EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 May 2015
EMA/COMP/209468/2015
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 14-16 April 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/105029/2015

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 17-19 March 2015 EMA/COMP/105033/2015

The minutes were adopted with no amendments.

1.3 Declaration of conflicts 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 {2-amino-8-[4-(pyrrolidinylcarbonyl)phenyl]-(3H-benzo[f]azepin-4-yl)}-N,N-dipropylcarboxamide for treatment of ovarian cancer, Right Track Regulatory Limited - EMA/OD/314/14

[COMP co-ordinator: B. Bloechl-Daum]

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 preclinical and preliminary clinical studies to justify the assumption of significant benefit over all authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 14 April 2015, the sponsor elaborated on the preclinical studies and the assumed mechanism of action. It was pointed out that infiltrating lymphocytes isolated from the tumours treated with the product, could exert antitumor effects when transferred to new tumour bearing subjects in vivo, thereby supporting an elicitation of immune response by the product. With regards the clinical data, the sponsor again presented the available clinical studies and elaborated in particular with regards to two cases of heavily pretreated patients, who received the product in combination with doxorubicin.

The COMP reflected in particular on the preliminary clinical data included in the application. It was considered that they do not contradict the available preclinical data, but it is difficult to draw firm conclusions with the limitations being the uncontrolled nature of the observations and the combination

[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).

with other treatments. However, the available preclinical data do support additive effects when the product is added on to doxorubicin, in a valid model of the condition. This was considered relevant for the justification of both the medical plausibility and significant benefit.

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

The intention to treat the condition with the medicinal product containing {2-amino-8-[4-(pyrrolidinylcarbonyl)phenyl]-(3H-benzo[f]azepin-4-yl)}-N,N-dipropylcarboxamide was considered justified based on preclinical data in a model of the condition showing inhibition of tumour growth in combination with pegylated liposomal doxorubicin.

The condition is chronically debilitating due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

The condition was estimated to be affecting less than 3 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 {2-amino-8-[4-(pyrrolidinylcarbonyl)phenyl]-(3H-benzo[f]azepin-4-yl)}-N,N-dipropylcarboxamide may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that support the potential of improved efficacy when administered in combination with pegylated liposomal doxorubicin, based on an alternative immunomodulatory mode of action. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for {2-amino-8-[4-(pyrrolidinylcarbonyl)phenyl]-(3H-benzo[f]azepin-4-yl)}-N,N-dipropylcarboxamide, for treatment of ovarian cancer, was adopted by consensus.

2.1.2 Product for treatment of myasthenia gravis - EMA/OD/321/14

[COMP co-ordinator: V. Stoyanova]

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 treatment of myasthenia gravis, the sponsor should further elaborate on any available data demonstrating that the observed changes in antibody- and receptor levels in the preclinical model are translatable into clinically relevant effects.

In addition the sponsor is invited to present any available functional outcomes from the in vivo model study. In absence of functional data in the proposed condition it would be difficult to conclude on the potential clinical effects of the proposed product.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the available 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 14 April 2015, the sponsor discussed the available preclinical data in an in vivo model developed by the sponsor, and

argued that anti-acetylcholine receptor antibodies is a relevant endpoint, on the basis of literature showing an association between concentration of these antibodies and clinical classification score in myasthenia gravis patients treated with immunosuppressing drugs. With regards to the assumption of significant benefit, the sponsor assumed a clinically relevant advantage stemming from a new mechanism of action.

The COMP considered that in the absence of functional endpoints in the proposed in vivo settings, it is difficult to accept the proposed model as valid and that the medical plausibility of the product cannot be established. In the absence of data, the significant benefit may also not be considered. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 April 2015, prior to final opinion.

2.1.3 Autologous human peripheral blood Vdelta1+ T lymphocytes activated in vitro by cytokine and monoclonal antibody treatment for treatment of chronic lymphocytic leukaemia/ small lymphocytic lymphoma, Lymphact - Lymphocyte Activation Technologies S.A. - EMA/OD/006/15

[COMP co-ordinator: K. Kubáčková]

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

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 should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations. It is suggested that the sponsor refer to a recent publication M. Sant 2014, Lancet Oncology.

- Significant benefit

The sponsor is proposing that their product will offer an alternative mode of action to currently approved treatments which will offer a clinically relevant advantage as the basis for significant benefit.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the pre-clinical in vivo studies 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 14April 2015, the sponsor further elaborated on the issues raised. As for the significant benefit issue, the COMP considered that the product offered a clinically relevant advantage in patients who were refractory to treatment with all currently authorised treatments and were in end-stage disease as the basis for significant benefit.

The COMP also requested the sponsor to explain the basis for their calculation, in particular with regards to the fact that the prevalence calculation did not take into consideration current information on an increase in duration and survival of the condition. The impact of newer therapies on the improvement of the survival was a point acknowledged by one of the experts of the sponsor participating in the discussion.

It was acknowledged by the COMP and the sponsor that prevalence was difficult to calculate as the picture was changing due to an increase also in the incidence of the condition in more elderly patients. The COMP further noted that not all the potential databases were used in the sponsor's calculation. There was concern that the prevalence was an underestimate due to the assumptions not reflecting the current practice, impact of changing treatment algorithms and perceived improvements in survival reported in the literature.

Based on these assumptions the COMP was of the opinion that the sponsor had not presented a comprehensive and complete analysis of the potential changes in the prevalence of the condition and did not believe it could give a favourable opinion to support the granting of a recommendation for orphan designation.

In conclusion the COMP has considered:

The intention to treat the condition with the medicinal product containing Autologous human peripheral blood Vdelta1+ T lymphocytes activated in vitro by cytokine and monoclonal antibody treatment, was justified based on pre-clinical in vivo data showing a reduction in tumour size.

The condition is chronically debilitating and life-threatening due to development of anaemia, neutropenia, thrombocytopenia, lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulins leading to increased susceptibility to infections.

The COMP was of the opinion that the sponsor had failed to establish that the condition is affecting not more than 5 in 10,000 people at the time the application is made.

The COMP was of the opinion that the prevalence calculation presented by the sponsor was based on a limited number of publications and databases and the methodology used was not sufficiently adequate to encompass all the necessary considerations. The assumptions made during the oral presentation did not appear to consider either the impact of new therapies or changes in the incidence of the condition due to an aging population.

The product is intended for treatment of a life-threatening and seriously debilitating condition; the sponsor did not however submit the application on the basis of the second paragraph of Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products, and did not provide any data with the application that would allow an evaluation of a potential claim of insufficient return of the investment without incentives.

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 may be of significant benefit to those affected by the condition based on pre-clinical in vivo data

A negative opinion for product, for treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, was adopted by majority (24 negative votes out of 26). The Icelandic and Norwegian members were in agreement with the majority. The divergent position was appended to the opinion. The sponsor will have 90 days to appeal from the COMP decision.

2.1.4 Product for treatment of Rett syndrome - EMA/OD/316/14

[COMP co-ordinator: I. Barisic]

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 31 March 2015, prior to responding to list of issues.

2.1.5 Product for treatment of malignant mesothelioma - EMA/OD/324/14

[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 30 March 2015, prior to responding to list of issues.

2.1.6 **Fusion proteins composed by a genetically modified Cholera Toxin Subunit A1, peptides from the acetylcholine receptor alpha chain and a dimer of the D fragment from Staphylococcus aureus protein A** for treatment of myasthenia gravis, Toleranzia AB - EMA/OD/318/14

[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 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 treatment of myasthenia gravis, the sponsor is invited to clarify the number and the type of epitopes that will be contained in the product and their expected influence on its pharmacology.

The sponsor is also invited to further elaborate on the methodology of the animal model study presented, including:

  - the timing of treatment;
  - the validity of the scoring system used, including e.g. how parameters such as weakness and fatigue were measured;
  - the level of objectiveness of the lowest scores (one and two).

The sponsor is also invited to further elaborate on the results of the animal model study presented, and in particular:

  - the assumed clinical relevance of the results, taking into account that during the observation time reported by the sponsor the untreated group seems to have developed only rather mild (max 2) score.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the available 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 15 April 2015, the sponsor clarified the issues posed by the COMP.

The sponsor further elaborated on the nature and the composition of the product, and discussed the methodology and results of the preclinical studies. It was noted that the experimental autoimmune myasthenia gravis model used is a valid in vivo model considered as the gold standard for studying preclinical efficacy in myasthenia gravis. In those settings, the sponsor evaluated the clinical

manifestations of myasthenia gravis using a functional scoring system, and statistically significant effects were observed with the product.

In relation to the significant benefit, the proposed product, acting on the immune response, offers the possibility to tackle the clinical disease with a different mechanism of action directly targeting the autoimmune component that causes myasthenia gravis, which may result in a clinically relevant advantage of improved efficacy.

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

The intention to treat the condition with the medicinal product containing fusion proteins composed by a genetically modified cholera toxin subunit A1, peptides from the acetylcholine receptor alpha chain and a dimer of the D fragment from *Staphylococcus aureus* protein A was considered justified based on preclinical data showing improvement of functional endpoints with the proposed product.

The condition is chronically debilitating due to recurrent crisis characterized by muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing. Crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment.

The condition was estimated to be affecting approximately 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 fusion proteins composed by a genetically modified cholera toxin subunit A1, peptides from the acetylcholine receptor alpha chain and a dimer of the D fragment from *Staphylococcus aureus* protein A may be of significant benefit to those affected by the condition. The sponsor provided preclinical data showing improvement of muscular function. The mechanism of action of the product which is targeting the immune response differs from the currently authorized treatments for the condition. This offers the potential of using the product in combination with some of the currently authorized treatments. The Committee considered that this could constitute a clinically relevant advantage for the patients affected by the condition.

A positive opinion for fusion proteins composed by a genetically modified cholera toxin subunit A1, peptides from the acetylcholine receptor alpha chain and a dimer of the D fragment from *Staphylococcus aureus* protein A, for treatment of myasthenia gravis, was adopted by consensus.

2.1.7 Product for prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy - EMA/OD/317/14
[COMP co-ordinator: B. Dembowska-Bagińska]

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:

- Proposed condition

The sponsor is requested to discuss the validity of the condition in terms of either a distinct medical entity or a justified subset, taking into consideration the revised guideline of the format and content of applications (ENTR/6283/00 Rev 04) of March 2014. The attention of the sponsor is drawn primarily to the general requirements and special considerations of page 7 of the above mentioned guideline. Any

current classification system such as the ICD-10 classification should be discussed in the context of delineating the condition proposed for designation.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially 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 any relevant 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 15 April 2015, the sponsor further discussed the validity of the proposed condition by referring to older previous published opinions of the COMP. The sponsor also referred to the K12.3 code of ICD-10 classification, to support their view that the condition is valid for designation.

The COMP considered that the K12.3 code refers to ulcerative oral mucositis in general and includes several underlying etiologies, including drug and radiation induced, viral and non-otherwise specified cases. It was also noted that this code was introduced first in the version of 2010 and appeared in its current format in versions 2014 and 2015. The latest versions were introduced after the previous designations.

In this context, the COMP considered that the previous opinions cannot be used as a basis to validate the proposed condition, because firstly it is the legal responsibility of the sponsor to justify the criteria each time and secondly because the referenced classification has in the meantime evolved. It was considered that the sponsor had not described a distinct medical entity in terms of etiology, pathophysiology, histopathology and clinical characteristics.

With regards to the significant benefit the COMP considered that there are again no data submitted that would allow even an indirect comparison versus the authorised counterparts.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 April 2015, prior to final opinion.

2.1.8 **AASSGVSTPGSAGHDIITEQPRS** for treatment of Huntington's disease, Centre National de la Recherche Scientifique (CNRS) - EMA/OD/325/14

[COMP co-ordinator: V. Stoyanova]

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 treatment of Huntington's disease, the sponsor should further elaborate on:

  - the interpretation of the results obtained in the R6/2 in vivo model as the therapeutic benefit does not appear to be clearly demonstrated in this single study.
  - how the data generated in a preventive setting would be applicable for the treatment of the condition.

- 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 pre-clinical in vivo 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 15 April 2015, the sponsor discussed additional pre-clinical data in the R6/2 model of the condition. Favourable effects of the product in particular with regards to cognitive and electrophysiological endpoints were discussed. These points complemented the initially submitted information regarding motor function improvements.

The Committee agreed that the condition, Huntington's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing AASSGVSTPGSAGHDIITEQPRS was considered justified based on pre-clinical in vivo data using valid models of the condition showing a potential beneficial effect on behavioural and motor function.

The condition is chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications.

The condition was estimated to be affecting approximately 1.3 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 AASSGVSTPGSAGHDIITEQPRS may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate that the product reduces the progression of motor symptoms and modulates behaviour in a model of the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for AASSGVSTPGSAGHDIITEQPRS, for treatment of Huntington's disease, was adopted by consensus.

2.1.9 **Triamcinolone acetonide** for treatment of non-infectious uveitis, S-cubed Limited - EMA/OD/320/14

[COMP co-ordinator: A. Magrelli]

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

In order to justify the significant benefit the sponsor is invited to further discuss potential assumptions of improved efficacy of the proposed product in relation to the authorised product Ozurdex.

In addition the sponsor is invited to further discuss the extrapolation of the clinical effects shown in Phase I/II using the Triesence formulation compared to the sponsor's own formulation in relation to the potential clinically relevant advantage or major contribution to patient care.

In the written response, the sponsor further elaborated on the issues raised. In particular, the sponsor further elaborated on the assumption of a clinically relevant advantage based on efficacy versus a vitreous implant containing dexamethasone currently authorized for the proposed condition.

The sponsor reported that the improvement in visual acuity and macular oedema achieved in a small study of patients treated with subchoroideal triamcinolone compares favourably with the results in trials with the authorised product.

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 triamcinolone acetonide was considered justified based on preclinical in vivo data, and on preliminary clinical data showing improvement of relevant endpoints in patients affected by the condition.

The condition is chronically debilitating due to visual loss, leading to significant visual impairment or legal blindness in up to 35% of patients.

The condition was estimated to be affecting less than 5 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 triamcinolone acetonide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that due to the administration route the product selectively targets the part of the eye affected by non-infectious uveitis therefore reducing the possible occurrence of side effects and adverse events related to different administration routes. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for triamcinolone acetonide for treatment of non-infectious uveitis was adopted by consensus.

2.1.10 **Adeno-associated viral vector serotype 9 containing the human HGSNAT gene** for treatment of mucopolysaccharidosis IIIC, Cochamo Systems Ltd - EMA/OD/322/14

[COMP co-ordinator: A. Magrelli]

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

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 does not provide information on how the proposed prevalence estimates were calculated from the data given in the cited literature hence the validity of the sponsor's estimate cannot be assessed. The sponsor should describe and justify the methodology used for the prevalence calculation.

In the written response the sponsor provided an updated prevalence estimate revising downwards the proposed figure to 0.5/10,000 in line with the request of the COMP.

The Committee agreed that the condition, mucopolysaccharidosis IIIC (Sanfilippo C syndrome), 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 *HGSNAT* gene was considered justified based on data from a pre-clinical in vivo model of the condition showing improvements in parameters relevant to the condition.

The condition is life-threatening and chronically debilitating due to progressive neurocognitive decline starting in infancy or early childhood with severe behavioural disturbances, initially hyperactive and challenging behaviour, seizures, loss of cognitive and motor skills, dysphagia, and frequent infections of the upper and lower airways. Death usually occurs within the third decade in constitutive forms or within the fourth to fifth decade of life in attenuated disease.

The condition was estimated to be affecting approximately 0.5 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 *HGSNAT* gene for treatment of mucopolysaccharidosis IIIC (Sanfilippo C syndrome) was adopted by consensus.

2.1.11 Reduced oxydized N acetyl heparin for treatment of plasma cell myeloma, Sigma-Tau Pharma Ltd - EMA/OD/277/14
[COMP co-ordinator: K. Kubáčková]

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

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 should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response the sponsor acknowledged the improvement in prognosis and recalculated the prevalence between 2.99 (based on survival of 4.5 years) and 4.06 (based on 6.1 years) in 10,000. The COMP noted that this is in accordance to previous designations for that condition (3.6/10,000).

The Committee agreed that the condition, plasma cell myeloma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing reduced oxidised N-acetyl heparin was considered justified based on preclinical data in relevant models showing improvements in tumour growth and reduction of kappa chain concentration in the serum.

The condition is chronically debilitating in particular due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 6 years.

The condition was estimated to be affecting approximately 3.6 in 10,000 people 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 reduced oxidised N-acetyl heparin may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that support the potential of improved efficacy of the product when used in combination with other authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for reduced oxidised N-acetyl heparin, for treatment of plasma cell myeloma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 2-(7-ethoxy-4-(3-fluorophenyl)-1-oxophthalazin-2(1H)-yl)-N-methyl-N-(2-methylbenzo[d]oxazol-6-yl)acetamide for treatment of cystic fibrosis, Clinical Network Services (UK) Ltd - EMA/OD/018/15
[COMP co-ordinator: J. Eggenhofer]

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

The intention to treat the condition with the medicinal product containing 2-(7-ethoxy-4-(3-fluorophenyl)-1-oxophthalazin-2(1H)-yl)-N-methyl-N-(2-methylbenzo[d]oxazol-6-yl)acetamide was considered justified based on preclinical data showing increased function of the defective chloride channel.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

The condition was estimated to be affecting approximately 0.8 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 2-(7-ethoxy-4-(3-fluorophenyl)-1-oxophthalazin-2(1H)-yl)-N-methyl-N-(2-methylbenzo[d]oxazol-6-yl)acetamide may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing that the proposed product acting as corrector of the function of the defective chloride channel in cystic fibrosis may offer the potential of translation into a disease-modifying effect in cystic fibrosis. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for 2-(7-ethoxy-4-(3-fluorophenyl)-1-oxophthalazin-2(1H)-yl)-N-methyl-N-(2-methylbenzo[d]oxazol-6-yl)acetamide, for treatment of cystic fibrosis, was adopted by consensus.

2.2.2 Product for treatment of non-infectious uveitis - EMA/OD/024/15

[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 May meeting.

2.2.3 5,7-Dichloro-2-dimethylaminomethyl-8-hydroxyquinoline hydrochloride for treatment of Huntington's disease, Prana Biotechnology UK Limited - EMA/OD/017/15

[COMP co-ordinator: A. Andrić]

The Committee agreed that the condition, Huntington's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 5,7-dichloro-2-dimethylaminomethyl-8-hydroxyquinoline hydrochloride was considered justified based on pre-clinical in vivo data and preliminary clinical data showing improvement in parameters associated with the condition.

The condition is life-threatening and chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications.

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 5,7-dichloro-2-dimethylaminomethyl-8-hydroxyquinoline hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in a relevant parameter when the product is used in combination with tetrabenazine. The Committee considered that this could constitute a clinically relevant advantage.

A positive opinion for containing 5,7-dichloro-2-dimethylaminomethyl-8-hydroxyquinoline hydrochloride, for treatment of Huntington's disease, was adopted by consensus.

2.2.4 Adult human bone-marrow derived, ex-vivo expanded, pooled allogeneic mesenchymal stromal cells for treatment of tromboangiitis obliterans (Buerger's disease), Regulatory Resources Group Ltd - EMA/OD/019/15

[COMP co-ordinator: J. Torrent-Farnell]

The Committee agreed that the condition, thromboangiitis obliterans (Buerger's disease), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adult human bone-marrow-derived, ex-vivo-expanded, pooled allogeneic mesenchymal stromal cells was considered justified based on pre-clinical in vivo and preliminary clinical data showing improved efficacy in valid end-points associated with the condition.

The condition is chronically debilitating due to the development of ulcers, gangrene and risk of amputation.

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 adult human bone-marrow-derived, ex-vivo-expanded, pooled allogeneic mesenchymal stromal cells may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product reduces resting pain and ulceration due to the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adult human bone-marrow-derived, ex-vivo-expanded, pooled allogeneic mesenchymal stromal cells for treatment of thromboangiitis obliterans (Buerger's disease) was adopted by consensus.

2.2.5 Product for prevention of bronchopulmonary dysplasia- EMA/OD/010/15
[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 May meeting.

2.2.6 **Allopurinol sodium** for treatment of perinatal asphyxia, ACE Pharmaceuticals BV - EMA/OD/004/15
[COMP co-ordinator: K. Westermark]

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

The intention to treat the condition with the medicinal product containing allopurinol sodium was considered justified based on preliminary clinical data supporting a reduction of long term adverse outcomes in treated patients affected by the condition.

The condition is chronically debilitating due to the long lasting neurological and developmental sequelae. The condition is also life threatening due to the high mortality associated to the most severe cases.

The condition was estimated to be affecting approximately 1 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 allopurinol sodium, for treatment of perinatal asphyxia, was adopted by consensus.

2.2.7 Product for prevention of scarring post glaucoma filtration surgery - EMA/OD/021/15
[COMP co-ordinator: I. Barisic]

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 May meeting.

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

[COMP co-ordinator: A. Magrelli]

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 May meeting.

2.2.9 Humanized anti-CD37 monoclonal antibody conjugated to maytansinoid DM1 for treatment of diffuse large B-cell lymphoma, ImmunoGen Europe Limited - EMA/OD/005/15
[COMP co-ordinator: F. Naumann-Winter]

The Committee agreed that the condition, diffuse large B-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised anti-CD37 monoclonal antibody conjugated to maytansinoid DM1 was considered justified based on pre-clinical in vivo showing tumour reduction and preliminary clinical data showing improved response.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening in patients not responding to treatment.

The condition was estimated to be affecting approximately 2.7 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 humanised anti-CD37 monoclonal antibody conjugated to maytansinoid DM1 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical and preliminary clinical data that demonstrate improved outcomes. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised anti-CD37 monoclonal antibody conjugated to maytansinoid DM1, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.2.10 Product for treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) - EMA/OD/014/15
[COMP co-ordinator: F. Naumann-Winter]

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 issues in writing before the Committee at the May meeting.

2.2.11 Product for treatment of follicular lymphoma - EMA/OD/013/15
[COMP co-ordinator: F. Naumann-Winter]

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 issues in writing before the Committee at the May meeting.

2.2.12 Product for treatment of nodal marginal zone lymphoma EMA/OD/015/15
[COMP co-ordinator: F. Naumann-Winter]

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 issues in writing before the Committee at the May meeting.

2.2.13 Product for treatment of splenic marginal zone lymphoma Limited - EMA/OD/016/15
[COMP co-ordinator: F. Naumann-Winter]

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 issues in writing before the Committee at the May meeting.

2.2.14 Product for treatment of hepatitis delta virus infection - EMA/OD/329/14
[COMP co-ordinator: A. Corrêa Nunes]

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 May meeting.

2.2.15 Trehalose for treatment of oculopharyngeal muscular dystrophy, Dr Ulrich Granzer - EMA/OD/008/15
[COMP co-ordinator: P. Evers/ M. Hoffmann]

The Committee agreed that the condition, oculopharyngeal muscular dystrophy, 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 a pre-clinical in vivo model of the condition showing improvements in skeletal muscle function.

The condition is chronically debilitating due to lowering (ptosis) of the eyelids and swallowing difficulties (dysphagia). With disease progression, additional skeletal muscles can be affected including the proximal muscles of the lower limb affecting gait.

The condition was estimated to be affecting approximately 0.1 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 oculopharyngeal muscular dystrophy, was adopted by consensus.

2.2.16 Triheptanoin for treatment of glucose transporter type-1 deficiency syndrome, Pharma Gateway AB - EMA/OD/007/15
[COMP co-ordinator: G. Capovilla]

The Committee agreed that the condition, glucose transporter type-1 deficiency syndrome, 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 showing an improvement in seizures, movement disorders and neuropsychological parameters.

The condition is chronically debilitating due to brain dysfunction leading to seizures (resistant to traditional seizure medications), electroencephalographic abnormalities, variable developmental delay, acquired microcephaly, hypotonia, and a complex movement disorder consisting of ataxia and paroxysmal dystonic attack.

The condition was estimated to be affecting approximately 0.1 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 glucose transporter type-1 deficiency syndrome, was adopted by consensus.

2.3. Appeal procedure

None.

2.4. Evaluation on-going

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

2.5. Validation on-going

The Committee was informed that validation was on-going for fifty one applications for orphan designation.

3. Requests for protocol assistance

3.1 For treatment of paroxysmal nocturnal haemoglobinuria *[Coordinator: K. Westermark]*

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

3.2 For diagnosis of gastro-entero-pancreatic neuroendocrine tumours *[Coordinator: K. Westermark]*

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

3.3 For treatment of plasma cell myeloma *[Coordinator: B. Bloechl-Daum]*

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues via written procedure on 21 April 2015.

3.4 For treatment of haemophilia A *[Coordinator: A. Magrelli]*

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

3.5 For treatment of ATTR amyloidosis *[Coordinator: K. Westermark]*

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

3.6 For treatment of malignant hyperthermia *[Coordinator: B. Bloechl-Daum]*

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues via written procedure on 21 April 2015.

4. Overview of applications

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

COMP co-ordinators were appointed for 1 application submitted and 25 upcoming applications.

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 Lenvima (lenvatinib); Eisai Ltd
[COMP co-ordinator: K. Kubáčková]

a) treatment of papillary thyroid cancer (EU/3/13/1121)

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:

The sponsor is requested to further elaborate on any data supporting a clinically relevant advantage or major contribution to patient care in particular with regards to sorafenib.

At this point in time the sponsor is arguing a clinically relevant advantage based on an indirect comparison of the results from the SELECT and DECISION studies. The sponsor is invited to discuss the comparability of population to draw conclusion on the justification of criteria and in particular elaborate on the effects observed on any refractory relapsed patients previously treated with and not eligible for sorafenib.

In its written response and during an oral explanation before the Committee on 14 April 2015, the sponsor reiterated that when comparing the populations of the two studies, there are grounds to suggest that the SELECT study participants had a poorer prognosis, based mainly on three points: a) mPFS was shorter in the placebo arm of SELECT compared to the DECISION trial, b) almost one fourth of treated patients in SELECT had received prior VEGF/R targeted therapy versus none in DECISION and c) a higher percentage of SELECT subjects had an ECOG performance status of 1 or 2, while a higher percentage on DECISION had a PS of 0.

Furthermore, the sponsor discussed in particular the comparison of PFS hazard ratios between the two studies and stressed that the respective confidence intervals are not crossed. The sponsor also used the formula log (HR (lenvatinib/sorafenib)) = log (HR (lenvatinib/placebo)) – log (HR (sorafenib/placebo)) to preform an indirect comparison of the lenvatinib arm versus the sorafenib arm yielding a HR favouring lenvatinib. The sponsor also reported, as requested by the COMP, results in patients from the SELECT study in patients who have previously received sorafenib.

Finally the sponsor discussed adjusted analyses of OS, to adjust for the bias due to treatment crossover. In the SELECT study, a pre-planned OS analysis was performed using the rank preserving structural failure time (RPSFT) model at the time of the primary PFS analysis. The RPSFT-adjusted HR was in favour of lenvatinib. The difference in OS between the 2 treatment arms became statistically significant as determined using the resampling method (bootstrapping). This was compared favourably to OS from the DECISION trial based on publicly available data.

The COMP considered that while the exercise could have further examined other prognostic covariates with regards to comparison of the populations of the two studies, there are always limitations when selecting prognostic covariates post hoc, and that the statement of the sponsor that “any benefit of lenvatinib over sorafenib cannot be attributed to selection of a more favourable patient population” was reasonable. It was also noted that placebo PFS is worse in SELECT than DECISION, but active performs better in SELECT than DECISION, which provides some degree of reassurance. The results for PFS appear convincing favouring lenvatinib. The results for Response Rate are also highly suggestive of improved effects of lenvatinib versus sorafenib on this endpoint.

It was also considered that the results for OS were more difficult to interpret due to cross-over from control to active in both studies. The rank preserving structural failure time model (RPSFT) is one possible (and indeed the most common) way of trying to account for this crossover, and has been appropriately conducted by the Company. The results of the RPSFT model do suggest that the HR for OS is smaller for lenvatinib, and such numerical superiority would be consistent with the clear improvement in response rate, and the benefit in PFS.

In conclusion, the COMP accepted that the indirect comparison between SELECT and DECISION confirmed the assumption of significant benefit, in particular based on prolongation of PFS.

The COMP concluded that:

The proposed therapeutic indication “Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)” falls entirely within the scope of the two designated orphan indications “treatment of follicular thyroid cancer” and “treatment of papillary thyroid cancer”, when the two designations are considered together.

The prevalence of papillary thyroid cancer (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 2.4 in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment with surgery and radio-iodine treatment and in case of development of metastasis with wide spread of the tumour.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Lenvima may be of potential significant benefit to those affected by the orphan condition is now confirmed. This is based on prolongation of progression free survival in patients with progressive, locally advanced or metastatic differentiated disease which compares favourably with the results to available data with sorafenib.

The Committee for Orphan Medicinal Products has recommended that Lenvima, lenvatinib, EU/3/13/1121 for treatment of papillary thyroid cancer is not removed from the Community Register of Orphan Medicinal Products.

b) treatment of follicular thyroid cancer (EU/3/13/1119)

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:

The sponsor is requested to further elaborate on any data supporting a clinically relevant advantage or major contribution to patient care in particular with regards to sorafenib.

At this point in time the sponsor is arguing a clinically relevant advantage based on an indirect comparison of the results from the SELECT and DECISION studies. The sponsor is invited to discuss the comparability of population to draw conclusion on the justification of criteria and in particular elaborate on the effects observed on any refractory relapsed patients previously treated with and not eligible for sorafenib.

In its written response, and during an oral explanation before the Committee on 14 April 2015, the sponsor reiterated that when comparing the populations of the two studies, there are grounds to suggest that the SELECT study participants had a poorer prognosis, based mainly on three points: a) mPFS was shorter in the placebo arm of SELECT compared to the DECISION trial, b) almost one fourth of treated patients in SELECT had received prior VEGF/R targeted therapy versus none in DECISION and c) a higher percentage of SELECT subjects had an ECOG performance status of 1 or 2, while a higher percentage on DECISION had a PS of 0.

Furthermore, the sponsor discussed in particular the comparison of PFS hazard ratios between the two studies, and stresses that the respective confidence intervals are not crossed. The sponsor also used the formula log (HR (lenvatinib/sorafenib)) = log (HR (lenvatinib/placebo)) – log (HR (sorafenib/placebo)) to preform an indirect comparison of the lenvatinib arm versus the sorafenib arm yielding a HR favouring lenvatinib. The sponsor also reported, as requested by the COMP, results in patients from the SELECT study in patients who have previously received sorafenib.

Finally the sponsor discussed adjusted analyses of OS, to adjust for the bias due to treatment crossover. In the SELECT study, a pre-planned OS analysis was performed using the rank preserving structural failure time (RPSFT) model at the time of the primary PFS analysis. The RPSFT-adjusted HR was in favour of lenvatinib. The difference in OS between the 2 treatment arms became statistically significant as determined using the resampling method (bootstrapping). This was compared favorably to OS from the DECISION trial based on publicly available data.

The COMP considered that while the exercise could have further examined other prognostic covariates with regards to comparison of the populations of the two studies, there are always limitations when selecting prognostic covariates post hoc, and that the statement of the sponsor that “any benefit of lenvatinib over sorafenib cannot be attributed to selection of a more favourable patient population” was reasonable. It was also noted that placebo PFS is worse in SELECT than DECISION, but active performs better in SELECT than DECISION, which provides some degree of reassurance. The results for PFS appear convincing favouring lenvatinib. The results for Response Rate are also highly suggestive of improved effects of lenvatinib versus sorafenib on this endpoint.

It was also considered that the results for OS were more difficult to interpret due to cross-over from control to active in both studies. The rank preserving structural failure time model (RPSFT) is one possible (and indeed the most common) way of trying to account for this crossover, and has been appropriately conducted by the Company. The results of the RPSFT model do suggest that the HR for OS is smaller for lenvatinib, and such numerical superiority would be consistent with the clear improvement in response rate, and the benefit in PFS.

In conclusion, the COMP accepted that the indirect comparison between SELECT and DECISION confirmed the assumption of significant benefit, in particular based on prolongation of PFS.

The COMP concluded that:

The therapeutic indication “Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)” falls entirely within the scope of the two designated orphan indications “treatment of follicular thyroid cancer” and “treatment of papillary thyroid cancer”.

The prevalence of follicular thyroid cancer (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.6 in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment with surgery and radio-iodine treatment and in case of development of metastasis with wide spread of the tumour.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Lenvima may be of potential significant benefit to those affected by the orphan condition is now confirmed. This is based on prolongation of progression free survival in patients with progressive, locally advanced or metastatic differentiated disease which compares favourably with the results of available data including sorafenib.

The Committee for Orphan Medicinal Products has recommended that Lenvima, lenvatinib, EU/3/13/1119 for treatment of follicular thyroid cancer is not removed from the Community Register of Orphan Medicinal Products.

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

5.2.1 Autologous tumour-derived immunoglobulin idiotype coupled to keyhole limpet haemocyanin for treatment of follicular lymphoma; Biovest Europe Ltd
(EU/3/06/394) *[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 May meeting.

5.2.2 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]*

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 issues in writing before the Committee at the May 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 Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

Marketing Authorisation Application withdrawal request on 23 March 2015.

5.3.4 Isavuconazonium sulfate; Basilea Medical Ltd:

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

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

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

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

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

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

5.3.9 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)

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

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

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

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

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

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

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

5.3.17 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)

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

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

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

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

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

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

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

5.3.25 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

5.3.26 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 Chair reported from the March meeting of the Working group on significant benefit. The group was mandated by the COMP to assist the European Commission with the revision of the Commission on Regulation (EC) No 141/2000 on Orphan medicinal products (2003/C 178/02). No conclusion could be reached during the first meeting and further discussions are needed. The COMP agreed to reply to EC requiring more time to deliver the COMP final conclusions. The working group on significant benefit will work on the response letter.

6.2 NCA/COMP Consultation on proposed process improvements for Orphan procedures (review and reconnect) – Workshop outcome

The EMA presented the outcome of the NCA consultation on proposals for process improvement.

6.3 Evaluation (and communication) of the Benefit/Risk Balance of medicinal products

The EMA presented the benefit-risk methodology steering group and invited COMP members to join should they think the work of the group can be of any interest for the COMP. B. Bloechl-Daum volunteered. Members who may decide to join the steering group after the COMP meeting were asked to contact EMA.

EMA also announced a workshop on significant benefit to be held on 7th December at EMA.

6.4 EU Network Training Centre

The EMA presented the EU Network Training Centre that was launched in January 2015.

6.5 COMP Working Plan 2015

The Chair presented the draft Work Plan 2015 for COMP members to comment on. Any comments on the work plan would be sent to the Chair before the May meeting.

7. Any other business

7.1 Harmonisation of committees' agenda and minutes

The EMA presented the common template for committees' agenda and updated the COMP on the result of the benchmarking analysis of the committee minutes.

7.2 Group on Patients Registries

The COMP representative in the EMA group working on patients registries reported from the last meeting of the group.

Date of next COMP meeting: 12-13 May 2015

List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 14-16 April 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 restrictions applicable to this meeting	
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	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Judit Eggenhofer	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova	Member	Netherlands	No interests declared	
Lars	Member	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Gramstad				
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions 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	
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	Participation in the meeting as observer allowed	