EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12th January 2011
EMA/CHMP/BWP/360642/2010

Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products

Draft

Draft Agreed by Biologics Working Party	Dec 2010
Draft Agreed by Blood Products Working party	Dec 2010
Adoption by Committee for medicinal products for human use for release for consultation	17th February 2011
End of consultation (deadline for comments)	30th April 2011
Agreed by Biologics Working Party	<Month YYYY>
Adoption by Committee for medicinal products for human use	<DD Month YYYY>
Date for coming into effect	<DD Month YYYY>[1]

This guideline replaces 'Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products' (CPMP/BPWG/BWP/561/03).

Comments should be provided using this template. The completed comments form should be sent to alberto.ganan@ema.europa.eu

Keywords	*Warning statements, plasma derived medicinal products, immunoglobulins, albumin, SmPC, package leaflet.*

[1] First day of the 7th month.

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Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products

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Executive summary

This guideline provides standard texts for warning statements on transmissible agents to be included in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products. The original guideline (CPMP/BPWG/BWP/561/03) was adopted by CHMP in October 2003 and came into operation in May 2004. This revision affects only the introduction, where an update related to vCJD and an addition concerning albumin as excipient are now included.

1. Introduction (background)

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. The measures taken to prevent infection resulting from the use of these products include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective steps for the inactivation / removal of a wide range of viruses in manufacturing processes.

All these measures are critically evaluated by the relevant Competent Authority(ies) for medicines for the granting and maintenance of the Marketing Authorisation of each plasma-derived medicinal product.

In 1994, CPMP recommended a standard text for the Summary of Product Characteristics (SmPC) and the user Package Leaflet to inform doctors and patients about the risk of transmission of infective agents associated with the administration of any human blood or plasma-derived medicinal products[2].

This warning text on transmissible agents has been reviewed and updated by the Blood Products Working Group (BPWG) and Biotechnology Working Party (BWP) in the core SmPCs for specific plasma-derived medicinal products approved since June 2000. The text can be modified if certain warnings are not valid for a specific product.

Additionally, since potential safety problems may be batch-related, a strong recommendation to health professionals is included that, every time that a plasma-derived medicinal product is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. Patients are also made aware of this recommendation through the warning statement in the user Package Leaflet.

This document updates the previous recommendations and states the warning to be included in the SmPC and Package Leaflet of any plasma-derived medicinal product.

This warning is part of Section 4.4, “Special warnings and special precautions for use” of the SmPC. As indicated by the title of this section, it is intended for clinically important warnings and precautions for use. Therefore, the recommended text should not be extended by other information that is not a warning or precaution (e.g. description of viral inactivation / removal steps or tests for specific viruses)[3]. The same considerations apply to the user Package Leaflet.

There are two changes in the approach to the warning statement from the previous recommendations. Firstly, reference to specific mandatory measures is removed, as it is not a warning or precaution, the information is available elsewhere[4], and the important message of the resulting text is clearer. Secondly, the warning gives information on the overall effectiveness of measures for the safety of the product, rather than highlighting whether inactivation / removal procedures can be considered

[2] CPMP “Background document on medicinal products derived from human blood or plasma”, 16 March 1994

[3] It is not the purpose of the SmPC or Package Leaflet to give technical details of manufacturing processes. Manufacturing details are not listed in Article 11 or Article 59 with Article 62 of Directive 2001/83/EC, where the information to be included in SmPC and Package Leaflets respectively is specified.

[4] Mandatory measures are published in the European Pharmacopoeia monograph for Human Plasma for Fractionation.

effective. Focussing on inactivation / removal procedures may be misleading, particularly in the case of B19 (i.e. capable of inactivating / removing several logs of infectivity) but the capacity of the step may be exceeded if there is a high viral load in the plasma pool.

This warning statement should indicate the remaining potential risk of transmitting infective agents by plasma-derived medicinal products. Guidance on assessing the risk of virus transmission is in preparation to support the use of the warning statements in this Note for Guidance.

The warning statements make specific reference to the viruses that have been transmitted in the past by plasma-derived medicinal products. The measures taken to prevent the transmission of enveloped viruses such as HIV, HBV and HCV are considered effective for all marketed products. Non-enveloped viruses, such as HAV and parvovirus B19, are more difficult to inactivate / remove and the effectiveness of measures for non-enveloped viruses differs among marketed products. Therefore, the information given in the SmPC and user Package Leaflet should highlight the remaining potential risk of transmission of the non-enveloped viruses, HAV and parvovirus B19, taking into account the characteristics of the safety measures taken and the results of the viral inactivation / removal studies performed by the Marketing Authorisation Holder.

No specific statement can be made about remaining potential risks with non-enveloped viruses in general. It is an objective, for all plasma-derived medicinal products, to incorporate effective steps for inactivation / removal of a wide range of viruses of diverse physico-chemical characteristics. This would provide some assurance of effectiveness for viruses that are at present unknown or emerging.

West Nile virus (WNV) has recently emerged in North America and has been transmitted by blood components. However, no plasma-derived medicinal product has been implicated in WNV transmission. A CPMP Position Statement on WNV and plasma-derived medicinal products was published in July 2003, which concludes that the steps currently in place are adequate to assure safety of plasma-derived medicinal products with respect to WNV. Considering these factors, no specific reference to WNV is included in the warning statements.

Consideration has been given to whether to include a specific reference to vCJD in the warning statements. Variant CJD is a complex subject, where current knowledge is incomplete. In 2003 it was concluded that inclusion of a specific reference at that time would give the impression that there was increased concern about potential transmissibility by plasma-derived medicinal products when this was not the case. Therefore, it was concluded that it is better to continue with the practice of providing specific information through CPMP Position Statements. This position has been reconfirmed in 2010 in conjunction with the update of the CHMP Position Statement on CJD.

The warning statement will continue to include a general warning that the possibility of transmitting infective agents cannot be totally excluded.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes. When albumin is used as excipient in medicinal products, there is no need to include any specific warning statement related to albumin. This is based on the good safety records of human albumin. In these products, human albumin should be declared in the List of excipients.

The following documents can be consulted for further information on plasma-derived medicinal products and transmissible agents:

- Note of Guidance on plasma-derived medicinal products (CPMP/BWP/269/95 rev 3.) http://www.ema.europa.eu/pdfs/human/bwp/026995en.pdf
- Report of EMEA Workshop on viral safety of plasma-derived medicinal products with particular focus on non-enveloped viruses (CPMP/BWP/BPWG/4080/00, 21 March 2001) and Addendum:

Conclusions and recommendations of the Biotechnology Working Party (BWP) and Ad-hoc Working Group on Blood Products (BPWG) (CPMP/BWP/BPWG/93/01, 28 March 2001) http://www.ema.europa.eu/pdfs/human/bwp/408000en.pdf

- CPMP Position Statement on West Nile Virus and plasma-derived medicinal products (EMEA/CPMP/BWP/3752/03) http://www.ema.europa.eu/pdfs/human/bwp/375203en.pdf
- CPMP Position Statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products (EMEA/CPMP/BWP/2879/02) http://www.ema.europa.eu/pdfs/human/press/pos/287902en.pdf
- Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with regard to vCJD risk (EMEA/CPMP/BWP/55136/03)

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003741.pdf
- European Public Assessment Reports for plasma-derived medicinal products authorised under the Centralised Procedure

  http://www.ema.europa.eu / Home / Find medicine / Human medicines

2. Warning on transmissible agents in SmPCs for plasma-derived medicinal products

In the following recommendations for the warning in section 4.4 “Special warnings and special precautions for use”, the choice of text indicated between < > depends on whether the measures taken are considered effective for the specified virus.

2.1. Plasma-derived medicinal products (except immunoglobulins and albumin)

“Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation / removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting invective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV

<, and for the non-enveloped virus<es> <HAV><and parvovirus B19>.>

<The measures taken may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).>[5]

It is strongly recommended that every time that {name product} is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Examples:

[5] Note: the statement about parvovirus B19 risk groups does not need to be included for products where the measures are considered effective for B19.

Measures effective for HAV and parvovirus B19

"The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19."

Measures effective for HAV but not parvovirus B19

"The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia)."

Measures not effective for HAV or parvovirus B19

"The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia)."

2.2. Additional text for plasma-derived medicinal products regularly/repeatedly administered except immunoglobulins

For coagulation factor products, antithrombin products, and other plasma-derived medicinal products regularly/repeatedly administered except immunoglobulins, include the following additional text before the final sentence on recording name and batch number of the product:

"Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived {product class e.g. factor VIII products, antithrombin products}."

2.3. Immunoglobulins

"Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation / removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV

<, and for the non-enveloped virus<es> <HAV><and parvovirus B19>.>

<The measures taken may be of limited value against non-enveloped viruses such as <HAV> <and> <parvovirus B19>.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that {name of the product} is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product."

2.4. Albumin

"Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time that {name of the product} is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product."

3. Text for section 4.8 Undesirable effects in SmPCs for plasma-derived medicinal products

"For safety with respect to transmissible agents, see 4.4."

4. Warning on transmissible agents in the package leaflets for plasma-derived medicinal products

A warning statement compatible with the text in the SPC is included in Section 2 **Before you take** {name of the product}.

In the following recommendations, the choice of text indicated between < > depends on whether the measures taken are considered effective for the specified virus.

4.1. Plasma-derived medicinal products (except immunoglobulins and albumin)

<Rapporteur to include text>

"When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus

<, and for the non-enveloped <hepatitis A >< and parvovirus B19> virus<es>.>

<The measures taken may be of limited value against non-enveloped viruses <such as> <hepatitis A virus> <and > <parvovirus B19>.

<Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).>[6]

It is strongly recommended that every time you receive a dose of {name of product} the name and batch number of the product are recorded in order to maintain a record of the batches used."

Examples:

Measures effective for HAV and parvovirus B19:

"The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses."

Measures effective for HAV but not parvovirus B19:

"The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia)."

Measures not effective for HAV or parvovirus B19:

"The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus. The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia)."

4.2. Additional text for plasma-derived medicinal products regularly/repeatedly administered except immunoglobulins

For coagulation factor products, antithrombin products, and other plasma-derived medicinal products regularly/repeatedly administered except immunoglobulins, include the following additional text before the final sentence on recording name and batch number of the product:

"Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived {product class e.g. Factor VIII products, antithrombin products}."

4.3. Immunoglobulins

"When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on

[6] Note: The statement about parvovirus B19 risk groups does not need to be included for products where the measures are considered effective for B19.

infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus

<, and for the non-enveloped <hepatitis A >< and parvovirus B19> virus<es>.>

<The measures taken may be of limited value against non-enveloped viruses <such as> <hepatitis A virus> <and > <parvovirus B19>.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of {name of product} the name and batch number of the product are recorded in order to maintain a record of the batches used."

4.4. Albumin

"When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time you receive a dose of {name of product} the name and batch number of the product are recorded in order to maintain a record of the batches used."

5. Implementation of this note for guidance

The warning statements may be used before the date for coming into operation of this Note for guidance.

5.1. Authorised products

In the case of albumin, no supporting data on the risk assessment for virus transmission are needed to support variation applications to update the product information to include the revised warning statement.

For all other plasma-derived medicinal products, the risk assessment and data to support claims that measures taken are considered effective for HAV and/or parvovirus B19 should be provided in support of a variation application to update the product information. Guidance on assessing the risk of virus transmission is in preparation to support the use of the warning statements. If no claims are made that measures taken are considered effective for HAV and/or parvovirus B19, no supporting data on the risk assessment for virus transmission are needed.

5.2. Application for Marketing Authorisation

See the guidance on assessing the risk of virus transmission for the risk assessments that should be provided.