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SCIENCE MEDICINES HEALTH

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Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 03-05 November 2020

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

03 November 2020, 08:30-19:30, virtual remote meeting

04 November 2020, 08:30-19:00, virtual remote meeting

05 November 2020, 08:30-13:15, virtual remote meeting

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

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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 that no restriction in the involvement of meeting participants in upcoming discussions was identified 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. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The COMP noted that Mr. Bruno Sepodes has resigned from being the COMP Member and thanked him for his dedicated work in the COMP.

1.2. Adoption of agenda

The agenda for 3-5 November 2020 was adopted with the addition of the following topic under 4.2:

- Puldysa

1.3. Adoption of the minutes

The minutes for 6-8 October 2020 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. autologous CD4+ and CD8+ T cells genetically modified with a lentiviral vector encoding a B-cell maturation antigen-specific chimeric antigen receptor - EMA/OD/0000034375

Celgene Europe B.V.; Treatment of multiple myeloma

COMP Rapporteur: Frauke Naumann-Winter

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

- Number of people affected

The sponsor used two approaches which appear to provide under-estimates of the current point prevalence for multiple myeloma. Extrapolation from Member States is not considered acceptable as EU wide incidence data are widely available in the European Cancer Information System (ECIS) database.

The sponsor was asked to 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 was requested to perform a sensitivity analysis of the reported calculations.

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the ["Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation"](#).

In the written response, the sponsor had adjusted the estimated multiple myeloma (MM) prevalence from their initially proposed 2.29 per 10,000 to a range of 3.68 to 4.88 per 10,000. Following the question raised by the COMP, data from the ECIS database 2020 was used in the revised estimate. It was noted that a crude incidence of 8.0/100,000 for EU-27 in 2020 is stated in ECIS. The sponsor proposed that disease duration varies depending on the disease stage at diagnosis, and the stage distribution was supported by published literature (single and multicentre studies). This resulted in a median OS (overall survival) of 4.6 to 6.1 years, and in a prevalence of 3.68 to 4.88 per 100,000.

As the sponsor offered two potential prevalence calculations the COMP deliberated on whether to accept at this stage 4.88 per 10,000 as the most conservative prevalence estimate, or 4.0 to stay in line with recent MM designations as the lower calculation was 3.68 in 10,000. The COMP concluded 4.0 in 10,000 was acceptable for the purpose of an initial orphan designation and concluded they could recommend granting the orphan designation.

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 CD4+ and CD8+ T cells genetically modified with a lentiviral vector encoding a B-cell maturation antigen-specific chimeric antigen receptor was considered justified based on preliminary clinical data showing an improvement in progression free survival in patients who are penta-refractory to previous treatments.

The condition is life-threatening and chronically debilitating, in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions.

The condition was estimated to be affecting approximately 4.0 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 CD4+ and CD8+ T cells genetically modified with a lentiviral vector encoding a B-cell maturation antigen-specific chimeric antigen receptor will

be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in heavily pre-treated patients including penta-refractory disease that demonstrated an objective response rate which compared favourably to outcomes reported for other authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD4+ and CD8+ T cells genetically modified with a lentiviral vector encoding a B-cell maturation antigen-specific chimeric antigen receptor, for treatment of multiple myeloma, was adopted by consensus.

2.1.2. tremelimumab - EMA/OD/0000038040

AstraZeneca AB; Treatment of hepatocellular carcinoma (HCC)

COMP Rapporteur: Frauke Naumann-Winter

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

- Significant benefit

The sponsor provided preliminary clinical data to support the improved efficacy of the combination of tremelimumab and durvalumab over the current standard of care in HCC. The sponsor provided limited information regarding the medical history and disease staging of enrolled patients. Proportion of patient who refused sorafenib treatment was not reported. Responses were also not analysed for first line and second line treatment separately, which makes the assessment of the effects observed difficult.

The sponsor was requested to provide the above-mentioned details of the clinical study and to provide the indirect comparison to the authorised products used in each setting and to indicate differences in ORR (Overall Response Rate), PFS (Progression-Free Survival) and OS data separately, where possible.

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

In the written response, the sponsor updated the description of the clinical data available to date. The sponsor performed a subgroup analysis showing the efficacy of the product in monotherapy and in combination with durvalumab in first- and second-line treatment. In addition, comparative analysis was submitted, based on an indirect comparison to published studies with currently authorised treatment options. The efficacy in terms of ORR and median OS of the tremelimumab and durvalumab combination therapy compared favourably with treatment using sorafenib and lenvatinib mainly in first line but it showed some improvements in other subgroups, too.

The sponsor was advised to consult the COMP at protocol assistance in preparing for the maintenance of the orphan status at marketing authorisation application. However, based on the written responses, the COMP found enough supporting evidence for the assumption of significant benefit. The oral explanation was therefore cancelled on 3 November 2020.

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 tremelimumab was considered justified based on clinical data showing achievement of objective responses

and a favourable effect on overall survival compared to published results with the standard of care.

The condition is chronically debilitating and life-threatening due to increased mortality and liver dysfunction. Median survival without therapy can be approximately 36 months for stage 0 and A, 16 months for stage B, 4-8 months for stage C and less than 4 months for stage D.

The condition was estimated to be affecting less than 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tremelimumab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in patients with advanced HCC (1st and 2nd line) that demonstrate that overall survival of patients treated with tremelimumab alone or in combination with durvalumab compared favourably to published results of other authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tremelimumab, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.1.3. - EMA/OD/0000039198

Treatment of peripheral artery disease (PAD) in patients with end-stage kidney disease receiving haemodialysis (ESKD)

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

- Intention to diagnose, prevent or treat

The sponsor was requested to justify peripheral artery disease in patients with end-stage kidney disease receiving haemodialysis 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 relevant guidelines (especially section A of [ENTR/6283/00](#)).

Patients in the subset should present distinct and unique evaluable characteristics with a plausible link to the condition and such characteristics should be essential for the product to carry out its action. It is not considered acceptable to restrict the condition PAD based on the feasibility of administering the product to the patient. Instead, the sponsor was asked to further justify why the proposed substance would not work outside the proposed subset.

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the ["Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation"](#).

In case the condition is changed to PAD the sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition.

- Significant benefit

In case the condition is changed to PAD, the sponsor would have to include a discussion on significant benefit over authorised medicinal products for PAD.

In the written response, and during an oral explanation before the Committee on 3 November 2020, the sponsor maintained the view that the proposed condition, and subset of PAD, would be the most suitable condition for orphan designation. The sponsor argued that diffuse extensive vascular calcification is a prominent pathological feature of PAD-ESKD, but not in general PAD. The primary reason for restricting the use of the proposed substance to PAD-ESKD patients is that patients outside of the subset are less likely to benefit from the treatment. The target of the proposed substance is the progressive vascular calcification in PAD-ESKD, which is different to the lipid-containing plaque characterising PAD at large. However, it could be argued that PAD-ESKD is a stage of PAD and according to [Guideline on the format and content of applications for designation as orphan medicinal products](#), stages are not acceptable to subset a condition. Furthermore, the argument that the product is less likely to work outside the proposed condition would also not be acceptable. To demonstrate that, the sponsor would have to show that the product is not active in a larger population. Therefore, it would not be possible, for the purpose of orphan designation, to subset PAD in according with the sponsor's suggestion.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 November 2020, prior to final opinion.

2.1.4. - [EMA/OD/0000038634](#)

Treatment of progressive multifocal leukoencephalopathy

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 whether there exists a scientific rationale for the development of the proposed product for treatment of progressive multifocal leukoencephalopathy (PML) the sponsor was requested to further elaborate on:

- the lack of (non-)clinical data of the proposed product in the condition,
 - the relevance of the clinical data in PML patients in the context of the natural history of the disease,
 - the potential of the proposed product to induce immune reconstitution inflammatory syndrome PML.
- Number of people affected

The sponsor seems to include only HIV+ patients in the calculation of the prevalence. However, the condition can be associated with other conditions characterised by immunodepletion.

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the ["Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation"](#).

The sponsor was requested to re-calculate the prevalence of the condition and justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

In the written response, and during an oral explanation before the Committee on 4 November 2020, the sponsor provided further explanation of the non-clinical data available to date and the information on a single clinical case of a patient treated with the proposed product. The only endpoints measured were related to total lymphocyte counts and JCV viral load reductions. The COMP questioned the validity of these endpoints as indicative of an efficacy in the condition. This is because literature related to this condition fails to demonstrate a causal relationship between lymphocyte counts or viral load and the PML prognosis. The sponsor elaborated on very long follow up times which would have to be planned for the demonstration of functional improvement in patients. Nevertheless, the COMP considered that such early clinical data would be necessary to support the designation of the product in PML. In addition, safety aspects of the immune reconstitution were discussed, and the COMP considered that they can be addressed in the clinical development and not at the stage of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 4 November 2020, prior to final opinion.

2.1.5. sotatercept - EMA/OD/0000037744

IDEA Innovative Drug European Associates (Ireland) Limited; Treatment of pulmonary arterial hypertension (PAH)

COMP Rapporteur: Eva Malikova

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 estimation and presentation of the prevalence estimate the sponsor was advised to refer to the ["Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation"](#).

The sponsor gave a range for the prevalence from 0.1 to 3 in 10,000. The method for calculating prevalence from incidence was not reported and should be justified and the sponsor was requested to provide a final prevalence estimate, not a range.

In the written response, the sponsor submitted and updated prevalence estimate including a discussion about the heterogeneity of reporting, the absence of population-based registries for PAH in the EU and inherited bias in the data. The reported prevalence of PAH in the EU by country and year assessed ranges from 0.066 to 0.31 with a median prevalence of 0.24. The estimated prevalence based on incidence (5 years duration) range from 0.055 to 0.54 with the median of 0.2 in 10,000. During the oral explanation, the sponsor also presented some worst-case scenarios in which the prevalence could be as high as 1.35.

The COMP accepted the highest estimate as proposed by the sponsor (1.35) and rounded it up to approximately 1.4, for the purpose of this designation.

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

The intention to treat the condition with the medicinal product containing sotatercept was considered justified based on a reduction in pulmonary vascular resistance and improvements in 6-minute walking test in patients treated with the product.

The condition is life-threatening and chronically debilitating due to progressive dyspnoea and right heart failure, leading to premature death.

The condition was estimated to be affecting approximately 1.4 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 sotatercept will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrated significant reduction in pulmonary vascular resistance and improvements in 6-minute walking test when sotatercept was used on top of authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sotatercept, for treatment of pulmonary arterial hypertension, was adopted by consensus.

2.1.6. - EMA/OD/0000038423

Treatment of Huntington's disease (HD)

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 whether there exists a scientific rationale for the development of the proposed product for treatment of Huntington's disease the sponsor should further elaborate on:

- the relevance of the non-clinical model used for the treatment of Huntington's disease, and the interpretation of the results obtained in the experiments with consideration to signs and symptoms outcome measures.
- Number of people affected

The sponsor provided a range between 0.21 and 2.21 per 10,000 as the final estimate. Normally the COMP requests a final point estimate for the purpose of orphan designation.

The sponsor was requested to 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 was asked to perform a sensitivity analysis of the reported calculations.

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the ["Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation"](#).

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from non-clinical in vivo data submitted to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 4 November 2020, the sponsor tried to bridge the data they had to the clinical setting and acknowledged the intrinsic limitations, in the non-clinical in vivo models of HD (including the BachHD model used in this application) which can recapitulate most of the features of the human disease and are typically associated with histopathological and morphological alterations in critical brain regions, neurochemical changes, synaptic dysfunction, as well as behavioural phenotypes including cognitive impairment and motor dysfunction. The sponsor failed to produce any functional data.

When clinical data are not available, the use of a surrogate endpoint (such as measurement of mutant Huntingtin protein in animal models) in the absence of HD-relevant functional measures, does not support medical plausibility. The COMP therefore continued to consider that medical plausibility remains hypothetical at this stage and results presented were not sufficient to support a designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 4 November 2020, prior to final opinion.

2.1.7. [human interleukin 12 fused with immunoglobulin G4 c-terminal Fc fragment - EMA/OD/0000035896](#)

VH Regulatory Consulting GmbH & Co. KG; Treatment of glioma

COMP Rapporteur: Dinko Vitezic

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

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any non-clinical or clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. The extrapolation from the observations pertaining to other products should be justified.

Moreover, it is well known that extrapolation from nonclinical or early clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data is required to justify safety arguments in most cases. The sponsor was asked to further elaborate on the potential risks with the product and how this compares with the safety profile of the current authorised medicinal products for the same condition.

In the written response, the sponsor noted that supportive evidence existed with other surrogate products releasing IL-12. This was considered relevant as the product is expected

to deliver high activity of IL-12 locally and designed to have high retention within the CNS. In particular, the effects of such a surrogate product suggesting synergy with temozolomide in the relevant glioma model discussed. The COMP was sceptical with regards to the bridging of the effects observed in studies with other products, but noted that all the referenced studies had commonalities with regards to the IL-12 mechanism of action. The potential for add-on effects in combination with the existing products was therefore considered justified.

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

The intention to treat the condition with the medicinal product containing human interleukin 12 fused with immunoglobulin G4 C-terminal Fc fragment was considered justified based on improved survival reported in a relevant model of the proposed condition.

The condition is chronically debilitating due to symptoms caused by the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

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.

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 human interleukin 12 fused with immunoglobulin G4 C-terminal Fc fragment will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in relevant models, supporting add-on effects to temozolomide and radiotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human interleukin 12 fused with immunoglobulin G4 C-terminal Fc fragment, for treatment of glioma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. adeno-associated virus serotype rh74 containing the human sarcoglycan beta gene - EMA/OD/0000007270

Sarepta Therapeutics Ireland Limited; Treatment of limb-girdle muscular dystrophy

COMP Rapporteur: Dinah Duarte

The Committee agreed that the condition, limb-girdle muscular dystrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype rh74 containing the human sarcoglycan beta gene was considered justified based on non-clinical in vivo data showing an improvement in respiratory function and muscle strength as well as preliminary clinical data showing improvement in walking tests and the North Star Assessment for Dysferlinopathy, a validated questionnaire.

The condition is chronically debilitating due to muscle wasting, consequent reduced mobility and debilitating fatigue.

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

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

A positive opinion for adeno-associated virus serotype rh74 containing the human sarcoglycan beta gene, for treatment of limb-girdle muscular dystrophy, was adopted by consensus.

2.2.2. - EMA/OD/0000020657

Treatment of renal transplant interstitial fibrosis and tubular atrophy

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 December 2020 meeting.

2.2.3. - EMA/OD/0000034920

Treatment of mitochondrial epilepsy

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 December 2020 meeting.

2.2.4. (R)-3-(1-(2,3-dichloro-4-(pyrazin-2-yl)phenyl)-2,2,2-trifluoroethyl)-1-methyl-1-(1-methylpiperidin-4-yl)urea fumarate - EMA/OD/0000035401

Helsinn Birex Pharmaceuticals Limited; Treatment of Prader-Willi syndrome

COMP Rapporteur: Dinah Duarte

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 (R)-3-(1-(2,3-dichloro-4-(pyrazin-2-yl)phenyl)-2,2,2-trifluoroethyl)-1-methyl-1-(1-methylpiperidin-4-yl)urea fumarate was considered justified based on data in a non-clinical model of the condition showing reductions in excessive food intake.

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 (R)-3-(1-(2,3-dichloro-4-(pyrazin-2-yl)phenyl)-2,2,2-trifluoroethyl)-1-methyl-1-(1-methylpiperidin-4-yl)urea fumarate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the product improved the signs of hyperphagia in the model of the condition. This could be added to the currently used growth hormone treatment to address

the clinically relevant aspect of the condition which is not treated by growth hormone alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (R)-3-(1-(2,3-dichloro-4-(pyrazin-2-yl)phenyl)-2,2,2-trifluoroethyl)-1-methyl-1-(1-methylpiperidin-4-yl)urea fumarate, for treatment of Prader-Willi syndrome, was adopted by consensus.

2.2.5. - EMA/OD/0000037806

Treatment of soft tissue sarcoma

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 December 2020 meeting.

2.2.6. - EMA/OD/0000037877

Treatment of focal segmental glomerulosclerosis (FSGS)

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 December 2020 meeting.

2.2.7. - EMA/OD/0000039384

Treatment of idiopathic hypersomnia

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 December 2020 meeting.

2.2.8. aspacytarabine - EMA/OD/0000039550

Granzer Regulatory Consulting & Services; Treatment of acute myeloid leukaemia (AML)

COMP Rapporteur: 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 aspacytarabine was considered justified based on preliminary data showing a complete response in 30% of patients who are unfit for standard treatment.

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 1.3 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 aspacytarabine will be of significant benefit to the population at risk of developing the condition. The sponsor has provided preliminary clinical data that demonstrate a complete response in myelodysplastic syndrome patients who have

converted to acute myeloid leukaemia and are difficult to treat for which there are no treatment options. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.9. dabrafenib mesylate - EMA/OD/0000040009

Novartis Europharm Limited; Treatment of glioma

COMP Rapporteur: Bozena Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing dabrafenib mesylate was considered justified based on preliminary clinical data showing a response in patients with glioma BRAF V600+ advanced solid tumours.

The condition is chronically debilitating due to symptoms caused by compression of the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor survival of less than 5% for glioblastoma multiforme patients.

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.

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 dabrafenib mesylate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a complete response in a subset of patients who have glioma BRAF V600+ advanced solid tumours. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for dabrafenib mesylate, for treatment of glioma, was adopted by consensus.

2.2.10. humanised IgG1 monoclonal antibody against the extracellular domain of receptor tyrosine kinase-like orphan receptor 1 coupled via a proteolytically cleavable maleimidocaproyl-valine-citrulline-para-aminobenzoate linker to monomethyl auristatin E - EMA/OD/0000040364

TMC Pharma (EU) Limited; Treatment of mantle cell lymphoma (MCL)

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against the extracellular domain of receptor tyrosine kinase-like orphan receptor 1 coupled via a proteolytically cleavable maleimidocaproyl-valine-citrulline-para-aminobenzoate linker to monomethyl auristatin E was considered justified based on

non-clinical data in a model of the condition supporting inhibition of tumour growth, as well as clinical observations in heavily pre-treated patients with relapsed/refractory disease who responded to treatment with the product.

The condition is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss.

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 humanised IgG1 monoclonal antibody against the extracellular domain of receptor tyrosine kinase-like orphan receptor 1 coupled via a proteolytically cleavable maleimidocaproyl-valine-citrulline-para-aminobenzoate linker to monomethyl auristatin E will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in heavily pre-treated patients with relapsed/refractory disease who responded to treatment with the proposed product. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against the extracellular domain of receptor tyrosine kinase-like orphan receptor 1 coupled via a proteolytically cleavable maleimidocaproyl-valine-citrulline-para-aminobenzoate linker to monomethyl auristatin E, for treatment of mantle cell lymphoma, was adopted by consensus.

2.2.11. - EMA/OD/0000040375

Treatment of glioma

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

The intention to treat the condition with the medicinal product containing trametinib dimethyl sulfoxide was considered justified based on preliminary clinical data showing some low grade glioma (LGG) patients who had investigator confirmed responses following trametinib monotherapy.

The condition is chronically debilitating due to symptoms caused by compression of the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor survival of less than 5% for glioblastoma multiforme patients.

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.

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 trametinib dimethyl sulfoxide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients with refractory BRAFV600+ low grade glioma responded to treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for trametinib dimethyl sulfoxide, for treatment of glioma, was adopted by consensus.

2.2.12. - EMA/OD/0000040482

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 December 2020 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 17 November 2020.]

2.2.13. - EMA/OD/0000040564

Treatment of primary biliary cholangitis

The COMP adopted a list of issues that will be sent to the sponsor.

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 December 2020 meeting.

2.2.14. 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide targeting CD49d RNA - EMA/OD/0000040669

Pharma Gateway AB; Treatment of Duchenne muscular dystrophy

COMP Rapporteur: Julian Isla

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

The intention to treat the condition with the medicinal product containing 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide targeting CD49d RNA was considered justified based on preliminary clinical observations in affected patients, indicating a stabilisation of motor function.

The condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles; this is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure;

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.

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 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide targeting CD49d RNA will be of significant benefit to those affected by the condition. The sponsor has provided clinical data indicating stabilisation of motor function in non-ambulatory patients with different genotypes. This reflects a population which is broader than the one targeted by the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide targeting CD49d RNA, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.15. 4-[(3S)-3-aminopyrrolidin-1-yl]-6-cyano-5-(3,5-difluorophenyl)-N-[(2S)-1,1,1-trifluoropropan-2-yl]pyridine-3-carboxamide - EMA/OD/0000040890

Scendea (NL) B.V.; Treatment of congenital hyperinsulinism

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing 4-[(3S)-3-aminopyrrolidin-1-yl]-6-cyano-5-(3,5-difluorophenyl)-N-[(2S)-1,1,1-trifluoropropan-2-yl]pyridine-3-carboxamide was considered justified based on non-clinical in vivo data showing an improvement in glucose levels and normalisation of insulin serum levels.

The condition is life-threatening due to severe hypoglycaemia and chronically debilitating due to symptoms of hypoglycaemia such as pallor, sweat, tachycardia and neurological effects of chronic hypoglycaemia.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for 4-[(3S)-3-aminopyrrolidin-1-yl]-6-cyano-5-(3,5-difluorophenyl)-N-[(2S)-1,1,1-trifluoropropan-2-yl]pyridine-3-carboxamide, for treatment of congenital hyperinsulinism, was adopted by consensus.

2.2.16. 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting glycogen synthase 1 pre-mRNA - EMA/OD/0000041239

Ionis Development (Ireland) Limited; Treatment of progressive myoclonic epilepsy type 2 (Lafora disease)

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, progressive myoclonic epilepsy type 2 (Lafora 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'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting glycogen synthase 1 pre-mRNA was considered justified based on non-clinical data in a model of the condition showing reduced aggregation of glycogen (Lafora bodies) and reduced neuronal hyperexcitability.

The condition is life-threatening and chronically debilitating due to myoclonic seizures and generalised convulsions which escalate over time. This is also associated with cognitive decline. Individuals die within ten years of onset, usually from complications related to nervous system degeneration and status epilepticus.

The condition was estimated to be affecting approximately 0.04 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'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting glycogen synthase 1 pre-mRNA, for treatment of progressive myoclonic epilepsy type 2 (Lafora disease), was adopted by consensus.

2.2.17. - EMA/OD/0000041257

Treatment of LAMA2 congenital muscular dystrophy

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 December 2020 meeting.

2.2.18. Adeno-associated viral vector serotype 9 encoding human *ATP7B* - EMA/OD/0000041492

Ultragenyx Germany GmbH; Treatment of Wilson disease

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, Wilson disease, 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 encoding human *ATP7B* was considered justified based on non-clinical in vivo data showing a normalisation of copper serum levels and reduction in liver damage.

The condition is chronically debilitating and can be life-threatening due to the toxic effects of copper, first accumulating in the liver and later in the brain, leading to psychosis. The liver disease can present with symptoms ranging from mildly elevated transaminases to acute liver failure or liver cirrhosis. Around 5% of all patients are diagnosed only when they develop fulminant acute liver failure, sometimes fatal.

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 adeno-associated viral vector serotype 9 encoding human *ATP7B* will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that the use of the product in a model of the condition results in maintained expression of human *ATP7B* in the liver resulting in therapeutic lasting effect. This compares favourably to existing medicinal products, which have to be administered daily. The product has also a potential to reduce liver damage in the condition, an aspect of the condition which is not treated by existing authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 9 encoding human *ATP7B*, for treatment of Wilson disease, was adopted by consensus.

2.2.19. synthetic oligonucleotide selectively targeting UBE3A antisense RNA transcripts - EMA/OD/0000041660

Roche Registration GmbH; Treatment of Angelman syndrome

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, Angelman 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 oligonucleotide selectively targeting UBE3A antisense RNA transcripts was considered justified based on non-clinical data demonstrating the ability to unsilence the paternal copy of UBE3A. In addition, literature data shows that the use of an analogous product improves symptoms of the condition.

The condition is chronically debilitating due to developmental delay, motor and cognitive impairment, hyperactivity and epileptic seizures that are often treatment resistant.

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 synthetic oligonucleotide selectively targeting UBE3A antisense RNA transcripts, for treatment of Angelman syndrome, was adopted by consensus.

2.2.20. [Allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express beta-domain deleted human factor VIII - EMA/OD/0000041698](#)

TMC Pharma (EU) Limited; Treatment of haemophilia A

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express beta-domain deleted human factor VIII was considered justified based on non-clinical data showing a reduce bleeding time in a relevant model of the condition.

The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or during surgery, which may be also be life-threatening.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express beta-domain deleted human factor VIII will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate a long-term, sustained increase in factor VIII, that would obviate the need for continuous treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express beta-domain deleted human factor VIII, for treatment of haemophilia A, was adopted by consensus.

2.2.21. - EMA/OD/0000041707

Treatment of glioma

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 December 2020 meeting.

2.2.22. (S)-N-(5-(4-(1-(benzo[d][1,3]dioxol-5-yl)ethyl)piperazin-1-yl)-1,3,4-thiadiazol-2-yl)acetamide, hydrochloride salt - EMA/OD/0000041855

Granzer Regulatory Consulting & Services; Treatment of progressive supranuclear palsy

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing (S)-N-(5-(4-(1-(benzo[d][1,3]dioxol-5-yl)ethyl)piperazin-1-yl)-1,3,4-thiadiazol-2-yl)acetamide, hydrochloride salt was considered justified based on improvements in motor and lung function in an in vivo model of tauopathy.

The condition is chronically debilitating due to progressive neurological impairment including development of parkinsonism, inability to walk, progressive paralysis and cognitive deterioration. The condition is also life-threatening, leading to premature death.

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.

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 (S)-N-(5-(4-(1-(benzo[d][1,3]dioxol-5-yl)ethyl)piperazin-1-yl)-1,3,4-thiadiazol-2-yl)acetamide, hydrochloride salt, for treatment of progressive supranuclear palsy, was adopted by consensus.

2.2.23. - EMA/OD/0000042012

Treatment of follicular 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 December 2020 meeting.

2.2.24. erlotinib - EMA/OD/0000042029

Institut Des Maladies Genetiques; Treatment of patients with Olmsted syndrome

COMP Rapporteur: Zsofia Gyulai

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

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

The intention to treat the condition with the medicinal product containing erlotinib was considered justified based on preliminary clinical observations supporting improvements with regards to hyperkeratosis and pain in three patients affected by the condition.

The condition is chronically debilitating in particular due to progressive keratoderma in the palms and soles, periorificial keratotic plaques, erythromelalgia, pruritus and pain, which may lead to impairment of mobility and amputation.

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

A positive opinion for erlotinib, for treatment of Olmsted syndrome, was adopted by consensus.

2.2.25. perflubron - EMA/OD/0000042068

Boyd Consultants Limited; Treatment of respiratory distress syndrome

COMP Rapporteur: Elisabeth Johanne Rook

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

The intention to treat the condition with the medicinal product containing perflubron was considered justified based on non-clinical data in a model of the condition showing improved oxygenation and clinical data in patients showing improved lung function.

The condition is life-threatening due to acute- and extra pulmonary complications leading to high mortality rates and chronically debilitating due to the consequences of hypoxia including encephalopathy and iatrogenic morbidity related to respiratory assistance, such as bronchopulmonary dysplasia and retinopathy of prematurity.

The condition was estimated to be affecting approximately 2.5 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing perflubron will be of significant benefit to those affected by the condition. The sponsor has provided clinical data supporting the possibility to treat patients who have failed previous treatments, including surfactant. In addition, an improved effect of oxygenation was demonstrated in a non-clinical model of the condition in which perflubron was used in combination with surfactant as compared to surfactant alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for perflubron, for treatment of respiratory distress syndrome, was adopted by consensus.

2.2.26. - EMA/OD/0000042079

Treatment of pericarditis

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 December 2020 meeting.

2.2.27. [sulindac - EMA/OD/0000042080](#)

Aparito Netherlands B.V.; Treatment of fragile X syndrome

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing sulindac was considered justified based on non-clinical data in a model of the condition demonstrating an improvement in behavioural tests linked to reduction of anxiety and aggression, and improved learning ability.

The condition is chronically debilitating due to developmental delay, severe neurobehavioral and neurocognitive complications.

The condition was estimated to be affecting less than 3 in 10,000 persons in the European Union, at the time the application was made.

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 sulindac, for treatment of fragile X syndrome, was adopted by consensus.

2.2.28. [- EMA/OD/0000042085](#)

Treatment of primary intracerebral hemorrhage (pICH)

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 December 2020 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 rapporteurs](#)

COMP coordinators were appointed for 16 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 26 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of desmoid tumours

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 marginal zone lymphoma

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 glioblastoma

The Committee was briefed on the significant benefit issues.

3.1.4. -

Treatment of ornithine transcarbamylase deficiency

The Committee was briefed on the significant benefit issues.

3.1.5. -

Treatment of diffused large B-cell lymphoma

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 systemic mastocytosis

The finalised letter was circulated for information.

3.2.2. -

Treatment of neuroblastoma

The finalised letter was circulated for information.

3.2.3. -

Treatment of immune thrombocytopenia

The finalised letter was circulated for information.

3.2.4. -

Treatment of non-infectious uveitis

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of ATTR amyloidosis-cardiomyopathy

The new request was noted.

3.3.2. -

Treatment of cutaneous T-cell lymphoma

The new request was noted.

3.3.3. -

Treatment of thalassaemia

The new request was noted.

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

None

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

4.2.1. - somapacitan - EMEA/H/C/005030/0000, EU/3/18/2068, EMA/OD/0000033719

Novo Nordisk A/S; Treatment of growth hormone deficiency

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 January 2020 meeting.

4.2.2. - selinexor - EMEA/H/C/005127, EMA/OD/087/14, EU/3/14/1355,
EMA/OD/0000043722

Karyopharm Europe GmbH; Treatment of plasma cell myeloma

The status of the procedure at CHMP was noted.

4.2.3. ELZONRIS – tagraxofusp - EMEA/H/C/005031, EMA/OD/064/15, EU/3/15/1567,
EMA/OD/0000004627

TMC Pharma (EU) Limited; Treatment of blastic plasmacytoid dendritic cell neoplasm

COMP Rapporteurs: Bożenna Dembowska-Bagińska; Brigitte Schwarzer-Daum

An opinion recommending not to remove Elzonris, recombinant human interleukin-3 truncated diphtheria toxin fusion protein, tagraxofusp, EU/3/15/1567 for treatment of blastic plasmacytoid dendritic cell neoplasm from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its November meeting.]

4.2.4. - pemigatinib - EMEA/H/C/005266, EMA/OD/038/18, EU/3/18/2066,
EMA/OD/0000039241

Incyte Biosciences Distribution B.V.; Treatment of biliary tract cancer

The COMP adopted a list of issues that will be sent to the sponsor.

The reply to the list of questions will be discussed at the December 2020 meeting.

4.2.5. - potassium - EMEA/H/C/005407, EMA/OD/016/17, EU/3/17/1888,
EMA/OD/0000032257

Advicenne Pharma S.A.; Treatment of distal renal tubular acidosis

The status of the procedure at CHMP was noted.

4.2.6. - moxetumomab pasudotox- EMEA/H/C/005322, EMA/OD/066/08, EU/3/08/592,
EMA/OD/0000013333

AstraZeneca AB; Treatment of hairy cell leukaemia

The status of the procedure at CHMP was noted.

4.2.7. - fedratinib

Celgene Europe BV

a) Treatment of primary myelofibrosis, EMEA/H/C/005026/0000, EMA/OD/069/10, EU/3/10/794, EMA/OD/0000029092

b) Treatment of post-essential thrombocythaemia myelofibrosis EMEA/H/C/005026/0000, EMA/OD/084/10, EU/3/10/810, EMA/OD/0000029093

c) Treatment of post-polycythaemia vera myelofibrosis EMEA/H/C/005026/0000, EMA/OD/092/10, EU/3/10/811, EMA/OD/0000029095

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 December 2020 meeting.

4.2.8. – idecabtagene vicleucel - EMEA/H/C/004662/0000, EU/3/17/1863, EMA/OD/0000035635

Accelerated assessment

Celgene Europe BV; Treatment of multiple myeloma

The status of the procedure at CHMP was noted.

4.2.9. Puldysa – idebenone - EMEA/H/C/005123, EMEA/OD/077/06, EU/3/07/437, EMA/OD/0000028997

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

The COMP noted the withdrawal of initial marketing authorisation application.

4.3. **Appeal**

None

4.4. **On-going procedures**

COMP co-ordinators were appointed for 7 applications.

4.5. **Orphan Maintenance Reports**

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Kaftrio - ivacaftor/tezacaftor/elexacaftor - EMEA/H/C/005269/II/0001, EMA/OD/0000001208, EU/3/18/2116, EMA/OD/0000042077

Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

CHMP Rapporteur: Johann Lodewijk Hillege

The status of the procedure at CHMP was noted.

5.2.2. Kalydeco - ivacaftor - EMEA/H/C/002494/II/0089, EMA/OD/010/08, EU/3/08/556, EMA/OD/0000042076

Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

CHMP Rapporteur: Maria Concepcion Prieto Yerro

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 30 October 2020.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report from CHMP

Documents were tabled for information.

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

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

None

7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

None

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. 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

The COMP noted that further discussions on the draft document are needed and agreed to have discussions in-between the plenaries. The final adoption of the work plan is foreseen in January 2021.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020 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. Nomination of COMP representative for ENCePP Steering Group 2021-2023

The COMP agreed that Frauke Naumann-Winter will continue to represent COMP in ENCePP Steering Group 2021-2023.

8.2. Letter from sponsor

The COMP noted the letter and agreed that the OMAR will be revised by the committee and response letter will be sent.

9. 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/

10. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 3-5 November 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva - Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Vasileios Loutas	Member	Cyprus	No interests declared	
Lenka Gaidadzi	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsafia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	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	Slovakia	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Virginie Hivert	Expert*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Meeting run with support from relevant EMA staff				

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