# Annex II

## Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

## Scientific conclusions

**Overall summary of the scientific evaluation of Cymevene i.v. and associated names** (see Annex I)

On 15 September 2014 the European Commission on behalf of all marketing authorisation holders presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products, Cymevene i.v. and associated names for which the MAH is F. Hoffman – La Roche Ltd. The referral procedure was initiated at the December 2014 meeting.

Cymevene i.v. was first approved in United Kingdom on 15 June 1988, which marks its International Birth Date (IBD). National approval was obtained in most of the European countries. Cymevene i.v. is approved in all EU Member States except Latvia, Malta and Slovenia.

Cymevene i.v. contains ganciclovir, a synthetic analogue of 2'-deoxyguanosine which inhibits replication of herpes viruses. Sensitive human viruses include human cytomegalovirus (HCMV), herpes-simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and hepatitis B virus.

Cymevene i.v. is administered parenterally by intravenous infusion over 1 hour. The medicinal product is available in vials of 10 ml as powder for concentrate for solution for infusion. The only strength of 500 mg is available.

### Summary of product characteristics (SmPC)

#### Section 4.1 - Therapeutic indications

The MAH submitted documentation to support both indications of treatment and prevention of the CMV disease.

For treatment in adults, the studies have been conducted by MAH in patients with AIDS. Ten clinical studies were conducted during the period from 1986 till 1996 in patients with AIDS. The majority of these studies were open-label controlled studies. In most of the studies efficacy of ganciclovir 2.5 mg/kg, 5 mg/kg, 6 mg/kg i.v. b.i.d. doses used for 2 weeks (induction treatment) and later 5 mg/kg or 6 mg/kg maintenance doses were evaluated for treatment of CMV retinitis in AIDS patients. Results of these studies demonstrated beneficial effect on progression of disease, relapse of CMV infections and incidence of the disease.

The treatment of CMV disease in stem cell transplant (SCT) and solid organ transplant (SOT) recipient is recommended by guidelines, the data supporting the proposed indication are obtained from published literature.

There are no MAH-sponsored studies of CMV treatment in stem cell transplant recipients. Various clinical treatment guidelines advise on appropriate treatment and prevention of CMV disease in stem cell transplant recipients. One non-systematic review of CMV disease diagnosis, prevention, and treatment in hematopoietic stem cell transplant (HSCT) recipients was conducted. In allogenic HSCT recipients, the review concluded that CMV disease should be treated with antiviral agents such as ganciclovir or foscarnet with 2-3 weeks of induction therapy followed by 3-4 weeks of maintenance therapy.

There are no MAH-sponsored studies of CMV treatment in oncology patients. Treatment guidelines[1] recommend using ganciclovir for CMV prophylaxis in allogenic stem cell transplant recipients and in patients receiving alemtuzumab therapy.

[1] https://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf

There are no MAH-sponsored studies of CMV treatment in stem cell transplant recipients but various clinical treatment guidelines advise on appropriate treatment and prevention of CMV disease in these patients.

For the prevention of CMV disease, ganciclovir is only indicated in transplant recipients and patients receiving cancer chemotherapy. Clinical trials included only patients with haematological malignancy. MAH state that other oncology patients receiving chemotherapy do not routinely require CMV prophylaxis but certain high-risk patients, such as Asian patients, particularly those receiving rituximab or hyper-CVAD chemotherapy, may benefit.

In patients with AIDS prevention of CMV disease is no longer recommended because the highly active antiretroviral therapy (HAART) has reduced the risk of CMV disease in patients with AIDS. Before the introduction of HAART, approximately 30% of patients with AIDS experienced CMV retinitis, making CMV prophylaxis necessary.

The MAH has not conducted formal studies in the paediatric patient population. The amended therapeutic indication (and posology) for adolescents from 12 years of age is based on non-company sponsored ganciclovir studies and treatment guidelines[2]. The inclusion criteria regarding the age of eligible patients in ganciclovir studies are variable. Some of the studies are conducted predominantly in adults, but also included children. Although data are scarce the benefit-risk conclusion and posology can in the CHMP view, be extrapolated to adolescents of 12 years and older considering the very serious nature of the disease it is indicated for.

The use of ganciclovir in paediatric transplant recipients and patients with AIDS/HIV is recommended in current authoritative treatment guidelines. The safety and efficacy of ganciclovir in children under 12 years of age has not been established. Additional data in this population need to be submitted in the future via the appropriate regulatory procedure.

The CHMP after assessing all the currently available data they concluded that the harmonised therapeutic indication for Cymevene i.v. should be amended as follows:

*Cymevene is indicated in adults and adolescents from 12 years of age for the:*
- *treatment of cytomegalovirus (CMV) disease in immunocompromised patients;*
- *prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy).*

*Consideration should be given to official guidance on the appropriate use of antiviral agents.*

[2] Department of Health and Human Services. Panel on Opportunistic Infections in HIV-exposed and HIV-Infected Children. 2013 [cited April 2014].

**Section 4.2 - Posology and methods of administration**

The harmonised information on posology was presented by the MAH per indication, i.e. standard dosage for treatment of CMV disease in adults and adolescents from 12 years of age with normal renal function and standard dosage for prevention of CMV disease in adults and adolescents from 12 years of age with normal renal function using prophylaxis or pre-emptive therapy.

Special dosage instructions for patients with renal impairment, older people and paediatric patients are provided. The dosage recommendations proposed by MAH are in line with the indications. Cymevene is indicated for use in adults and adolescents from 12 years of age. Clinical studies, pharmacodynamics data, and treatment guidelines are provided to support the use of the same dose in adults and adolescents for treatment and prevention of CMV disease.

Cymevene must only be given by intravenous infusion over 1 hour. The high pH of ganciclovir can result in severe tissue irritation if the product is given by intramuscular or subcutaneous injection and toxicity may be increased if intravenous administration is rapid. Caution regarding the need to administer Cymevene by intravenous infusion over 1 hour and the hazards associated with other routes or rates of administration were provided. In addition the wording on precautions of handling the product has been harmonised.

**Section 4.3 – Contraindications**

There were no major discrepancies between the existing wordings in the individual Member States. Two contraindications were finally in this section regarding the cross-hypersensitivity and the breast-feeding.

**Section 4.6 - Fertility, pregnancy and lactation**

The information on pregnancy and breastfeeding was different in the individual Member States. The CHMP agreed on a common wording.

The safety of ganciclovir for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. In animals studies ganciclovir was associated with reproductive toxicity and teratogenicity. Therefore, ganciclovir should not be used in pregnant women unless the clinical need for treatment of the woman outweighs the potential teratogenic risk to the foetus.

It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfed infant cannot be excluded. Therefore, breastfeeding must be discontinued during treatment with ganciclovir.

**Section 4.8 – Adverse events**

Safety and efficacy data from valganciclovir studies conducted in children were also presented as relevant to the safety and efficacy of ganciclovir (clinical use of valganciclovir, the pro-drug of ganciclovir, has been approved in EU for paediatric SOT recipients for prevention of CMV disease.) These additions to the safety information were considered relevant and were accepted by the CHMP.

**Labelling**

The labelling was reviewed during this procedure and changes were introduced, mainly to align with the QRD template.

**Package Leaflet**

Following all the changes in the SmPC there were amendments made to the package leaflet (PL). The final PL wording was agreed by the CHMP.

**QUALITY – MODULE 3**

The MAH submitted a proposal for harmonisation of the Quality module.

Based on the review of data the CHMP adopted a harmonised Module 3.

**Grounds for the variation to the terms of the marketing authorisation(s)**

In conclusion, based on the assessment of the MAH's proposals and responses and following the discussions of the Committee, the CHMP adopted harmonised sets of product information documents of Cymevene i.v. and associated names.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet;
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee;

the CHMP was of the opinion that the benefit/risk ratio of Cymevene i.v. and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the variation to the terms of the marketing authorisations for which the summary of products characteristics, labelling and package leaflet as set out in Annex III of the CHMP opinion for Cymevene i.v. and associated names (see Annex I).