5 October 2017
EMA/COMP/583563/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 05-07 September 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

05 September 2017, 09:00-18:00, room 2F

06 September 2017, 08:30-19:00, room 2F

07 September 2017, 08:30-12:00, room 2F

Disclaimers

Some of the information contained in this set of 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 set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Further information with relevant explanatory notes can be found at the end of this document.

Note on access to documents

Some documents mentioned in the 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

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 05-07 September 2017 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 11-13 July 2017 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/088/17

Treatment of growth hormone deficiency

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 potential major contribution to patient care in the condition.

The sponsor is requested to discuss the arguments for significant benefit *vs.* Somatropin Biopartners and to elaborate on the results from the clinical study to justify the assumption of significant benefit on this product.

In the written response, and during an oral explanation before the Committee on 05 September 2017, the sponsor acknowledged that Somatropin Biopartners was still authorised. Significant benefit was argued based on safety and a major contribution to patient care due to the ease of use of the product. The COMP indicated that the safety data was too preliminary for an assumption of significant benefit. The COMP recognised that the proposed delivery of the product could improve compliance however, as there was no appropriate patient reported outcome an evaluation of the major contribution to patient care could not be assumed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 05 September 2017, prior to final opinion.

2.1.2. - EMA/OD/089/17

Treatment of pulmonary arterial hypertension

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 pulmonary arterial hypertension, the sponsor should further elaborate on:

- the lack of reproducibility of the therapeutic effect of the proposed product on survival from studies,
- the lack of effect on survival with the treatment combination of the proposed product and sildenafil.

- Significant benefit

The sponsor is invited to further justify the significant benefit in relation to the currently authorised products for the treatment of pulmonary arterial hypertension, keeping in mind the current treatment algorithm of the condition.

This should be supported by data showing advantages of the proposed product as compared to the authorised ones on relevant pulmonary arterial hypertension clinical endpoints, e.g. haemodynamic and pathology parameters, in models where the proposed product was used in therapeutic setting.

In the written response, and during an oral explanation before the Committee on 05 September 2017, the sponsor presented the merits of the pre-clinical *in vivo* model to establish the plausibility of the product in the condition. The COMP discussed at length the strengths and weaknesses of the model proposed for both the medical plausibility and significant benefit. The COMP was of the opinion that better pre-clinical *in vivo* models existed to establish both criteria and that the model proposed by the sponsor was not strong enough to establish if the product met the criteria.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 September 2017, prior to final opinion.

2.1.3. - EMA/OD/292/16

Treatment of ATTR amyloidosis

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 15 August 2017, prior to responding to the list of issues.

Notes:
There has been 1 designation for this condition: EMA/OD/098/13 Phosphorothioate oligonucleotide targeted to transthyretin

Designation withdrawn: EMA/OD/194/13 Synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues

2.1.4. - EMA/OD/090/17

Treatment of glioblastoma

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 15 August 2017, prior to responding to the list of issues.

Notes:
Designation withdrawn: EMEA/OD/012/00 Fluorouracil

2.1.5. - EMA/OD/059/17

Treatment of short bowel syndrome

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 COMP has assessed the same set of data previously and has established that the level of evidence is insufficient to establish medical plausibility. Medical plausibility cannot be established without additional interventional data in short bowel syndrome patients or specific preclinical models of short bowel syndrome. In the absence of specific and relevant data in the written responses submitted to the Committee, the COMP had insufficient evidence and justification to invite the Sponsor to present an Oral Explanation at the COMP Plenary Meeting.

- Number of people affected

The COMP has assessed the same set of data previously and has established that the current methodology and data is insufficient to establish prevalence. In the absence of specific and relevant epidemiological data/methodology in the written responses submitted to the Committee, the COMP had insufficient evidence and justification to invite the Sponsor to present an Oral Explanation at the COMP Plenary Meeting.

- Significant benefit

The COMP has assessed the same set of data previously and has established that the level of evidence is insufficient to establish significant benefit. Significant benefit cannot be established without additional interventional data in short bowel syndrome patients or specific preclinical models of short bowel syndrome, which allow for the positioning of the product in the phase of intestinal adaption of short bowel syndrome. In the absence of specific and relevant data in the written responses submitted to the Committee, the COMP had insufficient evidence and justification to invite the Sponsor to present an Oral Explanation at the COMP Plenary Meeting.

In the written response, the sponsor claimed that the bibliographical data which covered some preliminary pre-clinical *in vivo* data generated in models of the condition were sufficient for the establishment of the plausibility and significant benefit. The COMP was of the opinion that the data was inconclusive and not adequate to establish either criteria as it did not take into consideration some of the other therapies used to treat the condition. The sponsor believed that the incidence of parenteral nutrition was sufficient to establish the prevalence. The COMP was not of the same opinion indicating that certain forms of the condition did not need this form of nutrition and therefore not all the patients who could be affected were included.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 September 2017, prior to final opinion.

2.1.6. Melatonin - EMA/OD/039/17

Therapicon Srl; Treatment of partial deep dermal and full thickness burns

COMP coordinator: Martin Možina

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 sponsor is invited to present relevant preclinical or clinical data specific to the condition supporting the significant benefit of the proposed product *versus* the existing authorised products and supportive intensive care measures used in the condition.

In absence of relevant data in the written responses submitted to the Committee, the COMP had insufficient evidence and justification to invite the sponsor to present an oral explanation at the COMP plenary meeting.

In the written response, the sponsor presented published data concerning a pilot clinical trial without any information regarding the study methodology and the handling of a large variety of burn severities across treatment and control arms. It remained unclear if the standard of care included the authorised treatments for which significant benefit need to be established. Therefore, the COMP concluded that significant benefit was not justified for the purpose of orphan designation.

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on bibliographic preclinical data demonstrating that treatment with the product reduced necrosis, stasis and inflammation in valid preclinical models of the condition.

The sponsor has established that the condition is chronically debilitating and life-threatening.

Partial deep dermal and full thickness burns (hereinafter referred to as “the condition”) was estimated to be affecting less than 1.5 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 not provided sufficient justification for the assumption that the medicinal product containing melatonin will be of significant benefit to those affected by the condition. Preliminary clinical data from a single centre pilot clinical study were presented to demonstrate that add-on therapy of melatonin to best standard of care improved mortality, wound healing and infections when compared to best standard of care alone. However, the sponsor has not provided sufficient information to confirm that the pilot trial methodology was adequate to demonstrate unbiased and objective outcomes to the purpose of demonstration of significant benefit. Furthermore, there was no clarity on the definition of ‘best standard of care’ provided by the sponsor and if it included all products authorised in the European Union. Therefore, the COMP concluded that insufficient evidence was provided to establish a clinically relevant advantage of melatonin over all authorised products for the treatment of partial deep dermal and full thickness burns.

A negative opinion for melatonin, for treatment of partial deep dermal and full thickness burns, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.1.7. - EMA/OD/091/17

Treatment of growth hormone deficiency

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 potential major contribution to patient care in the condition.

The sponsor is requested to discuss the arguments for significant benefit *vs.* Somatropin Biopartners and to elaborate on the results from clinical studies to justify the assumption of significant benefit of this product.

In the written response, and during an oral explanation before the Committee on 06 September 2017, the sponsor acknowledged that Somatropin Biopartners was still authorised. Significant benefit was argued based on safety and a major contribution to patient care due to the ease of use of the product. The COMP indicated that the safety data was too preliminary for an assumption of significant benefit. The COMP recognised that the proposed delivery of the product could improve compliance however, as there was no appropriate patient reported outcome, an evaluation of the major contribution to patient care could not be assumed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 September 2017, prior to final opinion.

2.1.8. (S)-3-((S)-2-(2-((2,6-difluorophenyl)amino)-2-oxoacetamido)propanamido)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid - EMA/OD/079/17

Pharma Gateway AB; Treatment of primary sclerosing cholangitis

COMP coordinator: Bożenna 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:

- Number of people affected

The sponsor has provided a limited bibliographical submission covering publications from 1984 to 2005 and proposes a prevalence of 2 in 10,000. There have been more recent publications from 2013 and 2015 as well as the establishment of European and National (UK) patient organisation websites which offer additional information regarding the incidence, point prevalence and survival of these patients. It has been stated for example that incidence has been increasing recently. These developments have not been adequately considered in the calculation and therefore it is difficult to establish what the current prevalence could be.

For the calculation and presentation of the prevalence estimate the sponsor 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 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 their preclinical *in vivo* studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 6 September 2017, the sponsor indicated that the product offers anti-apoptotic and hepatoprotective activity which is not possible with ursodeoxycholic acid (UDCA). The sponsor made an indirect comparison to data produced with UDCA in similar pre-clinical *in vivo* models. Hepatic histological examination revealed that there were significantly fewer necrotic foci in animals treated with the sponsor's product when compared with similar data obtained with the use of UDCA. The sponsor highlighted that these findings would support the hepatoprotective effect which is specific to the mode of action of the product. The COMP accepted these arguments for the basis of significant benefit.

The Committee agreed that the condition, primary sclerosing cholangitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (S)-3-((S)-2-(2-((2,6-difluorophenyl)amino)-2-oxoacetamido)propanamido)-4-oxo-5-(2,3,4,6-tetrafluorophenoxy)pentanoic acid was considered justified based on preliminary preclinical data showing an improvement in biochemical indices of hepatic and biliary damage.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia.

The condition was estimated to be affecting approximately 1.6 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-3-((S)-2-(2-((2,6-difluorophenyl)amino)-2-oxoacetamido)propanamido)-4-oxo-5-(2,3,4,6-tetrafluorophenoxy)pentanoic acid will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a significant reduction in hepatonecrosis associated with the mechanism of action of the product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (S)-3-((S)-2-(2-((2,6-difluorophenyl)amino)-2-oxoacetamido)propanamido)-4-oxo-5-(2,3,4,6-tetrafluorophenoxy)pentanoic acid, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.1.9. Cannabidiol - EMA/OD/076/17

GW Research Ltd; Treatment of West syndrome

COMP coordinator: Robert Nistico

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:

- Condition

The sponsor is invited to amend the proposed indication to “treatment of West syndrome” and update the corresponding prevalence conclusion if appropriate.

- Intention to treat

In the preliminary clinical settings discussed in the application, the impact on the potential efficacy of cannabidiol in combination with other products should be clarified, particularly in the context of PK interactions.

- Significant benefit

The applicant is requested to provide a comparative discussion of the effects of the proposed product *versus* all authorised products in the proposed condition, and in particular vigabatrin, ACTH and corticosteroids, in order to justify a clinically relevant advantage or a major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 6 September 2017, the sponsor indicated that in the United States the term infantile spasms had superseded the term West Syndrome. The COMP however reiterated that in Europe the

term continues to be West Syndrome so the sponsor accepted to amend the term used for the condition. The sponsor has submitted preliminary clinical data that they have generated from an expanded access programme which they have been conducting in the United States. They also supplied preliminary clinical data showing that there was minimal impact on the potential of the efficacy of cannabidiol when used with other products in this condition.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of West syndrome.

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

The intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on preliminary clinical observations supporting improved spasm control in refractory patients.

The condition is chronically debilitating and life-threatening in particular due to the development of epileptic seizures with possible long-term developmental disabilities, cognitive impairment and psychiatric complications.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cannabidiol will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a notable reduction in seizures in medicinal resistant epilepsy patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cannabidiol, for treatment of West syndrome, was adopted by consensus.

2.1.10. - EMA/OD/097/17

Treatment of neurodegeneration with brain iron accumulation

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

Neurodegeneration with brain iron accumulation (NBIA) should be justified as a distinct medical entity or the application should be split into several submissions to account for individual distinct medical entities falling under this umbrella term. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (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 neurodegeneration with brain iron accumulation, the sponsor should further elaborate on:

- the relevance of the preclinical model used for the treatment of NBIA, and the interpretation of the results obtained in the experiments,

- any clinical data available in patients suffering from NBIA, which could support medical plausibility in any of the NBIA subsets.

In the written response, and during an oral explanation before the Committee on 06 September 2017, the sponsor proposed to narrow the designation down to aceruloplasminaemia and stressed the fact that this particular disease is multi-systemic in nature and patient's life is at risk mostly due to the iron overload in the heart, liver and other peripheral tissues, in addition to the iron accumulation in the brain. However, the preclinical *in vivo* model that exists for this condition does not recapitulate the iron dyshomeostasis found in human disease. The Committee discussed the potential acceptability of such double bridging of data in view of the exceptional rarity of the condition. However, since the relationship of the iron overload and the pathophysiology leading to neurologic deterioration in this condition was not obvious, the Committee found such extrapolation unacceptable. Therefore the COMP was of the opinion that the data was insufficient to support the medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 September 2017, prior to final opinion.

2.1.11. Recombinant adeno-associated viral vector serotype 5 encoding *Staphylococcus aureus* Cas9 endonuclease and two guide RNAs complementary to two regions of intron 26 of the *CEP290* gene - EMA/OD/060/17

Pharma Gateway AB; Treatment of Leber congenital amaurosis

COMP coordinator: Armando Magrelli/Fernando Méndez Hermida

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 Leber congenital amaurosis, the sponsor should further elaborate on:

- the relevance of the preclinical model used for the treatment of Leber congenital amaurosis, and the interpretation of the results obtained in the experiments,
- the absence of gene expression data *in vivo*.

In the written response, and during an oral explanation before the Committee on 6 September 2017, the sponsor gave an overview of established preclinical models of the conditions to show that there is no valid preclinical model that recapitulates the genotype and phenotype to study the proposed product using CRISPR-Cas gene editing technology. Nevertheless, the sponsor presented additional preclinical data to support medical plausibility from a transgenic preclinical model. The data demonstrate a dose dependent productive CRISPR-Cas gene editing rate in the neural retina after sub-retinal injection. The productive gene editing rate was further contextualised with clinical observations and studies outlining that a 10% of correction rate of foveal cones was sufficient to achieve a clinically relevant improvement in vision. The COMP considered that this was adequate to support the basis of medical plausibility.

Following review of the application by the Committee, it was agreed to rename the active substance to recombinant adeno-associated viral vector serotype 5 encoding *Staphylococcus aureus* Cas9 endonuclease and two guide RNAs complementary to two regions of intron 26 of the *CEP290* gene.

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

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector serotype 5 encoding *Staphylococcus aureus* Cas9 endonuclease and two guide RNAs complementary to two regions of intron 26 of the *CEP290* gene was considered justified based on preclinical data demonstrating that the product was able to correct disease genotype of *CEP290*-related Leber congenital amaurosis due to IVS26 mutation.

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

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.

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

A positive opinion for recombinant adeno-associated viral vector serotype 5 encoding *Staphylococcus aureus* Cas9 endonuclease and two guide RNAs complementary to two regions of intron 26 of the *CEP290* gene, for treatment of Leber's congenital amaurosis, was adopted by consensus.

2.1.12. Ofranergene obadenovec - EMA/OD/035/17

Envigo Pharma Consulting Limited; Treatment of ovarian cancer

COMP coordinator: Brigitte Blöchl-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:

- 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 ovarian cancer, the sponsor should further elaborate on the design, population, and results of the preliminary clinical study in patients affected by the condition. A copy of the study report is requested towards this end.

- Significant benefit

The arguments on significant benefit are based on the potential of improved efficacy in the condition, and an indirect comparison *versus* historical controls. The applicant is requested to discuss the comparability of the populations, treatments and results of the compared studies.

In the written response, the sponsor presented further background information on the preliminary clinical data to support the medical plausibility and significant benefit. The COMP considered that the response analysis and the improvement in survival in patients associated with therapeutic dose *versus* sub-therapeutic dose presented in the clinical data could be considered relevant to establish medical plausibility. Significant benefit was

established based on an indirect comparison to the published AURELIA trial for bevacizumab. Populations were not matched to allow for indirect comparisons, but were considered similar. For the purpose of orphan designation the crude indirect comparison was considered sufficient to demonstrate a survival benefit associated with treatment.

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 ofranergene obadenovec was considered justified based on preliminary clinical data demonstrating that treatment improved survival in recurrent platinum-resistant patients.

The condition is chronically debilitating in particular 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 approximately 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ofranergene obadenovec will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that treatment improved survival in recurrent platinum-resistant patients. An indirect comparison was conducted to show that the survival benefit compared favourably with the survival observed with authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ofranergene obadenovec, for treatment of ovarian cancer, was adopted by consensus.

2.1.13. Recombinant monoclonal antibody to sialic acid-binding Ig-like lectin 8 - EMA/OD/087/17

Envestia Limited; Treatment of mastocytosis

COMP coordinator: Bożenna Dembowska-Bagińska/Katerina Kopečková

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

- Number of people affected

The sponsor has provided a prevalence calculation which only covers patients with systemic mastocytosis which represent a third of all mastocytosis patients. Patents that have cutaneous mastocytosis have not been included.

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.

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

In the written response, the sponsor provided a revised prevalence calculation which included the paediatric population that had been omitted in the one first submitted. As noted the cutaneous forms of mastocytosis which appear generally in children had been underestimated. The sponsor has submitted a revised calculation taking children into account using several scenarios. The COMP accepted the basis of the revised prevalence calculation and recommended granting of the orphan designation.

Following review of the application by the Committee, it was agreed to rename the active substance to recombinant monoclonal antibody to sialic acid-binding Ig-like lectin 8.

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

The intention to treat the condition with the medicinal product recombinant monoclonal antibody to sialic acid-binding Ig-like lectin 8 was considered justified based on preclinical and clinical data showing a reduction in mast cells and eosinophils.

The condition is chronically debilitating due to symptoms caused by release of histamine and tryptase by the tumour cells, including flushing, tachycardia, pruritus, abdominal cramping, peptic ulcer disease, and diarrhoea. Infiltration of various organs by malignant cells in aggressive forms can be life-threatening, due to bone marrow failure, hepatomegaly with ascites and impaired liver function, splenomegaly with hypersplenism. Five-year survival rate is around 61% in systemic mastocytosis.

The condition was estimated to be affecting approximately 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 recombinant monoclonal antibody to sialic acid-binding Ig-like lectin 8 may be of significant benefit to those affected by the condition. The sponsor supported the assumption of significant benefit with preclinical and clinical data showing significant reduction in mast cells and eosinophils. The Committee considered that this constitutes a clinically relevant advantage for patients affected by mastocytosis.

A positive opinion for recombinant monoclonal antibody to sialic acid-binding Ig-like lectin 8, for treatment of mastocytosis, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/102/17

Treatment of sickle cell disease

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 October (03-05) meeting.

2.2.2. - EMA/OD/120/17

Treatment of subarachnoid haemorrhage

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 October (03-05) meeting.

2.2.3. - EMA/OD/119/17

Treatment of gastrointestinal stromal tumours

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 October (03-05) meeting.

2.2.4. 5-amino-1-(2-methyl-1H-benzo[d]imidazol-5-yl)-1H-pyrazol-4-yl 1H-indol-2-yl ketone mono[(S)-2-hydroxysuccinate] - EMA/OD/124/17

Voisin Consulting S.A.R.L.; Treatment of biliary tract cancer

COMP coordinator: Ingrid Wang

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

The intention to treat the condition with the medicinal product containing 5-amino-1-(2-methyl-1H-benzo[d]imidazol-5-yl)-1H-pyrazol-4-yl 1H-indol-2-yl ketone mono[(S)-2-hydroxysuccinate] was considered justified based on preliminary clinical data showing that heavily pretreated patients affected by the condition responded to treatment.

The condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6 and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction.

The condition was estimated to be occurring in approximately 1.5 in 10,000 persons per year 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 5-amino-1-(2-methyl-1H-benzo[d]imidazol-5-yl)-1H-pyrazol-4-yl 1H-indol-2-yl ketone mono[(S)-2-hydroxysuccinate], for treatment of biliary tract cancer, was adopted by consensus.

2.2.5. Adenoviral vector of serotype 5 modified to contain a chimeric sequence consisting of a minimal urokinase-type plasminogen activator receptor promoter preceded by three Notch responsive elements, and coated with oligopeptide end-modified poly (beta -amino) esters - EMA/OD/111/17

Sagetis Biotech, S.L.; Treatment of pancreatic cancer

COMP coordinator: Fernando Méndez Hermida

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

The intention to treat the condition with the medicinal product containing adenoviral vector of serotype 5 modified to contain a chimeric sequence consisting of a minimal urokinase-type plasminogen activator receptor promoter preceded by three Notch-responsive elements, and coated with oligopeptide end-modified poly (beta-amino) esters was considered justified based on preclinical data demonstrating that the product achieved tumour volume reduction in valid preclinical models of the condition.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression, and life-threatening with a median survival of about 6 months.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adenoviral vector of serotype 5 modified to contain a chimeric sequence consisting of a minimal urokinase-type plasminogen activator receptor promoter preceded by three Notch-responsive elements, and coated with oligopeptide end-modified poly (beta-amino) esters will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product achieved tumour volume reduction in valid models of the condition when given in addition to currently authorised products paclitaxel and gemcitabine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adenoviral vector of serotype 5 modified to contain a chimeric sequence consisting of a minimal urokinase-type plasminogen activator receptor promoter preceded by three Notch-responsive elements, and coated with oligopeptide end-modified poly (beta-amino) esters, for treatment of pancreatic cancer, was adopted by consensus.

2.2.6. Autologous *ex-vivo*-expanded peripheral polyclonal lymphocytes enriched in activated natural killer cells - EMA/OD/125/17

CellProtect Nordic Pharmaceuticals AB; Treatment of multiple myeloma

COMP coordinator: Karri Penttila

Following review of the application by the Committee, it was agreed to rename the active substance to “autologous *ex-vivo*-expanded peripheral polyclonal lymphocytes enriched in activated natural killer cells”.

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

The intention to treat the condition with the medicinal product containing autologous *ex-vivo*-expanded peripheral polyclonal lymphocytes enriched in activated natural killer cells was considered justified based on preliminary clinical data showing complete response.

The condition is chronically debilitating and life-threatening due to the poor survival of patients with relapsed or refractory disease.

The condition was estimated to be affecting no more than 4.3 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous *ex-vivo*-expanded peripheral polyclonal lymphocytes enriched in activated natural killer cells will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that a complete response was obtained in patients who were eligible to

haemopoietic stem cell transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous *ex-vivo*-expanded peripheral polyclonal lymphocytes enriched in activated natural killer cells, for treatment of multiple myeloma, was adopted by consensus.

2.2.7. Bitopertin - EMA/OD/112/17

Roche Registration Limited; Treatment of beta-thalassaemia intermedia and major

COMP coordinator: Ioannis Kkolos

The Committee agreed that the condition, beta-thalassaemia intermedia and major, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing bitopertin was considered justified based on data in a model of the condition showing reduction of anaemia and haemolysis in response to treatment.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing bitopertin will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a normalisation of haematologic parameters which can lead to a reduction in the need for blood transfusions and subsequently reduce the need for iron chelators. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bitopertin, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

2.2.8. - EMA/OD/105/17

Treatment in solid organ 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 October (03-05) meeting.

2.2.9. Cannabidivarin - EMA/OD/100/17

GW Research Ltd; Treatment of Rett syndrome

COMP coordinator: Armando Magrelli/Giuseppe Capovilla

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 cannabidivarin was considered justified based on non-clinical data in a model of the condition demonstrating an improvement in survival and a delay in the development of motor, respiratory and cognitive impairment.

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

The condition was estimated to be affecting less than 0.8 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 in the European Union for patients affected by the condition.

A positive opinion for cannabidivarin, for treatment of Rett syndrome, was adopted by consensus.

2.2.10. - EMA/OD/116/17

Treatment of haemophilia B

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 October (03-05) meeting.

2.2.11. - EMA/OD/115/17

Treatment of Prader-Willi-Syndrome (PWS)

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 October (03-05) meeting.

2.2.12. - EMA/OD/117/17

Treatment of beta-thalassaemia intermedia and major

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 October (03-05) meeting.

2.2.13. Entospletinib - EMA/OD/040/17

Gilead Sciences International Ltd; Treatment of acute myeloid leukaemia

COMP coordinator: Frauke Naumann-Winter

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 entospletinib was considered justified based on preliminary clinical data showing complete response in patients receiving first line therapy.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes,

disseminated intravascular coagulation and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated.

The condition was estimated to be affecting approximately 1.1 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing entospletinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that a complete response rate can be achieved in a higher proportion of patients when the product is used in combination than with cytarabine and daunorubicin alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for entospletinib, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.14. Glasdegib maleate - EMA/OD/106/17

Pfizer Limited; Treatment of acute myeloid leukaemia

COMP coordinator: Jens Ersbøll

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 glasdegib maleate was considered justified based on preliminary clinical data showing complete response when the product is used in combination with decitabine and cytarabine.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated.

The condition was estimated to be affecting approximately 1.1 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing glasdegib maleate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a complete response in patients when the product was used in combination with decitabine and cytarabine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for glasdegib maleate, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.15. Glucopyranosyl lipid A - EMA/OD/103/17

Immune Design Ltd; Treatment of follicular lymphoma

COMP coordinator: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing glucopyranosyl lipid A was considered justified based on preclinical and preliminary clinical data showing partial response when the product is used in combination with radiotherapy.

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

The condition was estimated to be affecting approximately 3.6 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing glucopyranosyl lipid A will be of significant benefit to those affected by the condition. The sponsor has preclinical data indicating improved outcome of treatment, also in combination with radiotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for glucopyranosyl lipid A, for treatment of follicular lymphoma, was adopted by consensus.

2.2.16. Humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F - EMA/OD/077/17

GlaxoSmithKline Trading Services Limited; Treatment of multiple myeloma

COMP coordinator: Katerina Kopečková/Karri Penttila

Following review of the application by the Committee, it was agreed to rename the active substance to humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F.

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

The intention to treat the condition with the medicinal product containing humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F was considered justified based on preliminary clinical data showing responses in treated patients with relapsing or refractory multiple myeloma.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data

in heavily pretreated relapsed/refractory patients who have responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F, for treatment of multiple myeloma, was adopted by consensus.

2.2.17. - EMA/OD/109/17

Treatment of chronic thromboembolic pulmonary hypertension

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 October (03-05) meeting.

2.2.18. - EMA/OD/113/17

Treatment of haemophilia B

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 October (03-05) meeting.

2.2.19. - EMA/OD/127/17

Treatment of subarachnoid hemorrhage

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 October (03-05) meeting.

2.2.20. - EMA/OD/121/17

Treatment of peripheral T-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 October (03-05) meeting.

2.2.21. 2-[N-(2-hydroxyethyl)]-N-(4-methoxybenzenesulfonyl)]amino-N-(4-chlorocinnamyl)-N-methylbenzylamine - EMA/OD/055/17

Repositioning SAS; Treatment of Charcot-Marie-Tooth disease

COMP coordinator: Dinah Duarte/Annie Lorence

Following review of the application by the Committee, it was agreed to rename the active substance to 2-[N-(2-hydroxyethyl)]-N-(4-methoxybenzenesulfonyl)]amino-N-(4-chlorocinnamyl)-N-methylbenzylamine.

The Committee agreed that the condition, Charcot-Marie-Tooth disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-[N-(2-hydroxyethyl)]-N-(4-methoxybenzenesulfonyl)]amino-N-(4-chlorocinnamyl)-N-methylbenzylamine was considered justified based on preclinical data demonstrating that the product improved motor function in a valid model of the condition.

The condition is chronically debilitating due to the progressive deterioration of peripheral motor and sensory nerves which leads to functional impairment, pain, progressive disability and a reduction in the quality of life.

The condition was estimated to be affecting approximately 2.6 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 in the European Union for patients affected by the condition.

A positive opinion for 2-[N-(2-hydroxyethyl)]-N-(4-methoxybenzenesulfonyl)]amino-N-(4-chlorocinnamyl)-N-methylbenzylamine, for treatment of Charcot-Marie-Tooth disease, was adopted by consensus.

2.2.22. Pracinostat - EMA/OD/101/17

Helsinn Birex Pharmaceuticals Ltd; Treatment of acute myeloid leukaemia

COMP coordinator: Jens Ersbøll

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 pracinostat was considered justified based on preliminary clinical data showing improvements in overall response rates and overall survival.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated.

The condition was estimated to be affecting approximately 1.1 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing pracinostat will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate improvement in responses and overall survival in elderly patients when the product was used in combination with the standard of care in first line treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pracinostat, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.23. - EMA/OD/126/17

Treatment of microvillus inclusion disease

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 October (03-05) meeting.

2.2.24. Seladelpar - EMA/OD/114/17

Larode Ltd; Treatment of primary biliary cholangitis

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, primary biliary cholangitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing seladelpar was considered justified based on clinical data demonstrating improvement in markers of cholestasis.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia.

The condition was estimated to be affecting approximately 3.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing seladelpar will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who have not adequately responded to first line treatment responded well to treatment with seladelpar and achieved normalisation of biomarkers of cholestasis (such as alkaline phosphatase). In addition, these responses compared favourably to those reported with the use of the authorised second line treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for seladelpar, for treatment of primary biliary cholangitis, was adopted by consensus.

2.2.25. Siplizumab - EMA/OD/104/17

ITB-MED AB; Treatment in solid organ transplantation

COMP coordinator: Bożenna Dembowska-Bagińska

The Committee agreed that the condition, solid organ transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing siplizumab was considered justified based on preclinical data in a valid model of the condition and preliminary clinical observations supporting long term tolerance of transplanted subjects.

The condition is chronically debilitating and life-threatening due to complications such as ischemia - reperfusion injury, delayed graft function, and graft rejection.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing siplizumab will be of significant benefit to those affected by the

condition. The sponsor has provided preclinical and preliminary clinical data supporting long term tolerance of the transplant, with the potential to withdraw immunosuppression therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for siplizumab, for treatment in solid organ transplantation, was adopted by consensus.

2.2.26. Synthetic cyclic 8 amino acid analogue of human unacylated ghrelin - EMA/OD/066/17

Alizé Pharma; Treatment of Prader-Willi syndrome

COMP coordinator: Violeta Stoyanova

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

The intention to treat the condition with the medicinal product containing synthetic cyclic 8 amino acid analogue of human unacylated ghrelin was considered justified based on clinical data demonstrating improvement in postprandial glucose and insulin levels as well as reduction in food seeking behaviour.

The condition is life-threatening and chronically debilitating, in particular due to cognitive impairment, maladaptive behaviour and morbid obesity leading to increased cardiovascular morbidity and mortality.

The condition was estimated to be affecting approximately 0.3 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic cyclic 8 amino acid analogue of human unacylated ghrelin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that show reduction in food intake and food seeking behaviour, aspects of the condition that are not influenced by the currently authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic cyclic 8 amino acid analogue of human unacylated ghrelin, for treatment of Prader-Willi syndrome, was adopted by consensus.

2.2.27. - EMA/OD/067/17

Treatment of pancreatic 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 October (03-05) meeting.

2.2.28. - EMA/OD/107/17

Treatment of idiopathic pulmonary fibrosis

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 October (03-05) meeting.

2.2.29. - EMA/OD/110/17

Treatment of focal segmental glomerulosclerosis

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 October (03-05) meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

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 21 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 13 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of paroxysmal nocturnal haemoglobinuria

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

3.1.2. -

Treatment of congenital factor VII deficiency

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

3.1.3. -

Treatment of myelodysplastic syndromes

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

3.1.4. -

Treatment in solid organ transplantation

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

3.2. Finalised letters

3.2.1. -

Treatment of acute hepatic porphyria

The finalised letter was circulated for information.

3.2.2. -

Treatment of Prader-Willi syndrome

The finalised letter was circulated for information.

3.2.3. -

Treatment of haemophilia A

The finalised letter was circulated for information.

3.3. New requests

None

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

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

4.1.1. Soliris - eculizumab – Type II variation - EMEA/OD/062/14, EU/3/14/1304, EMEA/H/C/000791/II/0090

Alexion Europe SAS; Treatment of myasthenia gravis

CHMP rapporteur: Jorge Camarero Jiménez; CHMP co-rapporteur: Alexandre Moreau

Further to a change in the wording of the therapeutic indication, the opinion was re-adopted by written procedure after the CHMP July meeting.

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

4.2.1. Masipro – Masitinib – EMEA/OD/062/04, EU/3/04/242, EMEA/H/C/004159

AB Science; Treatment of Mastocytosis

The status of the procedure at CHMP was noted.

4.2.2. - Letermovir - EMA/OD/090/10, EU/3/11/849, EMEA/H/C/004536

Merck Sharp & Dohme Limited; Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk

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.

4.2.3. Zejula - Niraparib – EMA/OD/015/10, EU/3/10/760,EMEA/H/C/004249

Tesaro UK Limited; Treatment of ovarian 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 October (03-05) meeting.

4.2.4. Raxone - Idebenone –Type II variation - EMEA/OD/077/06, EU/3/07/437, EMEA/H/C/003834/II/0003

Santhera Pharmaceuticals (Deutschland) GmbH; Treatment of Duchenne muscular dystrophy

CHMP rapporteur: John Joseph Borg; CHMP co-rapporteur: Andrea Laslop

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 7 applications.

4.5. Public Summary of Opinions

The draft public summaries of the COMP opinions adopted last month were endorsed for publication on the EMA website.

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Blincyto (blinatumomab) - Type II variation – EMEA/OD/029/09, EU/3/09/650, EMEA/H/C/003731/II/0018

Amgen Europe BV - The Netherlands; Treatment of acute lymphoblastic leukaemia

CHMP rapporteur: Alexandre Moreau

The status of the procedure at CHMP was noted.

5.2.2. Nplate - Recombinant megakaryopoiesis-stimulating protein Romiplostim –Type II variation - EMEA/OD/008/05, EU/3/05/283, EMEA/H/C/000942/II/0060/G

Amgen Europe BV; Treatment of idiopathic thrombocytopenic purpura

CHMP rapporteur: Concepcion Prieto Yerro; CHMP co-rapporteur: Paula Boudewina van Hennik

The status of the procedure at CHMP was noted.

5.2.3. Bosulif – Bosutinib –Type II variation - EMEA/OD/160/09, EU/3/10/762, EMEA/H/C/002373/II/0025/G

Pfizer Limited; Treatment of chronic myeloid leukaemia

CHMP rapporteur: Harald Enzman

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

5.2.4. Kalydeco – Ivacaftor – Type II variation - EMEA/OD/010/08, EU/3/08/556, EMEA/H/C/002494/II/0063/G

Vertex Pharmaceuticals; Treatment of cystic fibrosis

CHMP rapporteur: Concepcion Prieto Yerro

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

5.2.5. Inovelon – Rufinamide – Type II variation - EMEA/OD/047/04, EU/3/04/240,EMEA/H/C/000660/II/0045

Eisai Ltd; Treatment of Lennox-Gastaut syndrome

CHMP rapporteur: Alexandre Moreau

COMP coordinators were appointed.

5.2.6. Translarna – Ataluren - Type II variation - EMEA/OD/106/04, EU/3/05/278, EMEA/H/C/002720/II/0037

PTC Therapeutics International Limited; Treatment of duchenne muscular dystrophy

CHMP rapporteur: Johann Lodewijk Hillege;

COMP coordinators were appointed.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 3 applications.

6. Application of Article 8(2) of the Orphan Regulation

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP Strategic Review & Learning meeting, 19-21 September 2017, Lisbon, Portugal

The Agenda for the SRLM, 19-21 September 2017 was adopted.

7.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 05 September 2017.

7.1.3. Non-Clinical Working Group

The working group on Non-clinical met on 06 September 2017.

7.1.4. Condition Working Group

The working group on Condition met on 07 September 2017.

7.1.5. COMP membership

The COMP welcomed Tim Leest as new member representing Belgium.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes July 2017

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

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

PCWP/HCPWP joint meeting – 19/20 September 2017

Documents were circulated in MMD.

Document(s) tabled:
Personalised medicines workshop report (EMA/185440/2017)
Draft Agenda AMR workshop – 19 September 2017 (EMA/765134/2016)
Draft agenda of the PCWP/HCPWP meeting - 20 September 2017 (EMA/370525/2017)

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. The Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

Documents were circulated in MMD.

Document(s) tabled:
COMP Work Plan 2017

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. EMA Business Pipeline activity and Horizon scanning

Documents were circulated in MMD.

Document tabled:
Upcoming Q3/2017 Update of the Business Pipeline report for the human scientific Committees

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 05-07 September 2017 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	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Ioannis Kkolos	Member	Cyprus	No interests declared	
Katerina Kopeckova	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	
Melinda Sobor	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	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Dan Henrohn	Member	Sweden	No participation in final deliberations and voting on:	4.2.2.
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	
Kerstin Westermark	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
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	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Expert - in person*	Patients' Organisation Representative	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.

Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/