-derived products. Therefore, the recommendation from the CPMP that recall of plasma products is not justified where a donor is later confirmed as having CJD is still valid.

As a matter of principle, blood and plasma is collected from healthy donors and appropriate selection and exclusion criteria and screening tests are applied to ascertain this as far as is possible. For CJD, the Council of Europe recommends exclusion of individuals who have in the past been treated with extracts derived from pituitary glands, who have been recipients of dura mater grafts or who have a family history of CJD[10]. These exclusion criteria are also included in the European Commission proposal for a Council Recommendation on the suitability of blood and plasma donors and the screening of donations[11].

3. Characteristics of nvCJD

The clinical profile and progression of nvCJD are different from sporadic, familial and iatrogenic CJD[12, 13]. There are also differences in the neuro-histopathological profiles of the two diseases. nvCJD affects teenagers or young adults and so far all patients were under the age of 50 at the onset of the disease. Usually they present with psychiatric or sensory disturbances or a combination of both. These early non-specific clinical signs may last several months and the diagnosis of nvCJD may not be suspected for some time. Later during the course of the disease, clinical signs evolve into a more typical picture of CJD. The overall length of the clinical phase may be more than a year. In contrast, sporadic CJD has a relatively fast clinical course and an average age of onset of 65 years with only a small percentage of cases younger than 50 years of age.

So far there have been a total of 24 cases of nvCJD (23 cases in the UK and one case in France[14, 15]). Although the incidence does not appear to be rising, it is considered too early to predict the future trend for nvCJD.

4. Evaluation of Any Potential Risk of Transmitting nvCJD via Plasma-derived Medicinal Products

There is currently no information from any study as to whether infectivity of the nvCJD agent can be found in blood, plasma or plasma fractions and, if present, whether it can be transmitted by intravenous transfusion. The information known about other TSE agents suggests that transmission by transfusion is very unlikely. However, it has to be borne in mind that nvCJD has different characteristics to other forms of CJD.

Results from studies in animals suggest that the lymphoreticular system (tonsils, lymph nodes and spleen) may be involved in the replication of the agents of TSE although the extent of involvement varies[16, 17, 18]. Protease-resistant prion protein, the abnormal form of a cellular protein associated with TSEs, has been observed in samples of tonsil and spleen taken at necropsy in nvCJD cases but not in

other CJD cases[6,19]. This finding may indicate an increased level of infectivity associated with the lymphoid system in nvCJD cases compared with other forms of CJD and, consequently, there may be an increased risk of infectivity being present in blood.

In conclusion, it is recognised that nvCJD is different to sporadic, familial and iatrogenic CJD. While knowledge of other TSE agents suggests that transmission of nvCJD by intravenous transfusion is very unlikely, in view of the lack of specific information on nvCJD, it is prudent to consider appropriate precautionary measures.

5. Precautionary Measures for nvCJD

Precautionary measures can be directed at selection/exclusion criteria for donors and screening tests for donations, processes of removal or inactivation of the agent, recall of batches where a donor subsequently develops nvCJD, and substitution with alternative non-plasma-derived products, where available.

5.1 Selection/exclusion criteria and screening tests for nvCJD

At the present time, there are no identifiable risk factors that can be used as exclusion criteria for nvCJD. There is also no laboratory test that could be used for screening of donors or donations.

5.2 Potential methods for inactivation/removal of the agent of nvCJD

At present there is no procedure that will inactivate the putative agent of nvCJD without destroying the activity of the product. The development of methods for the removal or inactivation of the agent of nvCJD is desirable. There are suggestions from experimental studies of the association of TSE infectivity with white blood cells[20, 21] and removal of this related cellular debris from plasma for fractionation might be beneficial.

5.3 Recall of batches where information becomes available post-donation

In view of the lack of adequate information on nvCJD, it is prudent to recall batches of plasma-derived medicinal products where a donor to a plasma pool subsequently develops nvCJD. Recall should also include medicinal products containing plasma-derived products as excipients. However, in both cases, consequences for essential medicinal products where alternatives are not available will need careful consideration by national authorities.

A case-by-case consideration would be appropriate where plasma-derived products have been used in the manufacture of other medicinal products.

CJD reference centres in Member States will be aware of strongly suspected cases of nvCJD some time before a definitive diagnosis is made. In these cases, if the patient has donated blood or plasma, the reference centres should inform the organisation involved in the collection of blood or plasma so that withdrawal can be actioned.

Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities, Official Medicines Control Laboratories, surveillance centres and the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted.

Albumin is used widely as an excipient in biological medicinal products. In this case it is usually present in small quantities. A single batch of albumin may be used to produce a number of batches of a medicinal product. Any recall of an albumin batch which has been used as excipient may result in a consequential recall of a number of products and could create severe shortages. To prevent this, in the short term, manufacturers should avoid using, as an excipient, albumin derived from countries where a number of cases of nvCJD have occured.

Development of substitutes for plasma-derived albumin for excipient use is encouraged although it is recognised that this can be difficult and requires a long-term approach.

5.4 Substitution with alternative products

For plasma-derived medicinal products derived from plasma collected in countries where a number of cases of nvCJD have occurred, national competent authorities undertaking precautionary measures on a case-by-case basis should take into account the therapeutic benefits, the purely theoretical risk, the processing of the product and the supply situation.

Use of recombinant products could be considered as an alternative treatment, where these are available. It is felt that this choice should remain within the remit of the physician, taking into account the needs of the individual patient. It should be noted that recombinant products are often stabilised with human albumin.

6. Recommendations and Proposals

6.1 As a precautionary measure, the CPMP considers it prudent to withdraw batches of plasma-derived medicinal products from the market if a donor to a plasma pool is subsequently strongly suspected or confirmed, by a recognised reference centre, of having nvCJD. This recommendation also includes medicinal products containing a plasma-derived product as an excipient. However, in both cases, consequences for essential medicinal products where alternatives are not available will need careful consideration by national authorities. A case-by-case consideration is recommended where plasma-derived products have been used in the manufacture of other medicinal products.

6.2 Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities, Official Medicines Control Laboratories, surveillance centres and the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted.

6.3 Since a recall involving albumin used as an excipient has the potential to cause major supply difficulties for essential products, manufacturers should avoid using, as an excipient, albumin derived from countries where a number of cases of nvCJD have occurred.

6.4 Despite the absence of any evidence of a risk of transmission, manufacturers will be encouraged to investigate further precautionary measures that may be applicable in the manufacturing process of plasma-derived medicinal products including the development of methods to remove or inactivate the agent of nvCJD. Development of substitutes for plasma-derived albumin as an excipient for medicinal products is encouraged.

6.5 Knowledge of CJD and other human TSE agents, and nvCJD in particular, is still incomplete. All studies contributing to the further understanding of TSEs, including experimental and epidemiological studies, should be urgently promoted. These should include:

- Continued surveillance of CJD and extension of the European network of surveillance centres.
- Development of laboratory tests that can improve clinical diagnosis and of tests that could eventually be used for the screening of blood donations or donors.
- Further research into tissue distribution of infectivity in nvCJD as compared with other forms of CJD.

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