3 September 2015
EMA/COMP/475182/2015
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 14-16 July 2015

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

14 July 2015, 09:00-18:30, room 3E

15 July 2015, 08:30-18:30, room 3E

16 July 2015, 08:30-13:00, room 3E

Disclaimers

Some of the information contained in this agenda/minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this agenda/minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda/minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as 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. Welcome and declarations of interest of members and experts

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the COMP plenary session to be held 14-16 July 2015. See July 2015 COMP minutes (to be published post September 2015 COMP meeting).

1.2. Adoption of agenda

COMP agenda for 14-16 July 2015 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 16-18 June 2015 were adopted with no amendments.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. Insulin human (rDNA) - EMA/OD/050/15

Sirius Regulatory Consulting Limited; Treatment of short bowel syndrome

COMP coordinator: Ana 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:

- 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 short bowel syndrome, the sponsor should further elaborate on the adequacy to extrapolate the presented bibliographic data to the proposed orphan medicine development. In this context, the sponsor was asked to discuss the seemingly deviating results regarding pre-clinical pharmacodynamic effects and clinical efficacy.

- Significant benefit

The arguments on significant benefit versus teduglutide are based on the new mechanism of action in the condition. The sponsor is reminded to include all authorised products into significant benefit considerations, including products that may only be authorised for the orphan condition in individual EU member states (*e.g.* cimetidine, UK). Therefore, the sponsor is invited to revisit the applied search methodology for authorised products across the European Union and to amend the significant benefit argumentation accordingly.

In the written response, and during an oral explanation before the Committee on 14 July 2015, the sponsor further elaborated on the issues raised. With regards to the medical plausibility issue, it was confirmed that the bibliographic studies were conducted by the applicant. The sponsor also recapitulated the observations in preclinical models of short

bowel syndrome as well as the preliminary clinical outcomes in patients affected by the condition. It was further clarified that the formulation used in the clinical study was very similar to the one under development, providing a rationale for bridging and extrapolation of the observations. The clinical results with regards to improvements in weight score and enteral feeds were also further discussed. The COMP accepted that the oral insulin product developed by the sponsor is sufficiently similar to allow for appropriate extrapolation for the purpose of the orphan designation, and notwithstanding the limitations of the clinical pilot proof of principle study with a small and heterogeneous patient population, accepted a clear trend for improvement in clinically relevant endpoints.

With regards to significant benefit considerations, the sponsor has proposed a new regenerative mode of action that targets intestinal adaption, which is supported by the preclinical in vivo data and preliminary clinical data in relevant endpoints. It was acknowledged that authorised H2 blockers only allow for symptomatic treatment while teduglutide is indicated for adult patients after intestinal adaption.

The Committee agreed that the condition, short bowel syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing insulin human was considered justified based on preclinical in vivo data in a valid disease model showing increased bowel and mucosal weight with treatment, and based on clinical data of a proof of concept study showing improved enteral intake with oral insulin treatment.

The condition is chronically debilitating due to severe nutritional deficiency, metabolic and/or septic complications and life-threatening liver failure and end stage renal disease.

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 insulin human may be of significant benefit to those affected by the condition. The currently authorised products include histamine receptor 2 antagonists to treat disease symptoms and teduglutide, which is indicated to treat adult patients with short bowel syndrome, when patients are stable following a period of intestinal adaptation after surgery. The sponsor has provided preclinical in vivo data that demonstrate that the oral insulin treatment augments intestinal adaption in a relevant short bowel disease model, and clinical data in short bowel syndrome patients showing improvement in enteral intake. Hence, the product presents a novel mechanism of action to treat short bowel syndrome patients by enhancing intestinal adaption. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for insulin human, for treatment of short bowel syndrome, was adopted by consensus.

2.1.2. - EMA/OD/038/15

Treatment of plasma cell myeloma

COMP coordinator: Katerina 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.

- Significant benefit

The sponsor is proposing that their product, a proteasome inhibitor, offers an alternative in patients who are resistant to bortezomib which is another similar proteasome inhibitor.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from their pre-clinical in vivo study to justify the assumption of significant benefit in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 14 July 2015, the sponsor provided additional information with regards to prevalence of the condition by adding NORDCAN as a source of information, and asserted that the proposed active substance is an upstream blocker of proteasome activity for which cross-resistance is not predicted and that it has demonstrated encouraging effect against plasma cell myeloma cell lines and in vivo xenograft models.

The COMP considered that in the absence of data in relevant preclinical or clinical settings, the sponsor's claim of treating refractory disease as a significant benefit basis may not be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 July 2015, prior to final opinion.

2.1.3. - EMA/OD/039/15

Treatment of cystic fibrosis

COMP coordinator: Judith Eggenhofer

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

It appears that the sponsor is citing data from the literature reporting effects of some of the extracts composing the proposed product that may be relevant to the treatment of cystic fibrosis. However no data are presented with the complete product mix in cystic fibrosis patients and/or in models of the condition.

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of cystic fibrosis, the sponsor was asked to further elaborate on:

- the relevance of the data reported for single components to the overall assumed clinical effects of the proposed product;

- the methodology of the studies presented to support the medical plausibility, including the chamber studies and the muco-ciliary clearance studies;

- the details of the studies describing the antibacterial activity;

- the extrapolation of data obtained in rhinosinusitis to the treatment of cystic fibrosis.

- Significant benefit

In order to further justify the significant benefit the sponsor is invited to further justify the potential clinically relevant advantage of the proposed product in relation to the currently authorized treatments for cystic fibrosis based on any available data.

In the written response, and during an oral explanation before the Committee on 14 July 2015, the sponsor elaborated on the mucosecretolytic, the anti-inflammatory and anti-bacterial effects of the constituents of the product, and asserted that it has been optimized to treat highly relevant symptoms of cystic fibrosis. It was further claimed that this optimized combination had also been identified to target additional CF-related mechanisms. The COMP considered that in the absence of data in relevant models of the condition with the proposed product, the medical plausibility and significant benefit could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 July 2015, prior to final opinion.

2.1.4. - EMA/OD/049/15

Treatment of uveal melanoma

COMP coordinator: Armando 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:

- Intention to diagnose, prevent or treat

The proposed condition should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of uveal melanoma, the sponsor was asked to further elaborate on:

- the relevance of the preclinical model used for the treatment of uveal melanoma, and the interpretation of the results obtained in the experiments and their specificity for uvea melanoma;

- the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition or other forms of melanoma.

- 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.

As it seems that the sponsor has excluded part of the population affected by condition.

- Significant benefit

Approved treatments for cutaneous melanoma appear to be also used for liver metastasis associated with uvea melanoma. The arguments on significant benefit are based on the new mechanism of action which targets the condition 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 in vivo pre-clinical 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 14 July 2015, the sponsor discussed the differences and similarities between uveal and other forms of melanoma, as well as the applicability of the proposed treatment in other types of the condition. Further clarifications on the prevalence calculations and significant benefit were also presented.

The COMP considered that uveal melanoma could not be considered a distinct condition from other melanomas, given the commonalities in the aetiology, histology and clinical characteristics. It was also considered that the proposed indication is not a justified subset, as the active substance might also work in other melanoma types. As such the proposed indication would not be a valid indication for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 July 2015, prior to final opinion.

2.1.5. Glycyl-L-2-methylprolyl-L-glutamic acid - EMA/OD/056/15

QRC Consultants Ltd.; Treatment of Rett Syndrome

COMP coordinator: Ingeborg 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Rett syndrome, the sponsor should further elaborate on:

- the relevance of the preclinical epilepsy model used to measure the effects of the sponsor's product for the treatment of Rett syndrome, and the interpretation of the results obtained in the experiments;

- the relevance of the Phase II clinical study in the treatment of Rett syndrome, and the interpretation of the results obtained in particular the six core parameters measured.

In the written response, and during an oral explanation before the Committee on 15 July 2015, the sponsor further elaborated on the preclinical and clinical data included in the application. In particular with regards to the preliminary clinical study, the sponsor discussed the endpoints studied [Motor Behavior Assessment (MBA), Clinical Global Impression of Improvement (CGI-I), Caregiver Top 3 Concerns Assessment, Aberrant Behaviour Checklist-total score (ABC), Clinical Severity Scale-Change Index (CSS), the modified apnea index] as well as the results from these assessments.

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

The intention to treat the condition with the medicinal product containing glycyl-L-2-methylprolyl-L-glutamic acid was considered justified based on preliminary clinical data in patients with the condition showing improvement in parameters associated with condition.

The condition is chronically debilitating and life-threatening particularly due to severe locomotor disability, sleep disturbances, seizures, respiratory complications, development of arrhythmias resulting in decreased life-expectancy.

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 glycyl-L-2-methylprolyl-L-glutamic acid, for treatment of Rett syndrome, was adopted by consensus.

2.1.6. Human allogeneic bone marrow derived osteoblastic-like cells - EMA/OD/053/15

Bone Therapeutics SA; Treatment of osteogenesis imperfecta and osteogenesis imperfecta-related disorders

COMP coordinator: Vallo Tillmann

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 committee could accept osteogenesis imperfecta (OI) as a distinct medical entity for orphan designation.

The sponsor is invited to further justify the proposed orphan condition encompassing osteogenesis imperfecta and osteogenesis imperfecta-related disorders as one distinct medical entity, focusing on clarifying commonalities and differences between osteogenesis imperfecta and the individual disorders of the osteogenesis imperfecta-related disorder group, with regards to aetiology, pathophysiology, histopathology, and clinical characteristics.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of osteogenesis imperfecta and osteogenesis imperfecta-related disorders, the sponsor is invited to:

- clarify the extent of evidence gathered for each of the studies presented to support medical plausibility;

- clarify if studies with the product have been performed in valid OI disease models (e.g. transgenic models of OI);

- discuss the adequacy of the presented bone-formation models.

- Number of people affected

The sponsor should conclude on one prevalence estimate for the proposed orphan condition (osteogenesis imperfecta and osteogenesis imperfecta-related disorders), while taking into account the above discussion on the validity of the proposed orphan condition as one distinct medical entity.

Regarding osteogenesis imperfecta: The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers of European origin. Non-European prevalence data cannot be used.

Regarding osteogenesis imperfecta-related disorders: The applicant quotes that due to the rarity of most of the OI-related disorders the prevalence is negligible and concludes on a prevalence estimate of below 0.1 in 10.000. It is unclear how this estimate was established in light of very limited evidence. The sponsor should justify the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 15 July 2015, the sponsor further elaborated on the nosology of genetic skeletal disorders. The data to justify medical plausibility were also discussed, referring to in vitro mineralisation assays and bone repair and engraftment in vivo. With regards to the in vivo models used, it was stressed that the nature of the product would necessitate its testing in immunodeficient preclinical models, while the already established transgenic models of osteogenesis imperfecta in the literature are immunocompromised. Moreover, the sponsor provided further clarifications with regards to the prevalence calculations.

The COMP, with regards to the condition, acknowledged that the genetic background of osteogenesis imperfecta in itself and in osteogenesis imperfecta related syndromes is diverse and that all the mentioned syndromes share certain clinical characteristics with regards to the fragility of the bone structure. Nevertheless, the COMP is of the opinion that the syndromes that were grouped by the sponsor into the term “osteogenesis imperfecta-related disorders” separate from the osteogenesis imperfecta in the context of other clinical characteristics, histopathology and pathophysiology. Therefore, the COMP decided to exclude “osteogenesis imperfecta-related disorders” from the condition and narrow the orphan indication to “treatment of osteogenesis imperfecta”.

With regards to the medical plausibility, the COMP acknowledged that studies in immunocompetent in vivo models could not be performed, and appreciated the clarification on the extent of evidence provided by the sponsor.

With regards to the prevalence, the COMP accepted the re-submitted prevalence calculation for osteogenesis imperfecta. Furthermore, the prevalence estimate methodology regarding osteogenesis imperfecta-related disorders has been clarified.

Following review of the application by the Committee, it was agreed to rename the indication to human allogeneic bone-marrow-derived osteoblastic cells.

The Committee agreed that the condition, human allogeneic bone-marrow-derived osteoblastic cells, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human allogeneic bone-marrow-derived osteoblastic cells was considered justified based on preclinical in vivo data demonstrating formation of new bone structures and improvement of bone repair.

The condition is chronically debilitating due to fragile bones, multiple fractures and bone deformations leading to persistent physical and functional limitations, pain and restrictions in daily life activities.

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 human allogeneic bone-marrow-derived osteoblastic cells, for treatment of human allogeneic bone-marrow-derived osteoblastic cells, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride - EMA/OD/085/15

Khondrion BV; Treatment of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

COMP coordinator: Giuseppe Capovilla

The Committee agreed that the condition, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride was considered justified based on data from a pre-clinical in vivo model of the condition showing an improvement in symptoms associated with the condition.

The condition is life-threatening due to reduced life-expectancy and chronically debilitating due to generalised tonic-clonic seizures, recurrent headaches, anorexia, recurrent vomiting, exercise intolerance, proximal limb weakness, sensorineural hearing loss and stroke-like episodes of transient hemiparesis or cortical blindness with the onset between the ages of 2 and 10 years.

The condition was estimated to be affecting approximately 0.06 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 (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride, for treatment of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, was adopted by consensus.

2.2.2. 2-(2-phenylvinyl)-4-[4- methylpiperazin-1-yl)]-6-(5-methyl-2H-pyrazol-3-yl-amino)-pyrimidine L(+) tartrate salt - EMA/OD/087/15

Dr Ulrich Granzer; Treatment of hepatocellular carcinoma

COMP coordinator: Daniel O'Connor

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

The intention to treat the condition with the medicinal product containing 2-(2-phenylvinyl)-4-[4-methylpiperazin-1-yl)]-6-(5-methyl-2H-pyrazol-3-yl-amino)-pyrimidine L(+) tartrate salt was considered justified based on preclinical data showing antitumor activity of the proposed product.

The condition is life-threatening because it is often discovered in advanced phase, and survival following diagnosis is approximately 6 to 20 months. The main chronically debilitating manifestations include abdominal pain, weight loss, ascites, encephalopathy, jaundice and variceal bleeding.

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 2-(2-phenylvinyl)-4-[4-methylpiperazin-1-yl)]-6-(5-methyl-2H-pyrazol-3-yl-amino)-pyrimidine L(+) tartrate salt may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing increased efficacy of the proposed product as compared to authorised products for the condition, and preliminary clinical data showing favourable clinical response in one patient with hepatocellular carcinoma relapsed after previous treatment with the currently authorised products for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by hepatocellular carcinoma.

A positive opinion for 2-(2-phenylvinyl)-4-[4-methylpiperazin-1-yl)]-6-(5-methyl-2H-pyrazol-3-yl-amino)-pyrimidine L(+) tartrate salt, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.2.3. 2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)- 2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl -(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidilyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidine, sodium salt - EMA/OD/084/15

PhaRA bvba; Treatment of diffuse large B-cell lymphoma

COMP coordinator: Frauke 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 2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)- 2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidilyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidine, sodium salt was considered justified based on pre-clinical in vivo studies demonstrating tumour volume reduction and improved survival with treatment in relevant disease models, and preliminary clinical data demonstrating that relapsed/refractory patients with the condition respond to the treatment with the product.

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 with 5-year survival rates reported as low as approximately one in four patients for the high risk group.

The condition was estimated to be affecting approximately 2.3 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'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)- 2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidilyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidine, sodium salt may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing complete or partial responses in relapsing patients, or in patients that are refractory to alternative treatment options. The Committee considered that this constitutes a clinically relevant advantage for patients affected by the condition.

A positive opinion for 2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)- 2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxyguanosylyl-(3',5'-phosphoryl)-2'-deoxycytidilyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-(3',5'-phosphoryl)-2'-deoxythymidylyl-(3',5'-phosphoryl)-2'-deoxyadenosyl-(3',5'-phosphoryl)-2'-deoxycytidylyl-

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2.2.4. Adeno-associated viral vector serotype 8 containing the human *MTM1* gene - EMA/OD/074/15

Audentes Therapeutics UK Limited; Treatment of X-linked myotubular myopathy

COMP coordinator: Flavia Saleh

The Committee agreed that the condition, X-linked myotubular myopathy, 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 8 containing the human *MTM1* gene was considered justified based on pre-clinical in vivo models of the condition showing improvement in motor function.

The condition is life-threatening due to a life-expectancy of usually less than two years although children with milder forms can live longer. It is chronically debilitating due to marked weakness and hypotonia, external ophthalmoplegia and respiratory failure. Milder forms are associated with neonatal low muscle tone, severe weakness, delayed developmental milestones (particularly gross motor milestones such as head control, crawling, and walking) and pulmonary complications.

The condition was estimated to be affecting approximately 0.02 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 8 containing the human *MTM1* gene, for treatment of X-linked myotubular myopathy, was adopted by consensus.

2.2.5. Adeno-associated virus serotype 9 vector containing human iduronate-2-sulfatase - EMA/OD/076/15

Laboratorios del Dr. Esteve, S.A.; Treatment of mucopolysaccharidosis type II (Hunter's syndrome)

COMP coordinator: Josep Torrent-Farnell

The Committee agreed that the condition, mucopolysaccharidosis type II (Hunter's 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 iduronate-2-sulfatase gene was considered justified based on a preclinical model of the condition where the sponsor has showed that treatment with the product improves iduronate-2-sulfatase activity and related pathology.

The condition is chronically debilitating due to neurological decline, cardiovascular and pulmonary complications and life-threatening as indicated by the survival of the patients that can be limited to 10-15 years.

The condition was estimated to be affecting not more than 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 adeno-associated viral vector serotype 9 containing the human iduronate-2-sulfatase gene may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data with a surrogate product that demonstrate improved central nervous system pathology and behaviour as a result of treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 9 containing the human iduronate-2-sulfatase gene, for treatment of mucopolysaccharidosis type II (Hunter's syndrome), was adopted by consensus.

2.2.6. Allogeneic umbilical cord blood cells treated ex vivo with 16,16-dimethyl prostaglandin E2 - EMA/OD/090/15

Fate Therapeutics, LTD; Treatment of acute lymphoblastic leukaemia

The Committee agreed that the condition, acute lymphoblastic leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic umbilical cord blood cells treated ex vivo with 16,16-dimethyl prostaglandin E2 was considered justified based on preclinical and preliminary clinical data showing faster homing and engraftment of the umbilical cord blood cells treated with the proposed product.

The condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymph nodes and other lymphatic organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage.

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 allogeneic umbilical cord blood cells treated ex vivo with 16,16-dimethyl prostaglandin E2 may be of significant benefit to those affected by the condition. The sponsor has provided preclinical and preliminary clinical data that demonstrate faster homing and engraftment of the haematopoietic cells, with earlier reconstitution of bone marrow function with the proposed product. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acute lymphoblastic leukaemia.

A positive opinion for allogeneic umbilical cord blood cells treated ex vivo with 16,16-dimethyl prostaglandin E2, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.2.7. - EMA/OD/077/15

Treatment of mantle cell lymphoma

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 September meeting.

2.2.8. - EMA/OD/078/15

Treatment of primary mediastinal large B-cell lymphoma

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 September meeting.

2.2.9. - EMA/OD/066/15

Treatment of Dravet Syndrome

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 September meeting.

2.2.10. - EMA/OD/065/15

Treatment of Lennox-Gastaut Syndrome

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 September meeting.

2.2.11. Fibrinogen-coated albumin spheres - EMA/OD/060/15

Fibreu Limited; Treatment of acute radiation syndrome

COMP coordinator: Adriana Andrić

The Committee agreed that the condition, acute radiation syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fibrinogen-coated albumin spheres was considered justified based on pre-clinical in vivo models of the condition showing improved survival following treatment.

The condition is life-threatening due to multiorgan failure and carcinogenesis and chronically debilitating due to hematopoietic, gastrointestinal, neurological and vascular symptoms associated with multiorgan dysfunction.

The condition was estimated to be affecting not more than 0.01 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 fibrinogen-coated albumin spheres, for treatment of acute radiation syndrome, was adopted by consensus.

2.2.12. Fixed-dose combination of fosfomycin disodium and tobramycin - EMA/OD/068/15

CURx Pharma (UK) Limited; Treatment of cystic fibrosis

COMP coordinator: Judith 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 fixed-dose combination of fosfomycin disodium and tobramycin was considered justified based on preliminary clinical data showing stable lung function over 28 days versus placebo.

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 less than 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 fixed-dose combination of fosfomycin disodium and tobramycin may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing stable lung function after a run in period with aztreonam, currently authorised for the condition. Furthermore, the product offers a broader antibiotic spectrum than tobramycin alone, also authorized for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by cystic fibrosis.

A positive opinion for fixed-dose combination of fosfomycin disodium and tobramycin, for treatment of cystic fibrosis, was adopted by consensus.

2.2.13. - EMA/OD/079/15

Treatment of retinal artery occlusion

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 September meeting.

2.2.14. Ibrutinib - EMA/OD/082/15

Janssen-Cilag International N.V.; Treatment of marginal zone lymphoma

COMP coordinator: Katerina Kubáčková

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 ibrutinib was considered justified based on preliminary clinical data in patients with the condition showing response.

The condition is chronically debilitating and life-threatening 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 up to 90%.

The condition was estimated to be affecting approximately 0.7 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 ibrutinib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate responses in relapse or refractory patients. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.15. - EMA/OD/083/15

Treatment of cervical cancer

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 September meeting.

2.2.16. - EMA/OD/088/15

Treatment of aneurysmal subarachnoid hemorrhage (aSAH)

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 September meeting.

2.2.17. - EMA/OD/062/15

Treatment of snakebite envenomation

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 September meeting.

2.2.18. Recombinant human acid ceramidase - EMA/OD/061/15

Plexcera Therapeutics EU Limited; Treatment of cystic fibrosis

COMP coordinator: Judith 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 recombinant human acid ceramidase was considered justified based on pre-clinical in vivo data using a valid model of the condition which showed a reduction in infections.

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 less than 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 recombinant human acid ceramidase may be of significant benefit to those affected by the condition. The sponsor has provided preclinical in vivo data that demonstrate that the product can reduce infections associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human acid ceramidase, for treatment of cystic fibrosis, was adopted by consensus.

2.2.19. - EMA/OD/067/15

Treatment of progressive supranuclear palsy

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 September meeting.

2.2.20. - EMA/OD/075/15

Treatment of hereditary angioedema

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 September meeting.

2.2.21. - EMA/OD/073/15

Treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia

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 September meeting.

2.2.22. - EMA/OD/092/15

Treatment of chronic iron overload requiring chelation therapy

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 September meeting.

2.2.23. - EMA/OD/071/15

Treatment of primary graft dysfunction following lung transplantation

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 September meeting.

2.2.24. CD33-directed antibody-drug conjugate consisting of an antibody conjugated to a DNA cross-linking pyrrolobenzodiazepine dimer drug - EMA/OD/089/15

Seattle Genetics UK, Limited; Treatment of acute myeloid leukaemia

COMP coordinator: Karri Penttila

The Committee agreed that the condition, acute myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing CD33-directed antibody-drug conjugate consisting of an antibody conjugated to a DNA cross-linking pyrrolobenzodiazepine dimer drug was considered justified based on preclinical in vivo studies showing tumour size reduction and improved survival with treatment in a relevant disease model, and preliminary clinical data showing that treatment improved bone marrow blast clearance in patients with the condition.

The condition is life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections.

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 CD33-directed antibody-drug conjugate consisting of an antibody conjugated to a DNA cross-linking pyrrolobenzodiazepine dimer drug may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate improved antineoplastic efficacy and improved tumour volume reduction when used on top of already authorised compounds. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for CD33-directed antibody-drug conjugate consisting of an antibody conjugated to a DNA cross-linking pyrrolobenzodiazepine dimer drug, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.25. Verucerfont - EMA/OD/063/15

Neurocrine Therapeutics Ltd; Treatment of congenital adrenal hyperplasia

COMP coordinator: Vallo Tillmann

The Committee agreed that the condition, congenital adrenal hyperplasia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing verucerfont was considered justified based on preclinical and preliminary clinical data showing an effect on plasma levels of biomarkers relevant to the condition.

The condition is life-threatening and chronically debilitating due to the development of adrenal insufficiency, precocious puberty, virilisation in females, hyponatremia, hyperkalaemia, dehydration and hypotension.

The condition was estimated to be affecting approximately 0.6 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 verucerfont may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing reduction of plasma levels in clinically relevant biomarkers of the condition in treated patients. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for verucerfont, for treatment of congenital adrenal hyperplasia, was adopted by consensus.

2.3. Revision of the COMP opinions

2.3.1. Lanreotide acetate - EMA/OD/027/15

Prof. Dr R.T. Gansevoort; Treatment of autosomal dominant polycystic kidney disease

COMP coordinator: Josep Torrent-Farnell

The Committee agreed that the condition, autosomal dominant polycystic kidney disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing lanreotide acetate was considered justified based on preliminary clinical data showing improvements in renal volume in patients affected by the condition.

The condition is life-threatening and chronically debilitating due to renal manifestations such as renal cyst infection, nephrolithiasis, and kidney failure requiring dialysis, as well as due to extra renal manifestations such as liver cysts, intracranial aneurysms, mitral valve prolapse and diverticulosis.

The condition was estimate to be affecting between 4.2 and 4.7 in 10,000 persons in the European Union, at the time the application was made. This calculation included a sensitivity analysis.

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 lanreotide acetate may be of significant benefit to those affected by the condition. This is based on a novel mechanism of action that targets receptors whose expression is not just limited to kidney tissue. Therefore the product may exert beneficial effects in extra-renal manifestations of the condition, which is also supported by bibliographic data in polycystic liver disease.

A positive opinion for lanreotide acetate, for treatment of autosomal dominant polycystic kidney disease, was adopted by consensus via written procedure on 21 July 2015.

2.4. COMP opinions adopted via written procedure following previous meeting

None.

2.5. Appeal

None.

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP coordinators

COMP coordinators were appointed for 4 applications submitted,19 upcoming applications and 1 amendment of an existing orphan drug designation application.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of follicular lymphoma

3.1.2. -

Treatment of graft-versus-host disease

3.1.3. -

Treatment of sickle cell disease

3.2. Finalised letters

3.2.1. -

Treatment of Niemann-Pick disease

The finalised letter was circulated for information.

3.2.2. -

Treatment of Graft-versus-Host disease

The finalised letter was circulated for information.

3.2.3. -

Treatment of Urea Cycle Disorders:

a) treatment of ornithine transcarbamylase deficiency;

b) treatment of carbamoyl-phosphate synthase-1 deficiency;

c) treatment of citrullinaemia type 1;

d) treatment of argininosuccinic aciduria;

e) treatment of hyperargininaemia;

f) treatment of N-acetylglutamate synthetase (NAGS) deficiency;

g) treatment of citrullinaemia type 2;

h) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) .

The finalised letter was circulated for information.

3.2.4. -

Treatment of pancreatic cancer condition

The finalised letter was circulated for information.

3.2.5. -

Treatment of Dravet syndrome

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of systemic sclerosis

The new request was noted.

3.3.2. -

Treatment of ovarian cancer

The new request was noted.

3.3.3. -

Treatment of acromegaly

The new request was noted.

3.3.4. -

Treatment of Prader-Willi syndrome

The new request was noted.

4. Review of orphan designation for orphan medicinal products for marketing authorisation

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

4.1.1. FARYDAK - panobinostat - EMEA/H/C/003725, EMA/OD/113/12, EU/3/12/1063

Novartis Europharm Ltd; Treatment of multiple myeloma

COMP coordinator: Frauke Naumann-Winter

Two lists of issues were sent to the sponsor for response. The sponsor was asked to elaborate on the following issues:

- Condition

The sponsor was requested to change the condition from multiple myeloma to plasma cell myeloma which is currently more in line with current WHO classification.

- Justification of significant benefit

The COMP has noted that there are many products authorised for use in this condition in Europe. The sponsor is asked to discuss in more detail the significant benefit of panobinostat within the context of the target patient population and authorised treatment alternatives recommended for use in these patients such as pomalidomide with regards to efficacy and safety.

- Prevalence

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:

http://www.ema.europa.eu/pdfs/human/comp/043601.pdf

The sponsor is therefore asked to re-address the prevalence of plasma cell myeloma in the EU, critically reviewing and discussing the following aspects:

- the impact of the change in classification between the orphan designation, the coding of condition in the literature or registries referred to, and the maintenance of the orphan designation at MA;
- the impact of the increasing survival of patients with MM due to improvements in treatment outcomes, especially in the last decade;
- the impact on potential rise in incidence in myeloma (e.g. refer to Turesson I, Velez R, Kristinsson SY, Landgren O. Mayo Clin Proc. 2010 Mar;85(3):225-30);
- the impact of potential spatial variation when data from individual EU Members States or regional registries are used and justify the validity of extrapolations to the entire EU is made.

Significant sources of bias for any extrapolation should be taken into account, e.g. due to the data collection process into cancer registries, or the impact of the delay between data collection, publication and the time of application for maintenance of orphan designation,

also in view of the potential temporal variation expected to occur due to an ageing population in the EU. Sensitivity analyses on critical assumptions were requested.

In its written responses, the sponsor appreciated that plasma cell myeloma is the more current term for the designated condition. With regards to the prevalence, the applicant provided an updated calculation as per the request of the committee, and presented an estimated complete prevalence in 2015 of 3.30 per 10,000 for the EU28.With regards to the significant benefit, the sponsor discussed the available options for relapsed patients affected by the condition and discussed the results of the large clinical phase III study in relapsed and refractory patients who had received 1-3 prior lines of therapy.

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 multiple myeloma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 3.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to the accumulation of monoclonal myelomatous cells in the bone marrow, causing disruption of the normal bone marrow function with pancytopenia and osteolysis. Opportunistic infections, hypercalcemia, and kidney failure are common clinical consequences of the disease. The median survival is 6 years.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Farydak may be of potential significant benefit to those affected by the orphan condition still holds due to an increase in progression-free survival in patients with relapsed and/or refractory multiple myeloma after having received at least two previous treatments including bortezomib and immune-modulatory agents.

An opinion not recommending the removal of Farydak, panobinostat (EU/3/12/1063) for treatment of multiple myeloma 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.

4.1.2. Kanuma - sebelipase alfa - EMEA/H/C/004004, EMA/OD/104/10, EU/3/10/827

Synageva BioPharma Ltd; Treatment of lysosomal acid lipase deficiency

COMP coordinator: Josep Torrent-Farnell

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 lysosomal acid lipase deficiency (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be not more than 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and median survival is 1 year and chronically debilitating due to massive accumulation of lipid material in a number of tissues and a disturbance in cholesterol and lipid homeostatic mechanisms, including substantial increases in hepatic cholesterol.

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 Kanuma, recombinant human lysosomal acid lipase, sebelipase alfa, (EU/3/10/827) for the treatment of lysosomal acid lipase deficiency 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.

4.1.3. Raxone - idebenone - EMEA/H/C/003834, EMA/OD/076/06, EU/3/07/434

Santhera Pharmaceuticals (Deutschland) GmbH; Treatment of Leber's hereditary optic neuropathy

COMP coordinator: Kerstin Westermark

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 Leber's hereditary optic neuropathy (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating, in particular due to visual loss and development of blindness.

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 Raxone, idebenone, (EU/3/07/434) for treatment of Leber's hereditary optic neuropathy 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.

4.1.4. Strensiq - asfotase alfa - EMEA/H/C/003794, EMA/OD/071/08, EU/3/08/594

Alexion Europe SAS; Treatment of hypophosphatasia

COMP coordinator: Vallo Tillmann

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 hypophosphatasia (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.5 in 10,000 persons in the Community, at the time the application was made.

The condition is chronically debilitating and life threatening due to impaired mineralization of bones and early mortality.

There is, at present, no satisfactory treatment that has been authorised in the Community for patients affected by the conditionthere 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 Strensiq, recombinant human tissue non-specific alkaline phosphatase - Fc - deca-aspartate fusion protein, asfotase alfa,(EU/3/08/594) for treatment of hypophosphatasia from the EC Register of Orphan Medicinal Products was adopted by consensus via written procedure on 22 July 2015.

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

4.1.5. Heparesc - human heterologous liver cells - ATMP - EMEA/H/C/003750

Cytonet GmbH&Co KG;

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EMA/OD/108/10, EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EMEA/OD/042/07, EU/3/07/470)

c) treatment of citrullinaemia type 1 (EMA/OD/105/10, EU/3/10/818)

d) treatment of hyperargininaemia (EMA/OD/106/10, EU/3/10/819)

e) treatment of argininosuccinic aciduria (EMA/OD/107/10, EU/3/10/820)

COMP coordinator: Kerstin Westermark

CHMP negative opinion was noted.

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

4.2.1. - isavuconazole – EMEA/H/C/002734

Basilea Medical Ltd;

a) treatment of invasive aspergillosis (EMA/OD/009/14, EU/3/14/1284)

b) treatment of mucormycosis (EMA/OD/010/14, EU/3/14/1276)

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 September meeting.

4.2.2. - susoctocog alfa – EMEA/H/C/002792, EMA/OD/043/10, EU/3/10/784

Baxalta Innovation GmbH; Treatment of haemophilia A

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 September meeting.

4.2.3. - recombinant l-asparaginase – EMEA/H/C/002661

medac Gesellschaft fuer klinische Spezialpraeparate mbH; Treatment of acute lymphoblastic leukaemia

Status of the procedure at the CHMP was noted.

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 4 applications.

5. Organisational, regulatory and methodological matters

5.1. Mandate and organisation of the COMP

5.1.1. Strategic Review & Learning meetings

COMP/PDCO Strategic Review & Learning Meeting under the Luxembourg Presidency to be held on 15-16 October 2015 in Bonn

All COMP members were invited to the joint PDCO/COMP SRL meeting organised under the Luxembourg presidency that will be hosted by BfArM. Members should register by 17 August. Regardless the joint meeting with PDCO, EMA cross agency rules regarding reimbursement for some non-NCA affiliated members apply as usual.

The Chair thanked DE for stepping in during the Luxemburg presidency. He is currently in contact with the PDCO Chair and DE colleagues for details of the preparation/agenda.

5.1.2. Election of Chair and Vice-Chair – 6 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.

5.2. Coordination with EMA Scientific Committees or CMDh-v

5.2.1. Enhanced early dialogue to foster development and facilitate accelerated assessment

The Committee was informed of the development of a new scheme that is designed to facilitate the development and accelerated assessment of innovative medicines of major public health interest in particular from the viewpoint of therapeutic innovation.

COMP members welcomed the initiative and asked for clarification on key challenges such as the criteria (based on data situation) to be used to identify ‘break-through’ products. Concerns were expressed that without an appropriate filter system in place, EMA could be overwhelmed with too weak applications (reference was made to experience gained with a

comparable initiative at FDA). It was stressed that the final accessibility for patients with costs/HTA considerations will have to be tackled at early stage to make sure that accelerated authorisations will result in the innovative medicines to be available to the patients. Some confusion regarding the overlap with this initiative with other initiatives, primarily adaptive licensing, was clarified. The involvement of patient organisation representatives to identify unmet medical needs as trigger for therapeutic innovation was encouraged based on experiences at COMP. Finally, the need for an appropriate and practical policy of conflict of interest in respect to Academia based on EMA standard rules was emphasised.

The COMP Chair asked for updates in the future.

5.2.2. Guidance on Uncertainty in EFSA Scientific Assessment

The guidance was circulated for comments.

5.3. Coordination with EMA Working Parties / Working Groups / Drafting Groups

5.3.1. Significant Benefit Working Group

The working group on Significant Benefit met on 17 July 2015.

5.3.2. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP)

EMA Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting agenda was circulated for information.

5.4. Cooperation within the EU regulatory network

5.4.1. European Commission

None.

5.5. Cooperation with International Regulators

5.5.1. Food and Drug Administration (FDA)

EMA/FDA teleconference on Orphan Medicines – 9 June 2015

The agenda was circulated for information.

5.5.2. Ministry of Health, Labour and Welfare (MHLW) - Pharmaceuticals and Medical Devices Agency (PMDA)

EMA/MHLW-PMDA teleconference on Orphan Medicines – 23 June 2015

The agenda was circulated for information.

5.5.3. EMA/MHLW/PMDA/NIBIOHN Orphan Drugs/ Orphan Devices Workshop

5.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None.

5.7. COMP work plan

Work plan 2015 tracking and drafting 2016

The rationale and principles for the new harmonised approach on committee work plan development and tracking was presented. Format and periods covered are now aligned between committees allowing linkage to the agency work programmes, identification of cross committee relevance and subsequent coordination. The newly developed tool helps to track the status in a given year by recording activities against objectives. It is foreseen to start draft work plans mid-year to achieve adjustment and finalisation between committee and EMA plans by start of the following year.

It was clarified that the overview of the cross-committee / cross agency relevance projects included in the presentation was not up to date. The Chair confirmed that at the scientific coordination board Chairs were consulted and it was differentiated between active drivers, involvement and interest only.

The Chair endorsed in principle the given timelines and welcomed the support by the secretariat in monitoring the progress.

5.8. Planning and reporting

5.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015 was circulated.

5.8.2. Overview of orphan marketing authorisations/applications

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

5.8.3. Meeting dates

The EMA presented COMP meeting dates for 2016-2018 to the Committee.

The rationale behind some changes in the meeting dates was explained with considerations to achieve a more even distribution per month while maintaining the procedure-determined order of committee meetings. Changes refer mainly to CVMP, COMP and HMPC.

COMP members were invited to send comments in writing.

5.8.4. Map for potential orphan medicinal product applicants for publication on EMA website

EMA presented the draft for the intended map to be published on the EMA website for companies to better visualise the principles of orphan designation/application. Some improvements were proposed and discussed. It was reminded that the graph may not reflect all details of COMP practice but aims to present to applicants the principles in a simple way. Some minor changes may be introduced and members may be consulted, otherwise the map was endorsed in principle.

6. Any other business

6.1. Eurordis Summer School

The report from the EURORDIS summer school was welcomed. EURODIS clarified the COMP involvement in the initiative and overlap with other initiatives and informed the COMP about the number of patient representatives trained annually.

List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 14-16 July 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	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Andri Andreou	Member	Cyprus	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	
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	
Sigurdur B. Thorsteinsson	Member	Iceland	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	Member	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Stoyanova				
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Flavia Saleh	Member	Romania	No interests declared	
Martin Možina	Member	Slovenia	No interests declared	
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	
Mario Ricciardi	Member	Patients' Organisation Representative		
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 meetings	
Julian Isla	Observer	Eurordis	No restrictions applicable to meetings	
Petronella Ottevanger	Expert - via telephone*		No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the product(s) they have been invited to talk about.