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Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 12-13 May 2015 meeting

Some documents mentioned in the agenda/minutes cannot be released at present within the framework of Regulation (EC) No 1049/2001 on access to documents because they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/252765/2015

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 14-16 April 2015 EMA/COMP/209468/2015

The minutes were adopted with no amendments.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare their potential conflict of interest.

In accordance with the Agency's Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests). No new or additional conflicts of interest were declared.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Allogeneic ex-vivo expanded human umbilical cord blood-derived mesenchymal stem cells for prevention of bronchopulmonary dysplasia, PSR Group B.V. - EMA/OD/010/15

[COMP co-ordinator: K. Westermark]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of bronchopulmonary dysplasia, the sponsor should further elaborate

With regards to the preclinical data:

- the settings of the preliminary clinical study in detail, including the timing of administration of the product;
- the absence of any data in larger preclinical models.

With regards to the preliminary clinical data:

- the population studied including gestational age;
- detail the results from this study including mortality preferably in a table format to allow for an overview of the outcome in individual patients;
- discuss any case matching performed to evaluate intubation times versus non-treated subjects;

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

- in light of the uncontrolled nature of the study, compare the results versus the expected epidemiology of the condition.

- Number of people affected

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor is invited to define the number of eligible patients to receive the treatment per year, and provide a revised calculation in line with the NIH consensus definitions.

In the written response, and during an oral explanation before the Committee on 12 May 2015, the sponsor further elaborated on the issues raised. In particular, the sponsor elaborated on the preliminary clinical data, the details of the population studied the matching controls, and the obtained results. Based on this comparison, bronchopulmonary dysplasia severity outcome was improved in a statistically significant level in the patients treated with the product. In addition to comparing the data obtained versus case-matched historical controls, the risk of death or moderate / severe BPD was estimated for each patient using an online tool from the US National Institute of Child Health and Human Development. Based on this exercise, the sponsor argued that the expected number of patients affected would be more than the number observed. The COMP considered that the medical plausibility based on the comparison with the historical controls was acceptable for the purpose of establishing the criterion of medical plausibility in the orphan designation framework.

As regards the number of affected patients eligible for prevention, the sponsor argued that the definitions of NIH refer to diagnostic criteria and not the definition of the at risk population. An estimate of 0.3/10,000 was proposed based on 32 weeks of gestational age, and an estimate of 1.2 per 10,000 based on very low birth weight. The COMP considered that the population previously considered for the prevention of the COMP should be calculated based on the 32 weeks, and that the COMP's previous knowledge should be retained, referring to a range of 1 to 3 in 10,000.

The Committee agreed that the condition, bronchopulmonary dysplasia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing allogeneic ex-vivo-expanded human umbilical cord blood-derived mesenchymal stem cells was considered justified based on preliminary clinical data supporting reduced incidence of bronchopulmonary dysplasia in treated newborns.

The condition is life-threatening and chronically debilitating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood.

The population of patients eligible for prevention of the condition was estimated to be between 1 and 3 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of prevention that has been authorised in the European Union for the population at risk of developing the condition.

A positive opinion for allogeneic ex-vivo-expanded human umbilical cord blood-derived mesenchymal stem cells for prevention of bronchopulmonary dysplasia was adopted by consensus.

2.1.2 **Antisense oligonucleotide directed against TGF-β2 mRNA** for prevention of scarring post glaucoma filtration surgery, Isarna Therapeutics GmbH - EMA/OD/021/15

[COMP co-ordinator: I. Barisic]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The sponsor was invited to justify scarring post-glaucoma filtration surgery as a distinct medical entity or a valid subset. For the purposes of orphan medicinal product designation, the sponsor's attention was drawn to the Orphan regulations and guidelines.

For a subset to be designated, it is the responsibility of the sponsor to demonstrate that the subset has unique features different from the broader condition, in this case scarring from other causes, and that the product would not work outside the proposed subset.

For further guidance of the characteristics of a valid medical condition and subset the sponsor can consult the EC Guideline ENTR/6283/00 Rev 4: "*The characteristics defining a distinct condition should determine a group of patients in whom development of a medicinal product is plausible, based on the pathogenesis of the condition and pharmacodynamic evidence and assumptions*" (http://ec.europa.eu/health/files/orphanmp/2014-03_guideline_rev4_final.pdf).

In the written response, and during an oral explanation before the Committee on 12 May 2015, the sponsor further elaborated on the issues raised. An overview of glaucoma filtration surgery was presented, and the sponsor discussed scarring as a complication of trabeculectomy. The role of TGF-β, target for the proposed product in the pathophysiology of scarring was also discussed.

The COMP discussed the aetiology, pathophysiology and clinical characteristics of the condition that was viewed as a complication of a medical procedure. The Committee also reflected on previous opinions from orphan regulatory history, with a view to draw parallels to other designated indications such as rejection after solid orphan transplantation. It was considered that in scarring post-glaucoma filtration surgery, scarring develops not as a consequence of glaucoma but in relation to abnormal repair of ocular tissue after surgery.

The COMP concluded that scarring post glaucoma filtration surgery is still a distinct medical entity, although future changes in classification and in the incidence of the condition (that is increasing due to increasing use of trabeculectomy) will need to be monitored in order to reconfirm the orphan status at the time of marketing authorization.

The Committee agreed that the condition, scarring post glaucoma filtration surgery, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing antisense oligonucleotide directed against TGF-β2 mRNA was considered justified based on preclinical data showing increased number and survival of the filtration blebs that are linked to normal repair of the ocular tissue, and reduction of ocular scarring in models of the disease.

The condition is chronically debilitating due to significant loss of visual acuity over time.

The population of patients eligible for prevention of the condition was estimated to be approximately 1.9 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of prevention that has been authorised in the European Union for the population at risk of developing the condition.

A positive opinion for antisense oligonucleotide directed against TGF-β2 mRNA for prevention of scarring post glaucoma filtration surgery was adopted by consensus.

2.1.3 3-{[2,3,5,6-tetrafluoro-3'-(trifluoromethoxy)biphenyl-4-yl]carbamoyl}thiophene-2-carboxylic acid for treatment of non-infectious uveitis, Panoptes Pharma Ges.m.b.H - EMA/OD/024/15

[COMP co-ordinator: K. Westermark]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 12 May 2015, the sponsor further elaborated on the issues raised and importantly presented figures with the effects of the product after intravitreal use in the Experimental Autoimmune Uveitis model. In that model, administration of the product via the above mentioned route resulted in fewer relapses of uveitis. The COMP considered that this this new route would be important for the justification of a clinically relevant advantage since it would allow for lowering systemic use of glycocorticosteroids and immunosuppressing medications

The Committee agreed that the condition, non-infectious uveitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-{[2,3,5,6-tetrafluoro-3'-(trifluoromethoxy)biphenyl-4-yl]carbamoyl}thiophene-2-carboxylic acid was considered justified based on data showing that treatment with the product resulted in improved clinical signs and histology in a relevant preclinical model of the condition.

The condition is chronically debilitating due to development of significant visual impairment or legal blindness.

The condition was estimated to be affecting less than 4.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 3-{[2,3,5,6-tetrafluoro-3'-(trifluoromethoxy)biphenyl-4-yl]carbamoyl}thiophene-2-carboxylic acid may be of significant benefit to those affected by the condition. This was considered on the basis of an intravitreal mode of administration that would allow for a reduction of systemic use of corticosteroids and immunosuppressing drugs. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 3-{[2,3,5,6-tetrafluoro-3'-(trifluoromethoxy)biphenyl-4-yl]carbamoyl}thiophene-2-carboxylic acid, for treatment of non-infectious uveitis, was adopted by consensus.

2.1.4 Product for treatment of retinal artery occlusion - EMA/OD/011/15

[COMP co-ordinator: A. Magrelli]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 24 April 2015, prior to responding to the list of issues.

2.1.5 **Synthetic 47-amino acid N-myristoylated lipopeptide, derived from the preS region of hepatits B virus** for treatment of hepatitis delta virus infection, MYR GmbH - EMA/OD/329/14

[COMP co-ordinator: A. Corrêa Nunes]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Medical plausibility

The sponsor is invited to discuss the mechanism of action of the product with relevance to any specific hepatitis D virus action as opposed to hepatitis B action. The sponsor should justify why any effects of the product cannot be attributed to treatment of hepatitis B.

- Prevalence

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor is invited to clarify the sources and applied populations with regards to the corrections in the HDV infected individuals, instead of using a flat rate of 5-10% HDV infected individuals in the HBsAg positive population.

In the written response, and during an oral explanation before the Committee on 12 May 2015, the sponsor argued against clinically relevant HBV effects by discussing the available clinical data. The effects on HDV RNA decline were considered independent from the HBV effects and it was specifically pointed out that HBsAg was not affected by the treatment.

The sponsor also further elaborated on the calculation of prevalence by defining the risk based population as average rate of 8% for 15% of HBsAg carriers from tertiary centres and average 2% rate for 85% of the rest HBsAg carriers.

The COMP reflected on whether the proposed condition is a valid condition for designation (a distinct medical entity or a justified subset as per the guideline on the format and content of applications). The Committee also examined the proposal in light of its previous deliberations for the same proposed indication, which focused on anti- HDV effects. A discussion on whether the proposed condition may be regarded as an intersection of two conditions (HBV and HDV infection) also ensued. After considering all aspects, the COMP considered that the proposed condition is a distinct medical entity, mainly on the basis of the different pathogen causing the condition. It was also considered that as long as the sponsor showed that there are effects for HDV viral levels, the medical plausibility may be considered acceptable. The prevalence was considered approximately 4 in 10,000 people in line with the previous COMP knowledge.

The Committee agreed that the condition, hepatitis delta virus infection, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic 47-amino-acid N-myristoylated lipopeptide, derived from the preS region of hepatits B virus was considered justified based on preliminary clinical data in patients affected by the condition where treatment with the product resulted in reduced HDV RNA levels.

The condition is chronically debilitating and life threatening due to the development of cirrhosis, portal hypertension and liver insufficiency.

The condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for synthetic 47-amino-acid N-myristoylated lipopeptide derived from the preS region of hepatits B virus for treatment of hepatitis delta virus infection was adopted by consensus.

2.1.6 obinutuzumab for treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), Roche Registration Limited - EMA/OD/014/15
[COMP co-ordinator: F. Naumann-Winter]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Orphan condition

After plenary discussion in the COMP the sponsor is invited to merge the three applications presented into one single application targeting “marginal zone lymphoma” as orphan condition.

- Number of people affected

Based on merging the three applications the sponsor is invited to provide a prevalence estimate for marginal zone lymphoma as a whole.

In the written response the sponsor merged the three applications for treatment of nodal, extranodal and splenic marginal zone lymphoma into “treatment of marginal zone lymphoma”, as requested by the COMP, based on the history of the disease arising from post-germinal center marginal zone B cells for the 3 subtypes, similar immunophenotype and treatments.

Following review of the application by the Committee, it was agreed to rename the condition to marginal zone lymphoma.

The Committee agreed that the condition, marginal zone lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing obinutuzumab was considered justified based on preclinical and preliminary clinical data showing antitumor activity of the product in models of the proposed condition and in patients affected by the condition.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, mucosa and bone marrow involvement with development of pancytopenia and increased risk of opportunistic infections. Five-year survival ranges from 30% to 90%.

The condition was estimated to be affecting approximately 0.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing obinutuzumab may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses with the proposed product in patients relapsing from previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by marginal zone lymphoma.

A positive opinion for obinutuzumab for treatment of marginal zone lymphoma was adopted by consensus.

2.1.7 obinutuzumab for treatment of nodal marginal zone lymphoma, Roche Registration Limited - EMA/OD/015/15
[COMP co-ordinator: F. Naumann-Winter]

This application has been merged into EMA/OD/014/15 with the revised condition.

2.1.8 obinutuzumab for treatment of splenic marginal zone lymphoma, Roche Registration Limited - EMA/OD/016/15
[COMP co-ordinator: F. Naumann-Winter]

This application has been merged into EMA/OD/014/15 with the revised condition.

2.1.9 obinutuzumab for treatment of follicular lymphoma, Roche Registration Limited - EMA/OD/013/15
[COMP co-ordinator: F. Naumann-Winter]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor should describe and justify the methodology used for the prevalence calculation, including the sources selected and the way the calculations were performed, resulting lower prevalence estimate than previously designated by the COMP.

Further to this, the sponsor is invited to revise the prevalence calculations as appropriate.

In the written response the sponsor further elaborated on the prevalence issue using IARC data for non-hodgkin lymphoma and literature references and provided an updated estimate of 2.13 per 10,000 for the 10-year FL prevalence.

The Committee agreed that the condition, follicular lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing obinutuzumab was considered justified based on preclinical and preliminary clinical data showing antitumor effect of the proposed product.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma.

The condition was estimated to be affecting approximately 2.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing obinutuzumab may be of significant benefit to those affected by the condition. The sponsor provided clinical data showing favourable responses with the proposed product in patients relapsing from previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by follicular lymphoma.

A positive opinion for obinutuzumab for treatment of follicular lymphoma was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of acromegaly - EMA/OD/031/15
[COMP co-ordinator: K. Westermark]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.2 Adeno-associated viral vector containing the human factor IX gene for treatment of haemophilia B, Baxter Innovations GmbH - EMA/OD/003/15
[COMP co-ordinator: A. Moraiti]

The Committee agreed that the condition, haemophilia B, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector containing the human factor IX gene was considered justified based on preclinical data showing protective levels of factor IX after treatment.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes and substantially prolonged bleeding upon injury.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector containing the human factor IX gene may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing protection against bleeding with the proposed product, without generation of inhibitory antibodies, a phenomenon which limits the use of the currently available treatments for haemophilia B. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by haemophilia B.

A positive opinion for adeno-associated viral vector containing the human factor IX gene, for treatment of haemophilia B, was adopted by consensus.

2.2.3 Adeno-associated viral vector serotype 9 containing the human SMN gene for treatment of spinal muscular atrophy, AveXis EU, Ltd - EMA/OD/028/15
[COMP co-ordinator: I. Bradinova]

The Committee agreed that the condition, spinal muscular atrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 containing the human *SMN* gene was considered justified based on preclinical data in a valid in vivo model of the condition, where administration of the product resulted in expression of the missing protein and improved motor function and survival.

The condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications.

The condition was estimated to be affecting less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for adeno-associated viral vector serotype 9 containing the human *SMN* gene for treatment of spinal muscular atrophy was adopted by consensus.

2.2.4 Product for prevention of avian influenza A virus - EMA/OD/036/15
[COMP co-ordinator: N. Sypsas]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.5 Product for treatment of avian influenza A virus - EMA/OD/012/15
[COMP co-ordinator: N. Sypsas]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.6 Product for treatment of hepatoblastoma - EMA/OD/023/15
[COMP co-ordinator: D. O'Connor]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.7 Product for treatment of hepatocellular carcinoma - EMA/OD/022/15
[COMP co-ordinator: D. O'Connor]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.8 Edaravone for treatment of amyotrophic lateral sclerosis, Mitsubishi Tanabe Pharma Europe Ltd - EMA/OD/032/15
[COMP co-ordinator: K. Westermark]

The Committee agreed that the condition, amyotrophic lateral sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing edaravone was considered justified based on pre-clinical in vivo data using a valid pre-clinical model of the condition.

The condition is life-threatening due to a median survival time from onset to death of 39 months.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing edaravone may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that when edaravone was used in combination with riluzole a significant benefit was seen concerning functional endpoints. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for edaravone for treatment of amyotrophic lateral sclerosis was adopted by consensus.

2.2.9 Product for treatment of autosomal dominant polycystic kidney disease - EMA/OD/027/15
[COMP co-ordinator: J. Torrent-Farnell]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.10 Product for treatment of Ebola virus disease- EMA/OD/030/15
[COMP co-ordinator: J. Torrent-Farnell]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.11 Product for treatment of type I plasminogen deficiency or hypoplasminogenemia - EMA/OD/313/14
[COMP co-ordinator: J. Torrent-Farnell]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond to the list of issue in writing before the Committee at the June meeting.

2.2.12 Product for treatment of neurotrophic keratitis- EMA/OD/029/15
[COMP co-ordinator: K. Westermark]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.13 Product for treatment of cutaneous T cell lymphoma - EMA/OD/033/15
[COMP co-ordinator: K. Kubáčková]

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.14 Trehalose for treatment of spinocerebellar ataxia, Dr Ulrich Granzer - EMA/OD/009/15
[COMP co-ordinator: G. O'Dea]

The Committee agreed that the condition, spinocerebellar ataxia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing trehalose was considered justified based on pre-clinical data in a valid model of the condition showing an improvement in motor function.

The condition is chronically debilitating due to slowly progressive incoordination of gait which is often associated with poor coordination of hands, speech, and eye movements.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for trehalose for treatment of spinocerebellar ataxia was adopted by consensus.

2.2.15 Triheptanoin for treatment of Very Long-chain Acyl-coenzyme A Dehydrogenase (VLCAD) Deficiency, Ultragenyx UK Limited - EMA/OD/026/15
[COMP co-ordinator: I. Barisic]

The Committee agreed that the condition, very long-chain acyl-CoA dehydrogenase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing triheptanoin was considered justified based on preliminary clinical data supporting an improvement in cardiac manifestations, hypoglycaemia and survival in patients affected by the condition.

The condition is chronically debilitating due to fatigue, hypoglycaemia, muscle wasting, rhabdomyolysis and life-threatening in particular due to cardiomyopathy.

The condition was estimated to be affecting less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for triheptanoin for treatment of very long-chain acyl-CoA dehydrogenase deficiency was adopted by consensus.

2.3. Appeal procedure

None.

2.4. Evaluation on-going

The Committee noted that evaluation was on-going for twenty two applications for orphan designation.

2.5. Validation on-going

The Committee was informed that validation was on-going for twenty two applications for orphan designation.

3. Requests for protocol assistance

3.1. 1st reports

3.1.1 For treatment of haemophilia A *[Co-ordinator: A. Magrelli]*

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.2 For treatment of ATTR amyloidosis *[Co-ordinator: K. Westermark]*

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.3 For treatment of Niemann-Pick disease, type C *[Co-ordinator: B. Bloechl-Daum]*

The Committee was briefed on the significant benefit issues in preparation of the June meeting.

3.1.4 For treatment of glioma *[Co-ordinator: B. Bloechl-Daum]*

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues

3.1.5 For treatment of Graft-versus-Host disease *[Co-ordinator: K. Westermark]*

The discussion was postponed to the June meeting.

3.1.6 For treatment of Urea Cycle Disorders *[Co-ordinator: A. Magrelli]*

The Committee was briefed on the significant benefit issues in preparation of the June meeting.

4. Overview of applications

4.1 Update on applications for orphan medicinal product designation submitted/expected

Co-ordinators were appointed for 2 applications submitted, 27 upcoming applications and 2 potential appeal procedures.

4.2 Update on orphan applications for Marketing Authorisation

An updated overview of orphan applications for Marketing Authorisation was circulated.

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

5.1. Orphan designated products for which CHMP opinions have been adopted

5.1.1 Hetlioz (tasimelteon) for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited
(EU/3/10/841) *[COMP co-ordinator: J. Torrent-Farnell]*

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to elaborate on the following issues:

- Prevalence

In view of the COMP's recommendation to amend the condition to non 24-hr sleep-wake syndrome the sponsor is invited to recalculate the prevalence. The assumptions made need to be further elaborated. For the calculation and presentation of the prevalence data it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation" document available on the Agency website.

In its written response the sponsor clarified the number of totally blind individuals in the European Union as opposed to the total number of blind in Europe as reported in the European Blind Association Network (EBAN). In view of the difficulty in establishing a more accurate calculation of the prevalence because of the under reporting, the sponsor further supplemented the prevalence calculation with two letters from specialists in the field as requested following the instructions from the guidance under "Points to Consider on the calculations and reporting of a prevalence of a condition for an orphan designation". The sponsor concluded on a prevalence of 3.3 in 10,000.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of non-24-hour sleep-wake disorder (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be not more than 3.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to excessive daytime sleepiness with consequences on the quality of life and activities of daily living.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

An opinion not recommending the removal of Hetlioz, tasimelteon (EU/3/10/841), from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion was adopted for publication on the EMA website.

5.2. Orphan designated products for discussion prior to adoption of CHMP opinion

5.2.1 Asfotase alfa for treatment of hypophosphatasia; Alexion Europe SAS (EU/3/08/594)

5.2.2 Panobinostat for treatment of multiple myeloma; Novartis Europharm Limited (EU/3/12/1063)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

5.2.3 Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879)

5.2.4 Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG:

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

5.2.5 Idebenone for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (EU/3/07/434)

5.2.6 Ibrutinib for treatment of lymphoplasmacytic lymphoma; Janssen-Cilag International NV (EU/3/14/1264)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

5.3. On-going procedures

5.3.1 Amikacin; Insmed Limited:

a) treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis (EU/3/06/387)

b) treatment of nontuberculous mycobacterial lung disease (EU/3/14/1259)

5.3.2 Blinatumomab for treatment of acute lymphoblastic leukaemia; Amgen Europe B.V. (EU/3/09/650)

5.3.3 Isavuconazonium sulfate; Basilea Medical Ltd:

a) treatment of invasive aspergillosis (EU/3/14/1284)

b) treatment of mucormycosis (EU/3/14/1276)

5.3.4 Cysteamine hydrochloride for treatment of cystinosis; Orphan Europe S.A.R.L. (EU/3/08/578)

5.3.5 Cysteamine hydrochloride for treatment of cystinosis; Lucane Pharma (EU/3/14/1341)

5.3.6 Efmoroctocog alfa for treatment of haemophilia A; Biogen Idec Ltd (EU/3/10/783)

5.3.7 Recombinant fusion protein linking human coagulation factor IX with human albumin for treatment of haemophilia B, CSL Behring GmbH (EU/3/09/723)

COMP co-ordinator was appointed.

5.3.8 Carfilzomib for treatment of multiple myeloma; Amgen Europe B.V. (EU/3/08/548)

5.3.9 Recombinant human parathyroid hormone for treatment of hypoparathyroidism; NPS Pharma UK Ltd (EU/3/13/1210)

5.3.10 Dexamethasone acetate for treatment of multiple myeloma; LABORATOIRES CTRS (EU/3/10/745)

5.3.11 Susoctocog alfa for treatment of haemophilia A; Baxter AG (EU/3/10/784)

5.3.12 Lumacaftor / ivacaftor for treatment of cystic fibrosis; Vertex Pharmaceuticals (U.K.) Ltd., (EU/3/14/1333)

5.3.13 Sirolimus for treatment of chronic non-infectious uveitis; Santen Oy (EU/3/11/898)

5.3.14 Glyceryl tri-(4-phenylbutyrate); Hyperion Therapeutics Limited:

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EU/3/10/734)

c) treatment of citrullinaemia type 1 (EU/3/10/735)

d) treatment of argininosuccinic aciduria (EU/3/10/736)

e) treatment of hyperargininaemia (EU/3/10/737)

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EU/3/10/738)

g) treatment of citrullinaemia type 2 (EU/3/10/739)

5.3.15 Lenalidomide for treatment of mantle cell lymphoma; Celgene Europe Limited (EU/3/11/924)

5.3.16 Recombinant human lysosomal acid lipase for treatment of lysosomal acid lipase deficiency; Synageva BioPharma Ltd (EU/3/10/827)

5.3.17 L-Asparaginase for treatment of acute lymphoblastic leukaemia; medac Gesellschaft fuer klinische Spezialpraeparate mbH (EU/3/04/258)

5.3.18 Selexipag for treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension; Actelion Registration Ltd. (EU/3/05/316)

5.3.19 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

5.3.20 Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes for adjunctive treatment in haematopoietic cell transplantation; MolMed S.p.A. (EU/3/03/168)

6. Procedural aspects

6.1 Significant Benefit Working group

The working group on Significant Benefit met on 12 May 2015.

6.2 Significant Benefit Working group subgroups

Significant Benefit Working group subgroups met on 13 May 2015.

6.3 COMP workplan: presentation of COMP survey results

The EMA presented the COMP survey results.

6.4 Election of Chair and Vice-Chair - October 2015

The COMP Rules of Procedure EMEA/COMP/8212/00/ Rev. 3 were circulated for information. The members were advised to submit their candidature to COMPSecretariat@ema.europa.eu by 21 September 2015.

6.5 Pharmacovigilance: Information systems and Services

The EMA presented the topic.

6.6 EU Medicines Agencies Network Strategy to 2020

The documents were circulated for information.

6.7 COMP Work Plan 2015

The COMP Work Plan 2015 was adopted.

7. Any other business

None.

Date of next COMP meeting: 16-18 June 2015

List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 12-13 May 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Katerina Kubacková	Member	Czech Republic	No participation in final deliberations and voting on:	2.2.7 - EMA/OD/022/15
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Judit Eggenhofer	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Dainis Krievins	Member	Latvia	No restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova	Member	Netherlands	No interests declared	
Bożenna	Member	Poland	No restrictions	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dembowska-Bagińska			applicable to this meeting	
Ana Corrêa Nunes	Member	Portugal	No interests declared	
Zuzana Batova	Member	Slovak Republic	No interests declared	
Martin Možina	Member	Slovenia	No restrictions applicable to this meeting	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Kerstin Westermark	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Birthe Byskov Holm	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Aikaterini Moraiti	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Observer	Eurordis	No restrictions applicable to this meeting	
Julian Isla	Observer	Eurordis	No restrictions applicable to this meeting	