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Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 16-18 June 2015 meeting

Some documents mentioned in the agenda/minutes cannot be released at present within the framework of Regulation (EC) No 1049/2001 on access to documents because they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/325374/2015

The agenda was adopted with the addition of a topic on the final COMP answer to EC request on revision of the 2003 Communication on orphan medicinal products under A.O.B.

1.2 Adoption of the minutes of the previous meeting, 12-13 May 2015 EMA/COMP/253668/2015

The minutes were adopted with no amendments.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare their potential conflict of interest.

In accordance with the Agency's Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests). No new or additional conflicts of interest were declared.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Synthetic hypericin for treatment of cutaneous T cell lymphoma, Kinesys Consulting Ltd - EMA/OD/033/15
[Co-ordinators: K. Kubáčková]

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

- Significant benefit

The sponsor should detail the results of any data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In addition, it is well known that extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments.

In the written response, and during an oral explanation before the Committee on 16 June 2015, the sponsor stressed that the only authorised products in the EU for the proposed condition are bexarotene and IFNα2, which are indicated for advanced stage or refractory patients. In contrast, the proposed product for designation is indicated for early stage first line treatment, which was also the population studied in the phase 2 study discussed in this application.

The sponsor also argued that the psoralens used in PUVA are not authorised for the condition, however, even though this treatment modality combines a non-medicinal element (UVA radiation) with a medicinal product (psoralen). The COMP reflected on whether PUVA, should be considered as a satisfactory treatment, and was of the view that since the psoralen constituent is off-label, significant

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

benefit would not have to be justified over PUVA. It was also considered that a potential use in first line setting is supported by the preliminary clinical data presented in the application.

The Committee agreed that the condition, cutaneous T 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 synthetic hypericin was considered justified based on preliminary clinical data showing a reduction in the size of lesions in treated patients affected by the condition.

The condition is chronically debilitating due to ulceration and erythroderma. The condition is life threatening in the most aggressive forms due to the risk of further malignant transformations.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic hypericin may be of significant benefit to those affected by the condition. The sponsor has presented preliminary clinical data that support the use of the product in early stages of the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic hypericin, for treatment of cutaneous T cell lymphoma, was adopted by consensus.

2.1.2 **Doxorubicin** for treatment of hepatoblastoma, Double Bond Pharmaceutical AB - EMA/OD/023/15

[Co-ordinators: D. O'Connor]

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 is invited to elaborate on the medical plausibility of this product regarding the anti-cancer efficacy in the light of missing data demonstrating the antineoplastic effect of the product in relevant disease models.

- Number of people affected

The sponsor is invited to clarify the search algorithms used to establish prevalence and should ensure to present a comprehensive and full assessment of published literature beyond the Orphanet estimation.

In the written response, and during an oral explanation before the Committee on 16 June 2015, the sponsor further elaborated on the issues raised.

With regards to the medical plausibility, the sponsor highlighted the non-clinical and clinical evidence in the published literature, where doxorubicin has been used in the context of the proposed condition. The COMP agreed that there is sufficient information in the public literature to support the use of doxorubicin. With regards to the prevalence issue raised, the sponsor further described the strategy to define prevalence of the condition and proposed a figure of 0.054 per 10,000. The COMP concluded that a prevalence of less than 0.1 in 10,000 should be used for the designation.

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

The intention to treat the condition with the medicinal product containing doxorubicin was considered justified based on clinical studies in the published literature describing doxorubicin containing regimens and sponsor-generated pre-clinical in vivo data demonstrating a higher relative concentration of doxorubicin in the liver compared to conventional doxorubicin formulations.

The condition is life-threatening and chronically debilitating due to symptoms related to the abdominal mass, spontaneous tumour ruptures and operative 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for doxorubicin, for treatment of hepatoblastoma, was adopted by consensus.

2.1.3 Product for treatment of hepatocellular carcinoma - EMA/OD/022/15
[Co-ordinators: D. O'Connor]

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 is invited to elaborate on the medical plausibility of this product regarding the anti-cancer efficacy in the light of missing data demonstrating the antineoplastic effect of the product in relevant disease models.

- Significant benefit

The sponsor states significant benefit could be based on better efficacy or safety, but provides insufficient evidence to support these statements against the authorised products including sorafenib. The sponsor is invited to provide further data to justify potential significant benefit considerations.

In the written response, and during an oral explanation before the Committee on 16 June 2015, the sponsor provided additional clarifications on the issues raised by the COMP. The medical plausibility was argued on the basis of published literature pertaining to preclinical and clinical data with the active substance in question. The significant benefit was argued versus sorafenib, on the basis of a potential improved efficacy and safety, but in absence of any specific data to support such claims. The COMP considered that the criterion of significant benefit could not be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 June 2015, prior to final opinion.

2.1.4 Product for treatment of acromegaly - EMA/OD/031/15
[Co-ordinators: K. Westermark]

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 assumes potential better efficacy of the proposed product as compared to the currently authorised ones based on target receptor affinity characteristics.
However the data presented, so far do not seem to support this claim. In particular, the proposed product showed comparable effect to that of authorised products with respect to growth hormone release from pituitary cell lines in vitro. The sponsor is therefore asked to further discuss the assumption of potential better efficacy and to produce any available additional data supporting such assumption.

In relation to the claim of potential better safety related to glucose tolerance the sponsor is invited to elaborate on the lack of dose-response effects in the preclinical data supporting this assumption.

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

In the written response, and during an oral explanation before the Committee on 16 June 2015, the sponsor further discussed the available preclinical data and anticipated a significant benefit for the proposed product based on improved efficacy and safety, without the negative impact of diabetes adverse events, medication and monitoring. The sponsor discussed in particular the effects of the product in growth hormone and prolactin secretion from human adenoma biopsies cultured in vitro. The sponsor discussed the effects of the product in healthy in vivo models on glucose levels, and discussed the future development plans. The COMP considered the claim of improved efficacy was not supported by the results of these studies, and that the safety is not known at this stage of development. Therefore the criteria for designation could not be considered met.

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

2.1.5 Product for prevention of avian influenza A virus - EMA/OD/036/15

[Co-ordinators: N. Sypsas]

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 prevention of avian influenza A virus, the sponsor should further elaborate on the results of the preclinical studies showing increased survival in treatment but not in preventive settings.

- Significant benefit

In order to further justify the significant benefit of the proposed product the sponsor is invited to further discuss the assumed benefits in relation to the existing treatments and in particular in relation to vaccines.

In the written response, and during an oral explanation before the Committee on 17 June 2015, the sponsor further discussed the expected clinical use of the product in the context of the preclinical studies with the product in post-exposure prophylactic settings. The COMP considered that the proposed clinical use would fall under a possible orphan designation for treatments, and that no data have been submitted to justify significant benefit versus vaccines.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 June 2015, prior to final opinion.

2.1.6 **Anti-H5N1 equine immunoglobulin F(ab')$_2$ fragments (Fabenflu)** for treatment of avian influenza, Fab'entech - EMA/OD/012/15

[Co-ordinators: N. Sypsas]

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 avian influenza A virus, the sponsor should further elaborate on the study design.

In the written response, and during an oral explanation before the Committee on 17 June 2015, the sponsor further elaborated on the available preclinical data and discussed how the results relate to the intended clinical use in post-exposure prophylaxis. The sponsor referred to the preclinical studies with the product and to the pharmacokinetic profile of similar products, which would not support the use in preventive settings. The sponsor also further clarified the design and results of the preclinical study used to support the application. The administration scheme used was in line with the pathophysiology of influenza and intending to cover the classical viral peak of the first days of infection. The COMP was of the opinion that the data of the sponsor do support the medical plausibility of using the product in post-exposure prophylaxis. The Committee was also of the opinion that the post-exposure prophylaxis use can fall under a treatment indication for the purpose of orphan medicinal product designation.

The COMP also reflected on the wording of the proposed indication and considered that it should be broadened to "avian influenza" as a whole. The COMP could not exclude activity of the product outside the proposed subset, and considered for the prevalence calculation other strains such as H7N7 of which cases have been reported in Europe. It was considered that the appropriate epidemiologic index for avian influenza is incidence, being the disease of short duration (days, weeks), either self-limiting or resulting into death in most severe cases. The final number considered by the COMP (less than 0.01 in 10,000) was based on the number of cases that have been reported in Europe in the past ten years. Following review of the application by the Committee, it was agreed to rename the indication to "avian influenza".

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

The intention to treat the condition with the medicinal product containing anti-H5N1 equine immunoglobulin F(ab')$_2$ fragments was considered justified based on in vitro data showing neutralization of H5N1 and preclinical in vivo data showing increased survival with the proposed product when administered after challenge with H5N1 virus.

The condition is life-threatening due to the possible development of severe pneumonia, acute respiratory disease syndrome and multi-organ failure.

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.

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 anti-H5N1 equine immunoglobulin F(ab')$_2$ fragments may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing increased survival when the product was used as post-exposure prophylaxis, offering the potential of being used in combination with antiviral products currently used for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for anti-H5N1 equine immunoglobulin F(ab')$_2$ fragments, for treatment of avian influenza, was adopted by consensus.

2.1.7 Lanreotide acetate for treatment of autosomal dominant polycystic kidney disease, Prof. Dr R.T.Gansevoort - EMA/OD/027/15
[Co-ordinators: J. Torrent-Farnell]

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

- Number of people affected

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

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

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

In the written response, and during an oral explanation before the Committee on 17 June 2015, the sponsor revisited the issues raised in the prevalence calculations, and further provided a comparative discussion versus tolvaptan regarding the clinically relevant advantage to support the significant benefit.

As regards the prevalence issue, the sponsor confirmed that point prevalence has been used as appropriate and argues that the calculation should be made on the basis of diagnosed cases only, because a) only these patients are relevant for treatment and b) the studies considering diagnosed and undiagnosed cases have methodological flaws since penetrance is variable and de novo mutations difficult to account for in family studies. As such the use of studies referring to undiagnosed patients as well was retained only for the purpose of a "worst case scenario". Furthermore, the sponsor argued that methods of calculation, other than the ones already used (such as using mutation frequency and penetrance), are not possible. Based on the above arguments the sponsor's position on the prevalence was not revised.

The COMP reflected on the prevalence calculation and considered the weighted average of all available literature studies including diagnosed and undiagnosed ADPKD patients (95% Confidence intervals 4.21- 4.68) should be considered. The COMP accepted that the condition was estimated to be affecting 4.2 to 4.7 in 10,000 persons in the European Union, at the time the application was made.

It was also noted that tolvaptan had in the meantime received a decision from the EC and was authorised in the EU for the treatment of the condition. With regards to the emerged significant benefit requirement, the sponsor argued that the target SSR2 receptors are expressed on all nephron segments, as well as in extrarenal tissues, while the V2 receptors (the target for the authorised product) is limited to the distal nephron and collecting duct of the kidney. According to the sponsor, this may result in improved efficacy, and have effects also on the extrarenal manifestations of the disease. An improved tolerability profile was also argued.

The COMP considered that the assumption of affecting intrarenal manifestations is acceptable, based on available bibliographic data for the effects of lanreotide in polycystic liver manifestations in patients with the proposed condition. The sponsor had provided in the initial application, a reference to an open-label clinical trial, published in 2014, where the efficacy of 6-month lanreotide treatment (120 mg, subcutaneously every 4 weeks) was investigated in ADPKD patients with symptomatic polycystic liver disease where both median liver volume and median kidney volume decreased with treatment. Based on those preliminary clinical data, the significant benefit was considered acceptable.

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

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

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

The condition was estimated to be affecting between 4.2 and 4.7 in 10,000 persons in the European Union, at the time the application was made. This calculation included a sensitivity analysis of the assumptions used for the estimation of prevalence.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing lanreotide acetate may be of significant benefit to those affected by the condition. This is based on a novel mechanism of action that targets receptors whose expression is not just limited to kidney tissue. Therefore the product may exert beneficial effects in extra-renal manifestations of the condition, which is also supported by bibliographic data in ADPKD and ADPLD.

A positive opinion for lanreotide acetate, for treatment of autosomal dominant polycystic kidney disease, was adopted by consensus.

2.1.8 Product for treatment of neurotrophic keratitis- EMA/OD/029/15

[Co-ordinators: K. Westermark]

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

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

The sponsor is requested to delineate a distinct etiology, pathophysiology, histopathology and clinical characteristics of the condition, supported as far as possible by international classification systems (such as an ICD-10 code).

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition, describe and justify the methodology used for the prevalence calculation, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

An expanded list of underlying aetiologies (Semeraro *et al*, 2014) should be taken into consideration for the purpose of calculating prevalence.

In the written response, and during an oral explanation before the Committee on 17 June 2015, the sponsor discussed the four main elements of the regulatory guidance for a valid orphan condition (etiology, pathophysiology, histopathology, clinical characteristics), and further referred to the ICD-10 code for "Neurotrophic Keratoconjunctivitis" (H16.23). The sponsor did not discuss explicitly why the condition cannot be considered a common consequence of different underlying conditions. It was acknowledged on the other hand that the pathophysiology of neurotrophic keratitis remains poorly understood in the literature.

As for the prevalence calculations, the sponsor argued that even though some of the causes referenced in the review paper were not explicitly mentioned they had been considered for the prevalence calculation. Furthermore, the sponsor conducted a Monte Carlo simulation to calculate the prevalence of the proposed condition and arrived at a figure of 3.24/10,000.

The COMP accepted the proposed condition as a distinct entity, but reflected on the prevalence issue and considered that significant uncertainties remain based on a) the multiplicity of assumptions used, given the plethora of underlying conditions included and the multiple levels of subsetting that have been performed for the calculation of respective prevalence figure b) the limited studies referenced for each of the condition examined which generate uncertainty regarding the generalisability of the results from the studies (as for example geographical representation) and c) the absence of a sensitivity analysis of the assumptions used as requested by the COMP.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 June 2015, prior to final opinion.

2.1.9 Product for treatment of Ebola virus disease - EMA/OD/030/15

[Co-ordinators: J. Torrent-Farnell]

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

- Intention to diagnose, prevent or treat

There is a high level of uncertainty on the relevance of the data presented by the sponsor to support the medical plausibility of the proposed product, since such data do not seem to underpin a specific role of the product in Ebola virus disease. The data presented refer rather to a number of

heterogeneous conditions, some of which with completely different pathogenesis and manifestations from Ebola.

Therefore the sponsor is invited to further clarify the specific role of the product in Ebola virus disease and to present any available data with the proposed product for the applied condition.

In the written response, and during an oral explanation before the Committee on 17 June 2015, the sponsor postulated that the product may reverse most of the pathophysiological manifestations characterizing Ebola, but did not present any data with the product in either relevant models of the condition or in affected patients. In the absence of relevant data with the product supporting the application, the COMP considered that the medical plausibility could not be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 June 2015, prior to final opinion.

2.1.10 Plasminogen (Human) Intravenous for treatment of plasminogen deficiency, ProMetic BioTherapeutics Ltd - EMA/OD/313/14
[Co-ordinators: J. Torrent-Farnell]

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

- Intention to diagnose, prevent or treat

The proposed condition should be justified as a distinct medical entity or a valid subset. It was noted that Type 1 plasminogen deficiency is a subset of a larger condition called plasminogen deficiency which consists of type 1 plasminogen deficiency and type 2 plasminogen deficiency. The COMP requests that the sponsor amend the condition therefore to plasminogen deficiency. Note that this is for the purposes of orphan medicinal product designation; and the applicant's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

The COMP considers that the condition to be designated is plasminogen deficiency. The sponsor is therefore requested to recalculate the prevalence reflecting this broader condition. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation"

In the written response the sponsor accepted the proposal by the COMP to change the condition to plasminogen deficiency. The sponsor also submitted a revised prevalence calculation to the COMP highlighting the difficulty in establishing the prevalence for plasminogen deficiency type II in Europe as very little data and publications exist in Europe for this condition. It is understood that this condition is more common in the Far East (Japan, China, South-east Asia) than in Europe where Type I is more common. As a result the sponsor had proposed a range for the condition which was from 0.02 in 10,000 to 3 in 10,000 as a rough estimate based on the small amount of data they could find.

The COMP discussed this and agreed to keep the lower number as the proposed range was so broad that it would be difficult to establish its relevance. The COMP therefore agreed to the lower prevalence of 0.02 in 10,000 for this designation as it is acknowledged that the sponsor will need to resubmit a prevalence calculation at the time of review of the MAA where a more complete analysis could be possible if more information emerges.

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

The intention to treat the condition with the medicinal product containing human plasminogen was considered justified based on preliminary clinical data in patients with the condition showing an improvement in the signs and symptoms measured.

The condition is chronically debilitating due to compromised extracellular fibrin clearance during wound healing, leading to pseudomembraneous (ligneous) lesions on affected mucous membranes (eye, middle ear, mouth, pharynx, duodenum and upper and lower respiratory tract). Ligneous conjunctivitis is by far the most common clinical manifestation. More than 12% of patients with severe hypoplasminogenaemia exhibit congenital occlusive hydrocephalus.

The condition was estimated to be affecting approximately 0.02 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for Plasminogen (Human) Intravenous, for treatment of plasminogen deficiency, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of plasma cell myeloma - EMA/OD/038/15
[Co-ordinators: K. Kubáčková]

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

2.2.2 2-((3-((4-((3-aminopropyl)amino)butyl)amino)propyl)amino)-N-((5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-8-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl)acetamide, tetrahydrochloride for treatment of acute myeloid leukaemia, Pierre Fabre Médicament - EMA/OD/037/15
[Co-ordinators: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing 2-((3-((4-((3-aminopropyl)amino)butyl)amino)propyl)amino)-N-((5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-8-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl)acetamide, tetrahydrochloride was considered justified based on preclinical and preliminary clinical data showing antitumor activity.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-((3-((4-((3-aminopropyl)amino)butyl)amino)propyl)amino)-N-((5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-8-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl)acetamide, tetrahydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing complete response in patients with acute myeloid leukaemia relapsed after previous treatments when the proposed product was used in combination with cytarabine, currently authorised for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patient population affected by the condition.

A positive opinion for2-((3-((4-((3-aminopropyl)amino)butyl)amino)propyl)amino)-N-((5S,5aS,8aR,9R)-9-(4-hydroxy-3,5-dimethoxyphenyl)-8-oxo-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl)acetamide, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.3 Adenovirus associated viral vector serotype 2 containing the human RPE65 gene for treatment of retinitis pigmentosa, Alan Boyd Consultants Ltd - EMA/OD/040/15

[Co-ordinators: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing adenovirus-associated viral vector serotype 2 containing the human *RPE65* gene was considered justified based on preclinical data supporting improvements in visual function following treatment with the product.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progresses to total blindness.

The condition was estimated to be affecting less than 3.7 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for adenovirus-associated viral vector serotype 2 containing the human *RPE65* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.4 Allogeneic human adult stem cells, isolated from skeletal muscle and expanded ex vivo for treatment of Duchenne muscular dystrophy, Karl Rouger - EMA/OD/041/15

[Co-ordinators: J. Torrent-Farnell]

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 allogeneic human adult stem cells, isolated from skeletal muscle and expanded ex vivo was considered justified based on pre-clinical in vivo data which showed improved muscle function.

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 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic human adult stem cells, isolated from skeletal muscle and expanded ex vivo may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate the potential for using the product in a broader population than those who currently receive approved treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic human adult stem cells, isolated from skeletal muscle and expanded ex vivo, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.5 **Artesunate** for treatment of malaria, Dr Ulrich Granzer - EMA/OD/043/15

[Co-ordinators: A. Lorence]

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

The intention to treat the condition with the medicinal product containing artesunate was considered justified based on clinical data showing efficacy in severe malaria.

The condition is life-threatening due to the possibility of severe systemic complications such as cerebral malaria, cardiogenic shock, acute renal failure, coagulation disorders and pulmonary oedema. The overall mortality rate of imported *Plasmodium falciparum* malaria in Europe is 0.4%.

Malaria (hereinafter referred to as “the condition”) was estimated to be affecting not more than 0.3 in 10,000 persons in the European Union, at the time the application was made. This value represents the annual incidence, which is to be considered a valid proxy for prevalence for conditions with duration of less than one year.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that artesunate may be of significant benefit to those affected by the condition. This appears justified by the superior clinical efficacy of artesunate administered intravenously as monotherapy in the treatment of severe malaria as compared to quinine, the only currently authorised product for intravenous use in the EU. The clinical superiority has been demonstrated in terms of significantly improved survival of patients with severe malaria treated with artesunate as compared to those treated with quinine in large comparative clinical trials. Artesunate was also characterised by better tolerability than quinine. Based on these results intravenous artesunate is recommended by the World Health Organization as first choice in the treatment of severe malaria. The superior clinical efficacy of intravenous artesunate compared to intravenous quinine may represent a clinically relevant advantage for patients affected by severe malaria in the European Union.

A positive opinion for artesunate, for treatment of malaria, was adopted by consensus.

2.2.6 Beloranib for treatment of craniopharyngioma, Dr Ulrich Granzer - EMA/OD/057/15
[Co-ordinators: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing beloranib was considered justified based on clinical data in craniopharyngioma patients affected by hypothalamic obesity, where treatment with the product resulted in improvements in eating behaviour and weight loss.

The condition is chronically debilitating due to hypothalamic/pituitary deficiencies, visual impairment, increased intracranial pressure, hypothalamic obesity, psychopathological symptoms, and/or cognitive problems.

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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for beloranib, for treatment of craniopharyngioma, was adopted by consensus.

2.2.7 Cannabidiol for treatment of perinatal asphyxia, GW Pharma Ltd - EMA/OD/042/15
[Co-ordinators: G. Capovilla]

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

The intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on in vivo preclinical models demonstrating reduction of brain damage when used alone or administered as an adjunct to other supportive strategies, as well as improvements in functional outcomes.

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

The condition was estimated to be affecting approximately 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 that has been authorised in the European Union for patients affected by the condition. A positive opinion for cannabidiol, for treatment of perinatal asphyxia, was adopted by consensus.

2.2.8 Product for treatment of cystic fibrosis - EMA/OD/039/15
[Co-ordinators: J. Eggenhofer]

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 July meeting.

2.2.9 Glycyl-L-2-methylprolyl-L-glutamic acid for treatment of Fragile X Syndrome, QRC Consultants Ltd - EMA/OD/055/15
[Co-ordinators: V. Tillmann]

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 glycyl-L-2-methylprolyl-L-glutamic acid was considered justified based on valid pre-clinical in vivo models which show an improvement in behavioural outcomes.

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

The condition was estimated to be affecting approximately 2.2 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for glycyl-L-2-methylprolyl-L-glutamic acid, for treatment of fragile X syndrome, was adopted by consensus.

2.2.10 Product for treatment of Rett Syndrome, QRC Consultants Ltd - EMA/OD/056/15
[Co-ordinators: I. Barisic]

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

2.2.11 Product for treatment of osteogenesis imperfecta and osteogenesis imperfecta-related disorders- EMA/OD/053/15
[Co-ordinators: V. Tillmann]

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 July meeting.

2.2.12 Humanized IgG4 monoclonal antibody directed against extracellular tau for treatment of progressive supranuclear palsy, Bristol-Myers Squibb Pharma EEIG - EMA/OD/044/15
[Co-ordinators: V. Stoyanova]

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 humanised IgG4 monoclonal antibody against extracellular tau was considered justified based on in vivo pre-clinical data in a relevant tauopathy disease model, where there were improvements in limp clasping and the latency to cross a beam.

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 life-threatening, 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.

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

A positive opinion for Humanized IgG4 monoclonal antibody directed against extracellular tau (BMS-986168), for treatment of progressive supranuclear palsy, was adopted by consensus.

2.2.13 Hydrocinnamate-[Orn-Pro-dCha-Trp-Arg](acetate) for treatment of amyotrophic lateral sclerosis, PBS Regulatory Consulting Group Limited - EMA/OD/051/15
[Co-ordinators: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing hydrocinnamate-[Orn-Pro-dCha-Trp-Arg]acetate was considered justified based on data in preclinical models of the condition supporting improvements in survival, motor score, and grip strength.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

The condition was estimated to be affecting not more than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing hydrocinnamate-[Orn-Pro-dCha-Trp-Arg]acetate may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product delays the onset of symptoms and improves motor function, grip strength and survival in preclinical models of the condition. The Committee considered that this constitutes a clinically relevant advantage over authorised treatments.

A positive opinion for hydrocinnamate-[Orn-Pro-dCha-Trp-Arg]acetate, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.14 Inecalcitol for treatment of acute myeloid leukaemia, Hybrigenics SA - EMA/OD/045/15
[Co-ordinators: B. Dembowska-Bagińska]

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 inecalcitol was considered justified based on preclinical data supporting improved survival in models of the condition when combined with demethylating agents.

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 overall 5-year relative survival with the currently available treatments is approximately 22%.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing inecalcitol may be of significant benefit to those affected by the condition. The sponsor has preclinical data supporting improved survival in models of the condition when the product is combined with demethylating agents. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.15 Product for treatment of short bowel syndrome - EMA/OD/050/15
[Co-ordinators: A. Corrêa Nunes]

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

2.2.16 Modified adenovirus serotype 5/35 containing a CMV promoter-driven transgene cassette with the human transgenes for a membrane-bound CD40 ligand (TMZ-CD40L) and full length 4-1BBL for treatment of pancreatic cancer, Lokon Pharma AB - EMA/OD/034/15
[Co-ordinators: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing modified adenovirus serotype 5/35 containing a CMV promoter-driven transgene cassette with the human transgenes for a membrane-bound CD40 ligand and full length 4-1BBL was considered justified based on preclinical data showing inhibition of tumour growth in a model of pancreatic cancer.

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

The condition was estimated to be affecting 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing modified adenovirus serotype 5/35 containing a CMV promoter-driven transgene cassette with the human transgenes for a membrane-bound CD40 ligand and full length 4-1BBL may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that combination with existing products results in improved antitumor effects. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for modified adenovirus serotype 5/35 containing a CMV promoter-driven transgene cassette with the human transgenes for a membrane-bound CD40 ligand (TMZ-CD40L) and full length 4-1BBL, for treatment of pancreatic cancer, was adopted by consensus.

2.2.17 Product for treatment of uveal melanoma - EMA/OD/049/15
[Co-ordinators: A. Magrelli]

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

2.2.18 Sarizotan hydrochloride for treatment of Rett syndrome, Newron Pharmaceuticals SpA - EMA/OD/058/15
[Co-ordinators: B. Bloechl-Daum]

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

The intention to treat the respiratory dysregulation in the condition with the medicinal product containing sarizotan hydrochloride was considered justified based on results with the product in a valid model of the condition which showed a decrease in apnoea incidence and a reduction in breathing irregularities.

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

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

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

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

2.2.19 Synthetic double-stranded RNA oligonucleotide specific to hydroxyacid oxidase 1 gene for treatment of primary hyperoxaluria type 1, Dicerna EU Limited - EMA/OD/052/15
[Co-ordinators: A. Magrelli]

The Committee agreed that the condition, primary hyperoxaluria type 1, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic double-stranded RNA oligonucleotide specific to hydroxyacid oxidase 1 gene was considered justified based on a preclinical model of the condition, where treatment with the product resulted in a reduction of oxalate levels in the urine and a reduction in crystal formation in the kidneys.

The condition is chronically debilitating and life-threatening, in particular because of recurrent nephrolithiasis and progressive nephrocalcinosis leading to renal damage. The majority of the patients reaches end stage renal disease during 3rd to 5th decade of life.

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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for synthetic double-stranded RNA oligonucleotide specific to hydroxyacid oxidase 1 gene, for treatment of primary hyperoxaluria type 1, was adopted by consensus.

2.2.20 Triheptanoin for treatment of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency, Ultragenyx UK Limited - EMA/OD/046/15
[Co-ordinators: I. Barisic]

The Committee agreed that the condition, long-chain 3-hydroxyacyl-coA dehydrogenase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing triheptanoin was considered justified based on observational clinical data showing lower morbidity and lower death rates in patients treated with the proposed product over a period of more than 10 years as compared with historical controls.

The condition is life-threatening and chronically debilitating particularly due to cardiomyopathy, hepatomegaly, myopathy, encephalopathy, neuropathy. Mortality in the first two years of age is estimated between 75 to 90%.

The condition was estimated to be affecting approximately 0.8 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for triheptanoin, for treatment of long-chain 3-hydroxyacyl-coA dehydrogenase deficiency, was adopted by consensus.

2.2.21 Triheptanoin for treatment of carnitine palmitoyltransferase II (CPT II) deficiency, Ultragenyx UK Limited - EMA/OD/048/15
[Co-ordinators: I. Barisic]

The Committee agreed that the condition, carnitine palmitoyltransferase II deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing triheptanoin was considered justified based on observational clinical data showing lower morbidity and lower death rates in patients treated with the proposed product over a period of more than 10 years as compared with historical controls.

The condition is life-threatening and chronically debilitating due to cardiomyopathy, hepatomegaly, myopathy, encephalopathy, neuropathy retinopathy. The majority of patients die before 2 years of age.

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

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

A positive opinion for triheptanoin, for treatment of carnitine palmitoyltransferase II deficiency, was adopted by consensus.

2.2.22 Triheptanoin for treatment of mitochondrial trifunctional protein (TFP) deficiency, Ultragenyx UK Limited - EMA/OD/047/15
[Co-ordinators: I. Barisic]

The Committee agreed that the condition, mitochondrial trifunctional protein deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing triheptanoin was considered justified based on observational clinical data showing lower morbidity and lower death rates in patients treated with the proposed product over a period of more than 10 years as compared with historical controls.

The condition is life-threatening and chronically debilitating due to cardiomyopathy, hepatomegaly, myopathy, encephalopathy, neuropathy retinopathy. The majority of patients die before 2 years of age.

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

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

A positive opinion for triheptanoin, for treatment of mitochondrial trifunctional protein deficiency, was adopted by consensus.

2.3. Appeal procedure

None.

2.4. Evaluation on-going

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

2.5. Validation on-going

The Committee was informed that validation was on-going for twenty five applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1 For treatment of Niemann-Pick disease, type C *[Coordinator: B. Bloechl-Daum]*

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

3.1.2 For treatment of Graft-versus-Host disease *[Coordinator: K. Westermark]*

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

3.1.3 For treatment of Urea Cycle Disorders *[Coordinator: A. Magrelli]*

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

3.1.4 For treatment of follicular lymphoma *[Coordinator: B. Bloechl-Daum]*

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

3.1.5 For treatment of pancreatic cancer *[Coordinator: B. Bloechl-Daum]*

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

3.1.6 For treatment of graft-versus-host disease *[Coordinator: K. Westermark]*

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

3.1.7 For treatment of Dravet syndrome *[Coordinator: A. Magrelli]*

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

3.2. Finalised letters

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

The finalised letter was circulated for information.

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

The finalised letter was circulated for information.

3.2.3 For treatment of glioma *[Coordinator: B. Bloechl-Daum]*

The finalised letter was circulated for information.

3.3. New requests

3.3.1 For treatment of sickle cell disease *[Coordinator: B. Bloechl-Daum]*

The new request was noted.

4. Overview of applications

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

COMP co-ordinators were appointed for 1 application submitted and 38 upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

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

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

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

5.1.1 Imbruvica. Ibrutinib for treatment of lymphoplasmacytic lymphoma; Janssen-Cilag International NV (EU/3/14/1264) *[Co-ordinators: J. Ersbøll]*

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

- Prevalence

The sponsor is invited to recalculate the prevalence estimate by discussing a) the appropriateness of the epidemiological index used b) the specific reference used for the non-Hodgkin lymphoma (NHL) population and c) reference of the conclusion for the time of review of criteria.

- Significant benefit

The sponsor is invited to further elaborate on the issue of significant benefit by discussing the results of the main pivotal study *vis a vis* the available data for all authorised products used in the treatment of these patients, including combination treatments.

A clinically relevant advantage or major contribution to patient care is expected based on data, and the sponsor should discuss any claims in the context of the uncontrolled nature of the pivotal study and the indirect nature of the comparisons attempted.

In its written response, and during an oral explanation before the Committee on 16 June 2015, the sponsor further elaborated on the issues raised. With regards to the prevalence issue, the sponsor discussed the sources for the calculation (NHL data from GLOBOCAN 2012) and the assumptions used (2.1% of NHL) in detail.

With regards to the significant benefit issue, the sponsor identified some therapies approved nationally in member states for the treatment of Waldenström's macroglobulinaemia (WM), including combination therapies with rituximab in Malta (this last point was contested at the oral explanation as discussed below). Historical comparisons of progression-free survivals (PFS) were performed, versus monotherapies and combination therapies. The sponsor stressed that while the ibrutinib pivotal trial comprises Relapsed/Refractory patients, the comparator studies include treatment naïve patients which would not favour the product.

The COMP discussed the historical comparisons presented, and identified an apparent overlap of the PFS curves of the product tested against combination treatments and especially against fludarabine-rituximab. It was, however, clarified during the process that such combinations were not nationally authorised and as such, off-label use of medicines would not be an appropriate comparator for the justification of significant benefit.

The sponsor also performed a study of "real world" data, surveyed from medical practice in several member states. This was considered of limited value for the justification of significant benefit, as the "real world" practice might be argued to be at times suboptimal.

It was also stressed during the oral explanation that the adopted CHMP indication also defines first line use in patients not eligible for chemo-immunotherapy.

The COMP considered that the prevalence of the condition has been justified to be approximately 0.1 in 10,000 people and that the significant benefit could be considered justified on the basis of responses seen in previously relapsed patients and for first line patients who are not eligible for other treatments, as per the approved indication.

The COMP concluded that:

The therapeutic indication "IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy" falls entirely within the scope of the designated orphan indication "treatment of lymphoplasmacytic lymphoma".

The prevalence of lymphoplasmacytic lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and life-threatening due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Imbruvica may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data in WM patients who have relapsed or were refractory to previous treatments, and responded to treatment with ibrutinib. Furthermore, the recommended indication covers use in first-line, in patients not eligible for chemo-immunotherapy; there are no authorised products for this group of patients. The Committee considered that this constitutes a clinically relevant advantage.

An opinion not recommending the removal of Imbruvica (ibrutinib) (EU/3/14/1264) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

5.1.2 Unituxin. Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879,) *[Co-ordinators: B. Dembowska-Bagińska]*

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

- Prevalence

In the maintenance report the sponsor epigrammatically argues that there is no reason as to why the prevalence of 1.1/10,000 cited in the original submission would have changed.

Instead, the sponsor is requested to submit a calculation of the prevalence at the time of the review in accordance to the document "points to consider on the calculation and reporting of prevalence (COMP/436/01)".

- Significant benefit

The sponsor is invited to discuss the existing products used in high-risk neuroblastoma patients who have completed induction therapy, ASCT and radiotherapy. Reference to treatment guidelines or consensus algorithms is expected.

In this setting, the sponsor should discuss how the results from the main pivotal study support an improved efficacy in the proposed group of patients. A comparison based on data is expected.

In its written response, the sponsor submitted an update on the prevalence calculation and citied in particular the Study from Rarecare. The final estimate has not been revised upwards compared to the designation stage. The COMP considered that less than 1.1 in 10,000 prevalence may be considered acceptable for the justification of the prevalence criterion.

As for the significant benefit issue, the sponsor identified three authorised products (melphalan, doxorubicin, vincristine), and stressed that there are no approved therapies specifically for maintenance treatment in high-risk settings. The COMP reflected on the current practice in the maintenance treatment of high risk patients, including immunotherapy and retinoids (off-label). It was acknowledged that no authorised products existed in the EU for this group of patients.

The COMP considered that significant benefit has been confirmed on the basis of the available clinical data showing that use of the product in the maintenance of previously treated high risk patients, results in prolongation of survival. The Committee considered that this constitutes a clinically relevant advantage.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

Neuroblastoma (hereinafter referred to as “the condition”) was estimated to be affecting approximately 1.1 in 10,000 persons in the European Union, at the time the application was made.

The condition is chronically debilitating and life threatening due to poor overall survival.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Unituxin may be of potential significant benefit to those affected by the orphan condition still holds. This is based on clinical data showing that use of the product in the maintenance of previously treated high risk patients, results in prolongation of survival. The Committee considered that this constitutes a clinically relevant advantage.

An opinion not recommending the removal of Unituxin, Chimeric monoclonal antibody against GD2, dinutuximab (EU/3/11/879) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

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

The COMP adopted a second list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing.

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

The status at the CHMP was noted and the discussion was postponed.

5.2.3 Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG:

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

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

The status at the CHMP was noted and the discussion was postponed.

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

The status at the CHMP was noted and the discussion was postponed.

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

The status at the CHMP was noted and the discussion was postponed.

5.3. On-going procedures

Update on on-going procedures

6. Procedural aspects

6.1 Significant Benefit Working group

The working group on Significant Benefit met on 18 June 2015.

6.2 EU Medicines Agencies Network Strategy to 2020

The EMA presented the EU Medicines Agencies Network Strategy to 2020 to the Committee.

6.3 Election of Chair and Vice-Chair - October 2015

The COMP Rules of Procedure EMEA/COMP/8212/00/ Rev. 3 were circulated for information. The members were advised to submit their candidature to COMPSecretariat@ema.europa.eu by 21 September 2015.

6.4 Draft agenda of the EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP)

The agenda was circulated for information.

6.5 Draft Agenda of the EMA Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting

The agenda was circulated for information.

6.6 Draft Agenda of the EMA Human Scientific Committees' Working Party with Healthcare Professionals' Organisations (HCPWP)

The agenda was circulated for information.

6.7 Work plan 2015 tracking and drafting 2016

The topic was postponed to July meeting.

6.8 Update to the CHMP Guideline on Conditional Marketing authorisation

The EMA presented the CHMP Guideline on conditional marketing authorisation. Concerns were expressed by the COMP on the requirements for demonstration of unmet medical needs (by providing major therapeutic advantages) in order for these to be aligned with the COMP requirements for demonstration of significant benefit for maintenance of the orphan designation. The comments will be further discussed with CHMP. The importance of obtaining feedback from the Health Technology assessment bodies on the guidelines during the public consultation was stressed.

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

6.10 Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy

The guideline was circulated for comments.

6.11 Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS)

The guideline was circulated for comments.

7. Any other business

7.1 Final COMP answer to EC request on Revision of the 2003 Communication on Orphan Medicinal Products

The Committee was informed that the final COMP answer had been sent to the European Commission.

Date of next COMP meeting: 14-16 July 2015

List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 16-18 June 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Katerina Kubacková	Member	Czech Republic	No participation in final deliberations and voting	2.1.3
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Judit Eggenhofer	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Dainis Krievins	Member	Latvia	No restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova	Member	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Zuzana Batova	Member	Slovak Republic	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Kerstin Westermark	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Birthe Byskov Holm	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Aikaterini Moraiti	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Observer	Eurordis	No restrictions applicable to this meeting	