18 January 2018
EMA/COMP/730551/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 05-07 December 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

5 December 2017, 08:30-18:30, room 2F

6 December 2017, 08:30-19:00, room 2F

7 December 2017, 08:30-12:30, 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

COMP agenda for 05-07 December 2017 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 30-31 October 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. N-(bromoacetyl)-3,3-dinitroazetidine - EMA/OD/166/17

Sirius Regulatory Consulting Limited; Treatment of small cell lung cancer

COMP coordinator: Ingrid Wang

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 small cell lung cancer, the sponsor should further elaborate on the presented preliminary clinical data regarding patent population, previous treatments and efficacy outcomes.

In the written response, the sponsor provided some further information on the available preliminary clinical data. The sponsor indicated a potential placement of the proposed product as a chemotherapy sensitiser in 3rd line after topotecan failure. Preliminary clinical data were discussed in support of the clinical positioning and the efficacy of the product in this setting. The COMP considered that the totality of evidence was sufficient to demonstrate medical plausibility and significant benefit for the purpose of orphan designation. The oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing N-(bromoacetyl)-3,3-dinitroazetidine was considered justified based on non-clinical and preliminary clinical data demonstrating that treatment was able to induce anti-tumour effects when used as chemotherapy sensitiser to platinum based chemotherapy.

The condition is chronically debilitating and life- threatening due to its rapid progression and the development of widespread metastases, with a 5-year overall survival of 5-10%.

The condition was estimated to be affecting approximately 1.2 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 N-(bromoacetyl)-3,3-dinitroazetidine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients responded to treatment with the proposed product as chemotherapy sensitiser to platinum based chemotherapy. The studied patients received best standard of care including authorised products and the observed treatment effects compared favourably to currently authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-(bromoacetyl)-3,3-dinitroazetidine, for treatment of small cell lung cancer, was adopted by consensus.

2.1.2. Pyrazolo[1,5-a]pyrimidine, 3-[4-chloro-2-(4-morpholinyl)-5-thiazolyl]-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,3-a]pyrimidine - EMA/OD/164/17

RegIntel Limited; Treatment of congenital adrenal hyperplasia

COMP coordinator: Vallo Tillmann

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of congenital adrenal hyperplasia, the sponsor should further elaborate on the data obtained in the clinical study and to complement them with all data available to date.

In the written response, the sponsor provided additional data from the previously presented clinical study. Interim data were provided showing a mean reduction from baseline in both adrenocorticotropic hormone (ACTH) and 17-hydroxyprogesterone (17-OHP) AUC0-10hr and a reduction in mean testosterone concentrations. The Committee considered these data as sufficient for the support of significant benefit at the time of orphan designation and consequently the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing pyrazolo[1,5-a]pyrimidine, 3-[4-chloro-2-(4-morpholinyl)-5-thiazolyl]-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,3-a]pyrimidine was considered justified based on clinical data showing an effect on plasma levels of biomarkers relevant to the condition.

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

The condition was estimated to be affecting 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 pyrazolo[1,5-a]pyrimidine, 3-[4-chloro-2-(4-morpholinyl)-5-thiazolyl]-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,3-a]pyrimidine will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients treated with the product in combination with the standard of care may achieve reduction of disease relevant biomarkers, which would in turn allow lowering the doses of glucocorticoid treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pyrazolo[1,5-a]pyrimidine, 3-[4-chloro-2-(4-morpholinyl)-5-thiazolyl]-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,3-a]pyrimidine, for treatment of congenital adrenal hyperplasia, was adopted by consensus.

2.1.3. - EMA/OD/160/17

Treatment of cerebral autosomal-dominant arteriopathy with subcortical infarcts and 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 if there exists a scientific rationale for the development of the proposed product for treatment of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the sponsor should present additional non-clinical data from valid models or more clinical data from patients affected by the condition.

In the written response, and during an oral explanation before the Committee on 6 December 2017, the sponsor provided some more information on the earlier provided data

and presented additional clinical data from one patient affected by the condition, who was treated with the proposed product. The COMP was of the opinion that the provided non-clinical and clinical data was too limited and did not allow elucidating the efficacy of the treatment. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 December 2017, prior to the final opinion.

2.1.4. Autologous skeletal myoblasts expanded ex vivo - EMA/OD/144/17

Assistance Publique - Hopitaux de Paris (APHP); Treatment of oculopharyngeal muscular dystrophy (OPMD)

COMP coordinator: Pauline Evers

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:

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of oculopharyngeal muscular dystrophy (OPMD), the sponsor should further elaborate on:

- the cell populations in the proposed product.
- the expected effects of cricopharyngeal myotomy alone in the context of the effects reported in the preliminary clinical study.
- the follow-up data on the '6 withdrawal patients' of the 2011-2013 cohort, ideally on endpoints that would allow comparison with the patients that received the product.
- the results from the presented clinical study and its relevance for the development of the product in the condition.
- the surgical technique used and the exact anatomic site of the product's injections (ideally complemented by intraoperative photographs or diagrams).

In the written response, and during an oral explanation before the Committee on 6 December 2017, the sponsor further clarified the cell populations within the proposed product. The COMP considered this question sufficiently addressed.

The issue of whether any effects could be attributed to the proposed product was examined by using external (bibliography) and internal (patients who only received myotomy) controls. It was pointed out that while myotomy would provide short term improvements (<6 m), the case is different for longer observation periods. The applicant cited a study by Coiffier et al (Otolaryngology–Head and Neck Surgery (2006) 135, 218-222) where the authors report that "one third of the patients exhibited a recurrence of symptoms within 3 years". This was juxtaposed to the sponsor's results with the proposed product, where improvements in swallowing were maintained for all patients at 12 months and for 80% patients at 24 months. The applicant thus argued that there are clinically relevant effects that may be attributed to the product. The COMP considered however that the results of this indirect comparison do not show improved effects, when the product is used in combination with surgery compared to surgery alone, and as such medical plausibility was difficult to justify.

It was also noted that three patients received myotomy only without cell injections, but no data from functional assessment in these patients were presented. Among these 3 patients,

one patient demonstrated an improved swallowing maintained after two years of follow up and for the two others, a deterioration of the swallowing was observed at one year.

Based on these points it can be argued that a) the external controls discussed do not support a clear improvement with the addition of cell injections with cricopharyngeal myotomy, and b) the potential internal controls have not been fully evaluated in a follow-up and are difficult to consider as well. Therefore the medical plausibility was not considered justified.

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

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

The COMP considered that the sponsor has not established the intention to treat the condition with the medicinal product containing autologous skeletal myoblasts expanded ex vivo:

The sponsor provided clinical observations in affected patients, and argued that the combination of the product with cricopharyngeal myotomy results in improved swallowing function.

However, the COMP was of the opinion that the preliminary clinical observations provided by the sponsor do not support improved swallowing function in combination with cricopharyngeal myotomy, when compared to the effects of cricopharyngeal myotomy alone, as attested in bibliographical sources.

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

A negative opinion for autologous skeletal myoblasts expanded ex vivo, for treatment of oculopharyngeal muscular dystrophy, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.1.5. - EMA/OD/161/17

Treatment of haematopoietic stem cell transplantation

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 appears to have provided a prevalence which was an underestimate based on data from The European Society for Blood and Marrow Transplantation (EBMT) Survey published in 2017. 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.

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".

- Significant benefit

The sponsor has not established how the product could be of significant benefit within the context of the treatment of patients who are going to receive haematopoietic stem cell transplantation. The sponsor should detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 5 December 2017, the sponsor provided a revised prevalence calculation of 0.64 in 10,000, which was accepted by the COMP.

The sponsor could not sufficiently substantiate the significant benefit of the proposed product *versus* authorised treatments in patients who are going to receive haematopoietic stem cell transplantation. In conclusion, the COMP was not in a position to recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 December 2017, prior to final opinion.

2.1.6. - EMA/OD/159/17

Treatment of haematopoietic stem cell transplantation

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 appears to have provided a prevalence which was an underestimate based on data from EBMT Survey published in 2017. 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.

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".

- Significant benefit

The sponsor has provided bibliographical data showing the well-established use of the product in the condition.

The sponsor has not established how the product could be of significant benefit within the context of the treatment of patients who are going to receive haematopoietic stem cell transplantation. The sponsor should detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 5 December 2017, the sponsor provided a revised prevalence calculation of 0.64 in 10,000, which was accepted by the COMP.

The sponsor could not sufficiently substantiate the significant benefit of the proposed product versus authorised treatments in patients who are going to receive haematopoietic stem cell transplantation. In conclusion, the COMP was not in a position to recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 December 2017, prior to final opinion.

2.1.7. Adeno-associated viral vector serotype 2/6 encoding zinc-finger nucleases and the human alpha L-iduronidase gene - EMA/OD/167/17

Quintiles Ireland Limited; Treatment of mucopolysaccharidosis type I

COMP coordinator: Armando Magrelli

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

- Number of people affected

The sponsor has used a bibliographical basis for the establishment of prevalence ranging from 1990 to 2012. There is no discussion regarding the impact of enzyme replacement therapy and well established registries which would help understand how the prevalence of the condition is evolving.

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.

In the written response, the sponsor acknowledged the potential impact of laronidase on improved survival of mucopolysaccharidosis type I patients since its introduction in 2003. The revised calculation included adjustments that take into considerations the improved survival and increase in patient numbers. The COMP accepted this revised calculation as reflecting the current situation in Europe and noted that this was an increase from the older calculations provided which were 0.025 in 10,000. The Committee agreed that the condition, mucopolysaccharidosis type I, 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 2/6 vectors encoding zinc finger nucleases and the human alpha L-iduronidase gene was considered justified based on non-clinical data showing a normalisation of glycosaminoglucans and attenuation of cognitive decline.

The condition is chronically debilitating due to facial dysmorphism, hepatosplenomegaly, upper airway obstruction, skeletal deformity, cardiomyopathy, central nervous system manifestations and life-threatening with death ensuing by adolescence if the severe form of the disease is left untreated.

The condition was estimated to be affecting approximately 0.05 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 2/6 encoding zinc-finger nucleases and the human alpha L-iduronidase gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating

an attenuation of cognitive decline. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 2/6 encoding zinc-finger nucleases and the human alpha L-iduronidase gene, for treatment of mucopolysaccharidosis type I, was adopted by consensus.

2.1.8. Adeno-associated viral vector serotype 2/6 encoding zinc-finger nucleases and the human iduronate 2-sulfatase gene - EMA/OD/168/17

Quintiles Ireland Limited; Treatment of mucopolysaccharidosis type II (Hunter's syndrome)

COMP coordinator: 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 mucopolysaccharidosis type II, the sponsor should further elaborate on the methodology used in the non-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

In the written response, the sponsor clarified some concerns of the COMP regarding the use of different vectors regarding their serotype. Furthermore, the sponsor discussed with data the levels of off-target gene expression in other tissues and the minimum level of gene-expression in order to maintain efficacy. Overall the COMP considered the responses provided were sufficient for recommending granting the orphan designation for this submission.

The Committee agreed that the condition, mucopolysaccharidosis type II (Hunter's syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype 2/6 vectors encoding zinc finger nucleases and the human iduronate 2-sulfatase gene was considered justified based on non-clinical data in a valid model of the condition showing a normalisation of glycosaminoglycan levels and attenuation of neurological decline.

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

The condition was estimated to be affecting approximately 0.02 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 2/6 encoding zinc-finger nucleases and the human iduronate 2-sulfatase gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating attenuation in neurological decline. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 2/6 encoding zinc-finger nucleases and the human iduronate 2-sulfatase gene, for treatment of mucopolysaccharidosis type II (Hunter's syndrome), was adopted by consensus.

2.1.9. - EMA/OD/096/17

Treatment of adult-onset Still's disease

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 17 November 2017, prior to responding to the list of issues.

2.1.10. - EMA/OD/129/17

Treatment of systemic juvenile idiopathic arthritis

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 16 November 2017, prior to responding to the list of issues.

2.1.11. Humanised Fc-engineered monoclonal antibody against CD19 - EMA/OD/155/17

MWB Consulting Ltd; Treatment of IgG4-related disease

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 proposed to extrapolate prevalence data from Japan to the whole of the EU. Meanwhile, individual organ specific manifestations of the condition are reported as cumulatively higher in numbers within the EU.

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.

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.

- Significant benefit

The sponsor claimed significant benefit based on the achievement of disease remission when the product was used in combination with steroid treatment. The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor should detail the results of any clinical data, including individual patient information to support the significant benefit assumption in the context of the current therapeutic management of patients. Any data that would allow teasing apart the effects of steroid treatment and the treatment with the proposed product would be considered of relevance for the significant benefit discussion.

In the written response, the sponsor provided an extensive discussion of prevalence and three ways of calculating the point prevalence of the condition based on a) data from Japan, b) prevalence of analogous disease and c) prevalence of individual organ manifestations. Based on triangulation estimates the sponsor proposed the mean prevalence of IgG4-RD to be 3.2 in 10.000 persons in the EU. The Committee accepted this estimate taking into account paucity of data available.

Additionally, the sponsor submitted detailed data from the previously discussed clinical study showing that patients who have previously not achieved full remission while on long term corticosteroid treatment achieved improvement on the Responder Index scale. Furthermore, patients who did not receive concomitant corticosteroids were reported to achieve similar responses and could be tapered off steroid treatment within 2 months. The Committee considered these data as sufficient for the support of significant benefit at the time of orphan designation and consequently the oral explanation was cancelled.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of IgG4-related disease and to rename the active substance to humanised Fc-engineered monoclonal antibody against CD19.

The Committee agreed that the condition, treatment of IgG4-related disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised Fc-engineered monoclonal antibody against CD19 was considered justified based on clinical data demonstrating successful induction of disease remission.

The condition is life-threatening due to fibrosis and end stage organ damage and chronically debilitating due to persistent inflammation in affected organs, weight loss, fevers, fatigue and pain.

The condition was estimated to be affecting less than 3.2 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 humanised Fc-engineered monoclonal antibody against CD19 will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that treatment with the product contributes to the disease remission in patients who do not respond adequately to corticosteroid treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for containing humanised Fc-engineered monoclonal antibody against CD19, for treatment of IgG4-related disease, was adopted by consensus.

2.1.12. - EMA/OD/152/17

Treatment of atypical haemolytic uremic syndrome

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 14 November 2017, prior to responding to the list of issues.

2.1.13. Adeno-associated viral vector serotype 5 encoding a microRNA targeted to human huntingtin gene - EMA/OD/151/17

uniQure biopharma B.V.; Treatment of Huntington's disease

COMP coordinator: Violeta Stoyanova

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Huntington's disease, the sponsor should present the final and mature non-clinical data from all ongoing and finalised non-clinical studies.

In the written response, the sponsor provided the full and mature non-clinical dataset as requested by the COMP. The non-clinical data from a valid model suggest that the product is able to maintain motor function, which confirms the trends that have been observed at interim analysis. The COMP was of the opinion that this is sufficient evidence for medical plausibility at orphan designation stage. The oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 5 encoding a microRNA targeted to human huntingtin gene was considered justified based on non-clinical data suggesting that the product is able to maintain motor function.

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

The condition was estimated to be affecting approximately 1.2 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 adeno-associated viral vector serotype 5 encoding a microRNA targeted to human huntingtin gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data suggesting that the product is able to maintain motor function. This treatment therefore intends to improve manifestations of the condition that are currently not addressed by the authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for containing adeno-associated viral vector serotype 5 encoding a microRNA targeted to human huntingtin gene, for treatment of Huntington's disease, was adopted by consensus.

2.1.14. - EMA/OD/095/17

Treatment of pancreatic cancer

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 17 November 2017, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/195/17

Prevention of radiotherapy-induced oral mucositis in head and neck cancer patients

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 meeting.

2.2.2. - EMA/OD/188/17

Treatment of chronic myeloid leukaemia

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 meeting.

2.2.3. - EMA/OD/193/17

Treatment of acute myeloid leukaemia

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 meeting.

2.2.4. – EMA/OD/170/17

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 January meeting.

2.2.5. Allogeneic umbilical cord blood CD34+ cells cultured *ex vivo* with Notch ligand Delta1 - EMA/OD/192/17

Voisin Consulting S.A.R.L.; Treatment in haematopoietic stem cell transplantation

COMP coordinator: Frauke Naumann-Winter

Following review of the application by the Committee, it was agreed to rename the active substance to allogeneic umbilical cord blood CD34+ cells cultured *ex vivo* with Notch ligand Delta1.

The Committee agreed that the treatment in haematopoietic stem cell transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic umbilical cord blood CD34+ cells cultured *ex vivo* with Notch ligand Delta1 was considered

justified based on preliminary clinical data demonstrating that treatment was able to improve the engraftment and reduce the incidence of acute graft-versus-host disease compared to historical control.

The condition is life-threatening due to relapse of the primary disease and graft-versus-host disease.

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 allogeneic umbilical cord blood CD34+ cells cultured *ex vivo* with Notch ligand Delta1 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that treatment was able to improve the engraftment and reduce incidence of acute graft-versus-host disease compared to historical control. Treatment was provided concomitantly with an umbilical cord blood cell graft and subsequently patients received the best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic umbilical cord blood CD34+ cells cultured *ex vivo* with Notch ligand Delta1, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.2.6. - EMA/OD/173/17

Treatment of cystic 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 January meeting.

2.2.7. - EMA/OD/305/16

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 January meeting.

2.2.8. Cannabidiol - EMA/OD/165/17

GW Research Ltd; Treatment of tuberous sclerosis

COMP coordinator: Dinah Duarte

The Committee agreed that the condition, tuberous sclerosis, 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 data showing a reduction in seizure frequency in patients with the condition.

The condition is chronically debilitating due to facial disfigurement and severe neurological symptoms and life-threatening due to the formation of multiple tumours.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cannabidiol will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating a relevant reduction in seizure frequency in patients refractory to anticonvulsant therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cannabidiol, for treatment of tuberous sclerosis, was adopted by consensus.

2.2.9. - EMA/OD/150/17

Treatment of graft-versus-host 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 January meeting.

2.2.10. Ciclopirox - EMA/OD/186/17

Atlas Molecular Pharma S.L.; Treatment of congenital erythropoietic porphyria

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing ciclopirox was considered justified based on non-clinical data in a valid model of the condition showing reduction in the accumulation of porphyrins in tissues and reduced splenomegaly.

The condition is life-threatening and chronically debilitating due to skin photosensitivity, anaemia, and liver complications.

The condition was estimated to be affecting less than 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 ciclopirox, for treatment of congenital erythropoietic porphyria, was adopted by consensus.

2.2.11. - EMA/OD/178/17

Treatment of Stargardt's 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 January meeting.

2.2.12. - EMA/OD/198/17

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 January meeting.

2.2.13. Gilteritinib - EMA/OD/175/17

Astellas Pharma Europe B.V.; Treatment of acute myeloid leukaemia

COMP coordinator: Karri Penttila

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

The intention to treat the condition with the medicinal product containing gilteritinib was considered justified based on preliminary clinical data demonstrating that patients responded to treatment.

The condition is life-threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

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 gilteritinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that relapsed or refractory patients responded to treatment. There are currently no authorised treatments for this patient population. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.14. - EMA/OD/171/17

Treatment of short bowel syndrome

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

2.2.15. - EMA/OD/189/17

Treatment of haemophilia A

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

2.2.16. - EMA/OD/190/17

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 January meeting.

2.2.17. Hydroxychloroquine sulphate - EMA/OD/177/17

Professor Pascale De Lonlay; Treatment of LIPIN1 disease

COMP coordinator: Michel Hoffmann

The Committee agreed that the condition, LIPIN1 disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing hydroxychloroquine sulphate was considered justified based on preliminary clinical data showing a reduction in rhabdomyolysis attacks and improvement in symptoms such as heart failure and the 6 minute walking test.

The condition is life-threatening and chronically debilitating due to complications associated with acute rhabdomyolysis attacks which breaks down and damages skeletal muscle. Mortality rate is around 10%, significantly higher when rhabdomyolysis is complicated by renal failure or by cardiac arrest with arrhythmia due to hyperkalaemia.

The condition was estimated to be affecting approximately 0.0005 in 10,000 persons in the European Union, at the time the application was made;

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 hydroxychloroquine sulphate, for treatment of LIPIN1 disease, was adopted by consensus.

2.2.18. Itacitinib - EMA/OD/169/17

Incyte Biosciences UK Ltd; Treatment of graft-versus-host disease

COMP coordinator: Martin Možina

The Committee agreed that the condition, graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing itacitinib was considered justified based on clinical data demonstrating improved overall response rate when the product is used on top of standard of care.

The condition is chronically debilitating and life-threatening in particular due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

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 itacitinib will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product leads to improved overall response rate when used in combination with corticosteroids in first line treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for itacitinib, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.19. - EMA/OD/191/17

Treatment in cardiopulmonary by-pass

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 meeting.

2.2.20. - EMA/OD/312/16

Treatment of hepatocellular carcinoma

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 meeting.

2.2.21. Metformin and L-citrulline - EMA/OD/154/17

Duchenne UK; Treatment of Duchenne muscular dystrophy

COMP coordinator: Ingeborg Barisic

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 metformin and L-citrulline was considered justified based on preliminary clinical data showing a reduction in the muscular decline.

The condition is life-threatening and chronically debilitating due to progressive weakness occurring throughout the proximal musculature affecting the muscles of the hips, thighs, pelvic area and shoulders and eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

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 metformin and L-citrulline will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a reduction in the decline in muscular function in a wider patient population than treated with

the currently authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for metformin and L-citrulline, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.22. N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea, hydrochloride salt - EMA/OD/179/17

Millendo Therapeutics Ltd; Treatment of congenital adrenal hyperplasia

COMP coordinator: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea, hydrochloride salt was considered justified based on clinical data in the condition demonstrating reductions in steroid hormone precursor levels.

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

The condition was estimated to be affecting 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 N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea, hydrochloride salt will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product lowers steroid precursor levels. This effect could allow for a more physiologic dosing of glucocorticoids. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea, hydrochloride salt, for treatment of congenital adrenal hyperplasia, was adopted by consensus.

2.2.23. - EMA/OD/180/17

Treatment of acromegaly

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 meeting.

2.2.24. Recombinant adeno-associated virus serotype 2/1 vector encoding human beta-hexosaminidase alpha and beta subunits - EMA/OD/182/17

University of Cambridge; Treatment of GM2 gangliosidosis

COMP coordinator: Lesley Greene/Fernando Méndez Hermida

The Committee agreed that the condition, GM2 gangliosidosis, 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 virus serotype 2/1 vector encoding human beta-hexosaminidase alpha and beta subunits was considered justified based on non-clinical data in models of the condition showing extension of survival, and the prevention of lysosomal storage and CNS inflammation.

The condition is life-threatening with a reduced life expectancy of 3 to 15 years in infantile and juvenile onset patients, and chronically debilitating due to ataxia, muscle weakness, loss of motor function, sight, hearing and development of seizures and dementia.

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.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 virus serotype 2/1 vector encoding human beta-hexosaminidase alpha and beta subunits, for treatment of GM2 gangliosidosis, was adopted by consensus.

2.2.25. - EMA/OD/176/17

Treatment of Myasthenia Gravis

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 meeting.

2.2.26. Sirolimus - EMA/OD/184/17

Rare Partners srl Impresa Sociale; Treatment of sickle cell disease

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on non-clinical data showing that treatment with the proposed product in valid models of the condition increased the life span of circulating sickle cell erythrocytes, and reduced the extent of important complications of sickle cell disease such as enlarged spleen size and hepatic iron accumulation.

The condition is life-threatening and chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections.

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 sirolimus will be of significant benefit to those affected by the condition. The sponsor has provided data showing that the combination of the proposed product with hydroxyurea, currently authorised for the condition, increased the levels of foetal haemoglobin in cells from patients affected by the condition more than either product alone. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for sirolimus, for treatment of sickle cell disease, was adopted by consensus.

2.2.27. Vatiquinone - EMA/OD/145/17

Edison Orphan Pharma BV; Treatment of RARS2 syndrome

COMP coordinator: Robert Nistico

Following review of the application by the Committee, it was agreed to rename the indication to treatment of RARS2 syndrome.

The Committee agreed that the condition, RARS2 syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing vatiquinone was considered justified based on preliminary clinical data showing improvement of status epilepticus and of other relevant outcome measures after treatment with the proposed product.

The condition is life-threatening and chronically debilitating due to early onset and rapidly progressing encephalopathy, status epilepticus, seizures, recurrent infections, spastic dystonic quadriplegia, and developmental delay. Of 29 patients described in the literature, five died before 5 years of age.

The condition was estimated to be affecting less than 0.001 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 vatiquinone, for treatment of RARS2 syndrome, was adopted by consensus.

2.2.28. - EMA/OD/185/17

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 January 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 1 application submitted and 23 upcoming applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of spinal muscular atrophy

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 plasma cell myeloma

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 sickle cell disease

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

3.1.4. -

Treatment of ornithine transcarbamylase deficiency

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

3.1.5. -

Treatment of Lennox-Gastaut syndrome

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

3.1.6. -

Treatment of mantle cell lymphoma

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

3.1.7. -

Treatment of acute myeloid leukaemia

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

3.1.8. -

Treatment of myelodysplastic syndromes

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

3.1.9. -

Treatment of Leber's hereditary optic neuropathy

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 chronic lymphocytic leukaemia

The finalised letter was circulated for information.

3.2.2. -

Treatment of idiopathic pulmonary fibrosis

The finalised letter was circulated for information.

3.2.3. -

Treatment of small cell lung cancer

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of Niemann-Pick disease, type C

The new request was noted.

3.3.2. -

Treatment of mucopolysaccharidosis type I

The new request was noted.

3.3.3. -

TKI inhibitor for treatment of gastrointestinal stromal tumors

The new request was noted.

3.3.4. -

Treatment of cutaneous T-cell lymphoma

The new request was noted.

3.3.5. -

Treatment of diffuse large B-cell lymphoma

The new request was noted.

3.3.6. -

Treatment of multiple myeloma

The new request was noted.

3.3.7. -

Treatment of glioma

The new request was noted.

3.3.8. -

Treatment of multiple myeloma

The new request was noted.

3.3.9. -

Treatment of paroxysmal nocturnal haemoglobinuria

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

4.1.1. Jorveza - budesonide - EMEA/H/C/004655, EMA/OD/078/13, EU/3/13/1181

Dr. Falk Pharma GmbH; Treatment of eosinophilic esophagitis

COMP coordinators: Geraldine O'Dea/Frauke Naumann-Winter

A list of issues was adopted on 31 October 2017.

An oral explanation was held on 5 December 2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted an opinion not to remove Jorveza from the EC Register of Orphan Medicinal Products by consensus. The Icelandic and Norwegian Members were in agreement with the Committee recommendation.

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

4.1.2. Adcetris - Brentuximab vedotin – Type II variation - EMA/OD/100/11, EU/3/11/939, EMEA/H/C/002455/II/0048

Takeda Pharma A/S - Denmark; Treatment of cutaneous T-cell lymphoma

COMP coordinator: Daniel O'Connor / Brigitte Bloechl-Daum / Kateřina Kopečková; CHMP rapporteur: Paula Boudewina van Hennik; CHMP co-rapporteur: Jan Mueller-Berghaus

A list of issues was adopted on 15 June 2017.

An oral explanation was held on 5 December 2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted an opinion not to remove Adcetris from the EC Register of Orphan Medicinal Products by consensus. The Icelandic and Norwegian Members were in agreement with the Committee recommendation.

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

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

4.2.1. Lenvima - Lenvatinib – Type II variation - EMEA/H/C/003727/II/0011/G, EMA/OD/287/14, EU/3/15/1460

Eisai Ltd; Treatment of hepatocellular carcinoma

CHMP rapporteur: Bart Van der Schueren; CHMP co-rapporteur: Robert James Hemmings

The status of the procedure at CHMP was noted.

4.2.2. - plitidepsin – EMEA/H/C/004354, EMEA/OD/044/04, EU/3/04/245

Pharma Mar SA; Treatment of multiple myeloma

The status of the procedure at CHMP was noted.

4.2.3. - expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue – EMEA/H/C/004258, EMEA/OD/054/09, EU/3/09/667

TIGENIX, S.A.U.; Treatment of anal fistula

A list of issues was adopted on 19 January 2017.

An oral explanation was held on 5 December 2017.

In the written response, and during an oral explanation before the Committee on 5 December 2017, the sponsor discussed the prevalence calculation and the significant benefit.

The COMP considered that the sponsor's methodology did not provide sufficient evidence on the prevalence of anal fistula of all potential aetiologies. The methodology did not take into consideration all available data sources from the scientific literature. In addition, the assumption that a maximum of 15% of Crohn's disease patients develop anal fistulas was not sufficiently substantiated, because there is scientific literature to suggest higher figures.

Furthermore, the COMP was of the opinion that the sponsor has failed to establish with the presented data that Alofisel is of significant benefit to the patients of the orphan condition as defined in the granted therapeutic indication. The observed improvement in combined remission did not lead to improvements in quality of life of patients as measured by secondary endpoints. Moreover, the clinical trial design and the overall outcome did not allow the COMP to quantify the clinically relevant advantage relative to the best standard of care including surgical procedures and authorised anti-TNF treatment with infliximab. Indirect comparisons of efficacy versus infliximab were attempted but not considered methodologically valid.

The Committee adopted an opinion to remove Alofisel from the EC Register of Orphan Medicinal Products by majority. The divergent positions were appended to this opinion. The sponsor will have 90 days to appeal from the COMP decision.

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 December meeting and upon adoption of CHMP opinion.*]

4.2.4. - rucaparib - EMEA/H/C/004272, EMA/OD/085/12, EU/3/12/1049

Clovis Oncology UK Ltd; Treatment of ovarian cancer

The status of the procedure at CHMP was noted.

4.2.5. Lamzede - velmanase alfa - EMEA/H/C/003922, EMEA/OD/074/04, EU/3/04/260,

Chiesi Farmaceutici S.p.A.; Treatment of alpha-Mannosidosis

The Committee adopted an opinion not to remove Lamzede from the EC Register of Orphan Medicinal Products by consensus. The Icelandic and Norwegian Members were in agreement with the Committee recommendation.

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 January meeting and upon adoption of CHMP opinion.*]

4.2.6. - glibenclamide - EMEA/H/C/004379, EMA/OD/149/15, EU/3/15/1589

Ammtek; Treatment of neonatal diabetes

The status of the procedure at CHMP was noted.

4.2.7. CRYSVITA - burosumab - EMEA/H/C/004275, EMEA/H/C/004275, EU/3/14/1351

Kyowa Kirin Limited; Treatment of hypophosphataemic rickets

A list of issues for written responses only was adopted on 31 October 2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted an opinion not to remove CRYSVITA from the EC Register of Orphan Medicinal Products by consensus. The Icelandic and Norwegian Members were in agreement with the Committee recommendation.

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 December meeting and upon adoption of CHMP opinion.*]

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for three applications.

4.5. Public Summary of Opinions

None.

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

5.1. After adoption of CHMP opinion

5.1.1. 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 COMP finally agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

5.2. Prior to adoption of CHMP opinion

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

Pfizer Limited - UK; Treatment of chronic myeloid leukaemia

CHMP rapporteur: Harald Enzmann

The status of the procedure at CHMP was noted.

5.2.2. Lynparza - (Olaparib) – EMEA/H/C/003726/X/0016/G, EMEA/OD/063/07, EU/3/07/501

AstraZeneca AB - Sweden; Treatment of ovarian cancer

CHMP rapporteur: Alexandre Moreau

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.

5.3. Appeal

None

5.4. On-going procedures

None

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, 26-28 March 2018, The Netherlands

Document(s) tabled:
Invitation COMP Strategic Review and Learning Meeting 26-28 March 2018

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 5 December 2017.

7.1.3. Non-Clinical Working Group

The working group on Non-clinical Models met on 10 November 2017.

7.1.4. Condition Working Group

The working group on Condition met on 23 November 2017.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

Document tabled:
PRIME eligibility requests - list of adopted outcomes November 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 – 20 September 2017

Action: For information

Document(s) tabled:
Minutes of the PCWP/HCPWP joint meeting held on 20 Sep 2017 (EMA/626905/2017)
Report of the Information session on antimicrobial resistance held on 19 Sep 2017
Draft Agenda - Training session for patients, consumers and healthcare professionals interested in EMA activities (21 Nov) - (EMA/662990/2017)
Agenda of the PCWP meeting with all eligible organisations (22 Nov) (EMA/663268/2017)

7.3.2. Scientific Advice Working Party (SAWP)

COMP: Bruno Sepodes

Scope: Re-examination of SAWP composition - call for interest to become one of the COMP representatives in the SAWP.

Action: For adoption

Document(s) tabled:
List of volunteers

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

Action: For information

Document(s) tabled:
COMP Work Plan 2018

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. Preparedness of the system and capacity increase

8.2. S-REPS: a new way of supporting COMP procedures with a CRM (Customer Relationship Management software)

The COMP noted the update.

8.3. User manual on COMP/EMA external representation

Document(s) tabled:
CxMP EMA external representation_presentation to committees
User Manual for CxMP/EMA external representation

The Committee was updated on the user manual on COMP/EMA external representation.

8.4. COMP Workshop on Prevalence

The workshop on Prevalence took place on 4 December 2017 at the EMA.

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 December 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	
Brigitte Blöchl-Daum	Member	Austria	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	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Mario Ricciardi	Member	Patients' Organisation Representative	No interests declared	
Kerstin Westermark	Member	Expert recommended by EMA	No participation in final deliberations and voting on:	5.2.2. Lynparza - (Olaparib) – EMEA/H/C/003726/X/0016/G, EMEA/OD/063/07, EU/3/07/501
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Sergio Bonini	Expert - via telephone*			4.1.1. Jorveza - budesonide - EMEA/H/C/004655, EMA/OD/078/13, EU/3/13/1181
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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/