The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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CPMP POSITION STATEMENT ON WEST NILE VIRUS AND PLASMA-DERIVED MEDICINAL PRODUCTS

Introduction

West Nile virus (WNV) is a recently emerged infection in North America where it is now endemic. It is an arthropod-borne 50 nm enveloped RNA virus belonging to the *Flaviviridae* family, first isolated in 1937 from a human patient in the West Nile region of Uganda. WNV and related viruses, including Japanese encephalitis and tick-borne encephalitis viruses, have since been found in various parts of Africa, Australia, Central and Southern Europe, the Middle East and North America.

The natural host of WNV is birds; crow species in the USA being especially susceptible. The virus also infects other animals (e.g. horses, dogs) and humans. Transmission is by mosquito and human-to-human transmission is not believed to occur in natural situations. Most WNV infections of humans are asymptomatic or are associated with mild symptoms (sudden onset of fever with malaise and headache) with a duration of 3-6 days. Approximately 1/150 of human infections is estimated to result in severe neurological disease[1], some of which may be fatal, with those most at risk being the elderly and the immunocompromised. Diagnosis is based on clinical evaluation plus specific laboratory tests.

Clinical symptoms in humans appear 2-14 days following infection. According to the available data, viraemia occurs within 1-3 days after infection and lasts 1-11 days; thus, an infected person could be viraemic prior to symptoms occurring, or may be viraemic but have an asymptomatic infection. Seroconversion (IgM) occurs 7-8 days post-infection.

WNV in North America

In 1999, WNV was isolated in the USA for the first time, in New York State, from a dead bird. Since then, the virus has spread extensively across North America with infections occurring mainly in the summer season in birds, animals and humans. In the summer epidemic of 2002 in the USA, >4000 human infections occurred resulting in 284 deaths.

In August 2002 in the USA, it became apparent that WNV could be transmitted by blood after four transplant recipients from a single organ donor developed WNV infection. The organ donor was subsequently shown probably to have been infected by a viraemic blood transfusion[2]. Since then, 21 confirmed cases of WNV transfusion-transmitted infection have been documented in the USA[3]. A few cases of transfusion-transmitted WNV have also occurred in Canada. However, no plasma-derived product has been implicated in WNV transmission.

WNV in Europe and the Mediterranean area

There has been no systematic surveillance for WNV in Europe. Sporadic outbreaks occur in animals and humans, mainly in southern and central Europe. Undiagnosed cases of human WNV infection may occur but a recent survey in the UK of patients with encephalitis found no WNV infections[4]. Following an outbreak of WNV in horses in the Camargue in 2000, surveillance in France did not detect an associated human outbreak[5, 6, 7]. In the Mediterranean area, the virus is endemic in Israel and human outbreaks have occurred within the past 10 years in Algeria and Tunisia.

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Donor deferral and donation screening

In North America, various measures are being adopted to assure the safety of blood and blood-derived medicinal products from WNV contamination. Donor deferral based on recent incidence of fever has been implemented [3] and, as of 1 July 2003, the USA and Canada are screening blood donations by NAT on a seasonal basis. To achieve this, several companies have recently developed suitably sensitive assays at the instigation of the FDA which has recommended a 95% detection limit of 100 genome copies/ml for testing of small pools so that donations containing 1000 copies/ml can be detected. Testing is not currently applied to donations of plasma used for the manufacture of plasma-derived medicinal products.

Within the EU, some Member States are temporarily deferring blood donors on return from North America during the seasonal period for WNV infection.

Risk assessment of WNV for plasma-derived medicinal products.

A proportion of plasma-derived medicinal products licensed within the EU is manufactured using plasma of US origin. Critical parameters for assessment of risk from emerging viruses include the nature of the virus and of the infection, the level of viraemia and its duration, viral loads in plasma pools, and the effectiveness of virus inactivation/removal steps. With this knowledge, an assessment can be made of the adequacy of current measures and consideration given to whether further measures are needed.

The viral safety of plasma-derived medicinal products derives from several approaches involving donor deferral, testing of donations, testing of plasma pools and viral inactivation/removal stages during plasma fractionation. The presence of validated and effective virus inactivation/removal steps is essential in safeguarding plasma-derived medicinal products. At its May 2003 meeting, the CPMP Biotechnology Working Party (BWP) held a breakout session on West Nile Virus to which members of the plasma fractionation industry and other experts were invited.

Since most humans infected with WNV are asymptomatic, donor deferral measures based on fever will be of limited value in detecting viraemic donors.

According to the available data, infection results in a short period of viraemia (1-11 days). Current data[8] indicate that levels of viraemia in most asymptomatic infected individuals are not high (1-5 x 10^3 genome copies/ml of plasma, with a worst case of 10^5 genome copies/ml found in one donation). Preliminary results from an investigation of samples collected in 2002 by the American Red Cross from an area of high incidence (Detroit and Cleveland) found the proportion of viraemic samples was 1 in 10^3. Further information on the incidence of infections in North American blood donors during 2003 and the levels of viraemia will become available from the introduction of NAT testing in July 2003.

All plasma-derived medicinal products are required to have effective inactivation/removal steps for enveloped viruses and these are validated using a variety of viruses. On the basis of existing validation data for enveloped viruses, it can be anticipated that the inactivation/removal steps incorporated in manufacturing processes for plasma-derived medicinal products will also be effective for WNV. At the May 2003 BWP breakout, data were presented by industry and the Paul Ehrlich Institute on studies using WNV itself, some of which used an avian strain isolated in New York in 1999.

The data demonstrate that a variety of procedures commonly used to inactivate viruses, including pasteurisation, solvent/detergent treatment and vapour heating, are effective against WNV. Nanofiltration (using a 15 nm filter) was also effective in its removal. The data on WNV was compared with data generated previously using model enveloped viruses and shown to be similar. These observations support the model virus concept by demonstrating that established inactivation/removal steps validated using model viruses can be effective against a newly-emerging enveloped virus, such as WNV. Some manufacturers had not performed specific studies with WNV but were confident, from a review of their validation data with model enveloped viruses, that the inactivation/removal steps already in place during manufacture are also effective for WNV.

As a follow-up to the BWP breakout session, the BWP has requested industry to provide their data presented on WNV for a full evaluation.

Conclusions

For WNV, the enveloped nature of the virus predicted its effective inactivation/removal during the manufacture of plasma-derived medicinal products and this has been demonstrated in several studies. Given the low levels and short period of viraemia in infected individuals, the data presented at the breakout session provided reassurance that the steps currently in place are adequate to assure viral safety of plasma-derived medicinal products with respect to WNV.

It is recommended that Marketing Authorisation holders using US or Canadian sourced plasma in their plasma-derived medicinal products provide the concerned regulatory authorities with their product-specific assessment of the effectiveness of their manufacturing process for inactivation/removal of WNV. This assessment should be supported by a summary of validation data for enveloped viruses (from Part II V - Virological Documentation, 3.2.A.2 CTD format). Any investigational studies using WNV itself should be provided.

It should be noted that the scope of this position statement is restricted to WNV and medicinal products derived from human blood or plasma. The risk situation for whole blood and labile blood products, which is not the same, is addressed by bodies other than the CPMP.

References

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