EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 October 2014
EMA/CHMP/BWP/196177/2014
Biologics Working Party (BWP)

Workshop on Viral safety of plasma-derived medicinal products with respect to hepatitis E virus

1. Introduction

Hepatitis E virus (HEV) is a causative agent of hepatitis in many countries and of emerging concern in industrialised 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 faecal–oral route and associated with contamination of drinking water. In industrialised 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.

HEV infection is widespread and blood/plasma donors are often asymptomatic. Therefore, there is a risk for viraemic blood donations. HEV has been recognised 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.

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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information about susceptibility of HEV to virus inactivation/removal steps used in the manufacture of plasma-derived medicinal products is scarce.

2. Purpose of the workshop

The purpose of this workshop is to obtain further information on the safety of plasma-derived medicinal products with respect to HEV.

It will provide the basis for deciding what further action may be needed, including the possible update of current guidance on plasma-derived medicinal products[1] and/or development of a reflection paper specifically on viral safety of plasma-derived medicinal products with respect to hepatitis E virus.

3. Time and location of the workshop

28 – 29 October 2014, European Medicines Agency

4. Organisation of the meeting

Organised by EMA, with the support of the Biologics Working Party (BWP) and Blood Products Working Party (BPWP). (Correspondence to BPWPSecretariat@ema.europa.eu)

5. Steering committee

Johannes Bluemel

Wahiba Oualikene-Gonin

Keith Chidwick

Karen Cristiano

Mahmood Farshid

Pablo de Felipe

Marja van de Bovenkamp

Glenda Silvester

7. Structure of workshop

Meeting with Industry (approximately 1.5 days) followed by closed session with regulators/OMCLs/EDQM

[1] 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
Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products. EMA/CHMP/BWP/360642/2010 rev. 1
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119001.pdf

Agenda

28 – 29 October 2014, European Medicines Agency, London, room 2A

EMA has moved, please note new address: 30 Churchill Place, London, E14 5EU

Chairperson: Johannes Bluemel

28 October 2014 9:30 – 18:00, meeting room 2A
29 October 2014, 09:00 – approx.11:40, closed session 11:50 - 13:00, meeting room 2A

NB. The workshop will be recorded and EMA experts from the network will be able to listen virtually.

Key Questions for the Workshop

1. **How serious are HEV infections and which patient populations may be particularly at risk?**
2. **Are plasma-derived medicinal products safe with respect to HEV?**
3. **Which steps are efficient to remove / inactivate HEV? (and which model viruses can be used to assess that?)**
4. **Do we need more virus validation data?**
5. **Do serum antibodies against HEV significantly neutralise?**
6. **NAT testing will be required in the Ph. Eur. for SD plasma. Should this also be required for any other products?**
7. **Do we need risk assessments and/or warning statements?**

Day 1

No.	Topic	Speaker	Timings[2]
1.	**Introduction**		
	Background and expectations for the workshop	Johannes Bluemel PEI, Germany	09:30-09:45
2.	**Transfusion-associated infections and clinical experience with HEV-infections** **Moderator: Johannes Bluemel, Rapporteur: Wahiba Oualikene-Gonin** *This session will focus on clinical outcomes of HEV infections and which patient populations may be particularly at risk.*		
	Clinical experience with HEV infections *Clinical manifestation of HEV infections, patients at potential risk (e.g. immunosuppressed, transplant recipients, patients with chronic liver disease), modes of transmission (risk from transfusion/plasma or other sources).*	Harry Dalton National Health Service, UK /University of Exeter, UK	09:45-10:10

[2] In general, speakers have 20 minutes for their presentation with an additional 5 minutes for questions

No.	Topic	Speaker	Timings[2]
	Transfusion transmitted infections in UK *Study looking back to identify the outcome for recipients receiving blood components subsequently found positive for HEV (publication). (Also, very brief information on the epidemiology of HEV infection in UK - incidence and prevalence in blood donations, viraemic loads as this will be picked up as a general topic in Session 3.)* http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61034-5%20/abstract	Richard Tedder Public Health England, UK	10:10-10:35
	Situation and cases in France (including associated with SD plasma) and clinical outcome *Summary of transfusion-transmitted infections in France, including level of viraemia (clinicians views on the risk, and discussions in France on possible safety measures)*	Wahiba Oualikene-Gonin ANSM, France	10:35-11:00
	Coffee break 11:00-11:20		
	Hepatitis E in recipients of allogeneic hematopoietic stem cell transplantation and organ transplantation	Annemiek van der Eijk Erasmus Medical Center, The Netherlands	11:20-11:45
	Hepatitis E virus in solid-organ transplant patients (including kidney-transplant patients)	Nassim Kamar Department of Organ transplantation and nephrology, CHU Rangueil, France	11:45-12:10
3.	**HEV-Detection and epidemiology of HEV in Blood/Plasma Donations** **Moderator: Johannes Bluemel, Rapporteur: Wahiba Oualikene-Gonin** *This session should define the contamination risk and potential measures to test/prevent contamination of plasma.*		
	HEV epidemiology *With focus on Europe (and briefly Latin America)* *To include epidemiology – incidence and prevalence, viraemic loads, duration of viraemia* *(Note: Latest data screening blood donors in USA will not be available in time for the meeting but should be available post-meeting. Canadian epidemiology see Session 4)*	Jose-Manuel Echevarria - did not attend in person - presentation was presented by P. Felipe National Centre of Microbiology,	12:10-12:35

No.	Topic	Speaker	Timings[2]
		Spain	
	Detection of HEV infections, and epidemiology in Italy (general population and specific study in blood/plasma donor population)	Anna Rita Ciccaglione Istituto Superiore di Sanità, Italy	12:35-13:00
	Lunch break 13:00 – 14:00		
	Experience from the Netherlands *Incidence of HEV in blood donors, transfusion risk*	Hans Zaajer Sanquin Blood Supply Foundation	14:00-14:25
	Potential testing methods for screening of donors and testing of plasma pools *Overview of test formats NAT + Ab assays. NAT, reference materials, WHO Standards/Genotype panel – data. HEV in plasma pools – frequency and level. Sensitivity and robustness of assays, standardisation issues*	Sally Baylis PEI, Germany	14:25-14:50
4.	**Solvent / Detergent treated (SD) Plasma and neutralisation by antibodies** **Moderator: Johannes Bluemel, Rapporteur: Wahiba Oualikene-Gonin**		
	SD Plasma *Investigation about potential HEV-transmission cases. Canadian epidemiology in blood donors*	Anton Andonov Public Health Agency of Canada (virtual link)	14:50-15:15
	SD plasma and neutralisation by antibodies see Abravanel et al, 2014 Also publication Takahashi et al 2010: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2849599/	Jacques Izopet CHU de Toulouse - Hospital Purpan, France	15:15-15:40
	Coffee break 15:40 – 16:00		
	Overall discussion on Sessions 2, 3 and 4: **Moderator: Johannes Bluemel, Rapporteur: Wahiba Oualikene-Gonin** *Panel of speakers. Patient organisations (ELPA, EHC/WFH, IPOPI) are invited to actively participate in this discussion. Note: European Liver Patient Association (ELPA) is concerned about this topic in connection with hepatitis B*		16:00-16:45

No.	Topic	Speaker	Timings[2]
	immunoglobulin for use in liver transplantation.		
5.	**Latest experience from studies on inactivation / removal of HEV** **Moderator: Johannes Bluemel, Rapporteur: Wahiba Oualikene-Gonin, Marja van de Bovenkamp** *This session should discuss the relevance of model viruses, feasibility of HEV culture systems and experiences with HEV-inactivation/removal.*		
	LFB HEV-Inactivation data, including cell culture systems	Benoit Flan LFB	16:45-17:10
	Baxter inactivation/removal data	Thomas Kreil Baxter	17:10-17:35
	CSL inactivation/removal data	Albrecht Gröner CSL Behring	17:35-18:00
	End of Day 1		

Day 2

No.	Topic	Speaker	Timings
	Grifols inactivation/removal data	Rodrigo Gajardo Grifols	09:00-09:25
	Investigation of inactivation procedures and antibody neutralisation	Mikihiro Yunoki Japan Blood Products Organisation	09:25-09:50
6.	**Risk assessment for plasma-derived medical products and implication for warning statements** **Moderators: Johannes Bluemel and Wahiba Oualikene-Gonin, Rapporteur: Keith Chidwick**		
	PPTA perspective	Ilka von Hoegen TBC	09:50-10:05
	IPFA perspective	Francoise Rossi	10:05-10:20

No.	Topic	Speaker	Timings
	Coffee break 10:20 - 10:40		
	Panel (speakers from Session 5 and 6 and Mahmood Farshid) to lead the discussion based on what has been heard in the workshop and come back to the key questions posed for the workshop. Patient organisations (ELPA, EHC/WFH, IPOPI) are invited to actively participate in this discussion. Furthermore, all those present at the workshop are invited to actively participate.		10:40-11:25
7.	**Summary and close of open session**	Johannes Bluemel	11:25-11:40
	Break 11:40 – 11:50		
8.	**Closed Session** with regulators (European, US and Canadian)/OMCLs/EDQM/Blood competent authorities)		11:50-13:00
	End of meeting		