EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2014
EMA/CHMP/BWP/78086/2014
Biologics Working Party (BWP)

Concept paper on viral safety of plasma-derived medicinal products with respect to hepatitis E virus

Agreed by Biologics Working Party	March 2014
Adopted by CHMP for release for consultation	25 April 2014
Start of public consultation	2 May 2014
End of consultation (deadline for comments)	31 July 2014

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

Keywords	virus safety, hepatitis E, plasma-derived medicinal products, blood products

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1. Introduction

Hepatitis E virus (HEV) is a causative agent of hepatitis in many countries and of emerging concern in industrialized countries. HEV is a non-enveloped, single-stranded, positive-sense RNA virus and a member of the family Hepeviridae. In developing countries, HEV (genotypes 1 and 2) is a major cause of acute hepatitis, transmitted by the fecal–oral route and associated with contamination of drinking water. In industrialized countries, HEV (genotypes 3 and 4) has been found to be more prevalent in the human population than originally believed. HEV genotypes 3 and 4 infect not only humans but also animals such as swine, wild boar, and deer. Zoonotic transmission of HEV genotypes 3 and 4 to humans can occur by consumption of contaminated meat or meat products or by contact with infected animals. These genotypes are generally less pathogenic than genotypes 1 and 2, although some exceptions have been reported. Chronic infection with HEV genotype 3 is an emerging concern among transplant recipients and may also occur in persons with HIV and certain hematologic disorders.

2. Problem statement

HEV infection is widespread and blood/plasma donors are often asymptomatic. Therefore, there is a risk for viraemic blood donations. HEV has been recognized as a transfusion transmissible agent since 2004 and transfusion-related cases have been documented in several countries (United Kingdom, France, Japan, Saudi Arabia, People's Republic of China). Recent analysis of blood and plasma donations has identified HEV-infected donors in Germany, Sweden, and United Kingdom. In these studies, frequency of viraemic donations ranged between 1:4000 and 1:7000. The duration of viraemia is usually between 4 to 6 weeks, and the viral concentration can reach 7 log10 RNA per ml. Consequently, HEV-RNA has been detected in plasma pools used for production of medicinal products.

3. Discussion (on the problem statement)

The published reports on frequency of viraemic blood donations and studies on plasma pools indicate that plasma pools used as starting material for manufacture of medicinal products can be contaminated with HEV. In addition there have been cases with post donation information, indicating that HEV-affected donations have entered plasma pools for fractionation.

This raises questions about the safety of the plasma-derived medicinal products. The Ph. Eur. monograph for human plasma pooled and treated for virus inactivation (1646) is under revision to include a test for HEV RNA (implementation date 1 January 2015). A WHO International Standard for HEV for use in the standardisation of HEV NAT assays has been established. Manufacture of other plasma-derived products includes process steps for inactivation/removal of non-enveloped viruses. However, their effectiveness against HEV is currently unclear. HEV is difficult to cultivate and current information about susceptibility of HEV to virus inactivation/removal steps used in the manufacture of plasma-derived medicinal products is scarce.

4. Recommendation

Further information is needed on the safety of plasma-derived medicinal products with respect to HEV. Therefore, an expert workshop will be organised in 2014 to address the relevant issues. The following points should be addressed.

- Transfusion-associated infections and clinical experience with HEV-infections.
- Latest information on the epidemiology of HEV infection with focus on blood and plasma donors.

- Duration of viraemia and virus loads of blood and plasma donations.
- Potential testing methods for screening of donors and testing of plasma pools (NAT, reference materials).
- HEV-specific antibodies and neutralisation.
- Latest information about the development of cell culture systems for HEV and their feasibility for validation of virus inactivation/removal.
- Latest experience from studies on inactivation/removal of HEV.
- Relevance of model viruses for evaluation of virus inactivation/removal of HEV.
- Safety of solvent-detergent treated plasma.
- Risk assessment for plasma-derived medical products and implication for warning statements.
- Perspective from patients.

This workshop will provide the basis for deciding what further action may be needed, including the possible update of current guidance on plasma-derived medicinal products and/or development of a reflection paper specifically on viral safety of plasma-derived medicinal products with respect to hepatitis E virus.

5. Proposed timetable

The workshop is intended to take place on 28-29 October 2014.

6. Impact assessment (anticipated)

Viral safety of plasma-derived medicinal products needs to be kept under review as viruses are identified that can be present in the plasma starting material. Initiating action with a workshop will provide an effective means of bringing together and discussing the currently available information on this topic. This will then allow further actions to be identified.

7. Interested parties

Blood products working party (BPWP).

Patient organisations (e.g. haemophilia patients (EHC, WFH), patients with primary immunodeficiencies (EPPIC, IPOPI)).

Industry organisations (IPFA, PPTA) and manufacturers of plasma-derived medicinal products.

The workshop may also be of interest to ECDC and blood competent authorities.

8. References to literature, guidelines, etc.

Guideline on plasma-derived medicinal products, EMA/CHMP/BWP/706271/2010

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500109627.pdf

84 Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and
85 package leaflets for plasma-derived medicinal products. EMA/CHMP/BWP/360642/2010 rev. 1

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