EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/COMP/248636/2013
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 14-15 May 2013 meeting

Note on access to documents

Documents under points 1.1 and 2 to 6 cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form 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

The Committee welcomed Ingeborg Barisic, the new observer from Croatia. The COMP also noted resignation from Dorthe Meyer representing Denmark and Janos Borvendeg, the CHMP representative in the COMP. The leaving members were thanked for their valuable input in the work of the Committee.

1.1 Adoption of the agenda, EMA/COMP/248633/2013

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting held on 16 - 17 April 2013 EMA/COMP/165816/2013

The minutes were adopted with minor corrections to point 2.2.9.

1.3 Conflicts of Interest

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

The COMP secretariat was informed as follows:

- EGAN received a grant from the sponsor who have submitted dossier to be considered for orphan designation at the current meeting (2.2.8). Nevertheless, no direct conflicts of interest have been identified for P. Evers, who represents EGAN in the COMP.

- K. Kubackova also declared a potential conflict of interest for point 2.2.8.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 For treatment of (localized) neuroendocrine tumours - EMA/OD/002/13
[Co-ordinators: K. Kubáčková / S. Aarum]

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:

- Medical plausibility

The sponsor has proposed that bibliographical data with other products support the use of their product for treatment of neuroendocrine tumours. The sponsor should present any data that they may have generated on their own with their product in the proposed condition to support the medical plausibility.

- Prevalence

The sponsor should justify the sources of the prevalence data and indicate on which population the prevalence calculation is based. In this case the COMP would need to see all forms of neuroendocrine tumours as currently defined in current publications.

[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).

The sponsor was invited to re-calculate the prevalence estimate based on relevant epidemiological studies and registries for the proposed orphan condition neuroendocrine tumours.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition. This is based on extrapolation from bibliographical data with other products. Since the sponsor has not submitted any data of their own which would support the significant benefit, the sponsor should further elaborate on this.

- Development of medicinal product

The sponsor should clarify if the product applied for will be developed, and provide detailed information and update the Committee on the current stage of development of the product.

In the written response and during an oral explanation before the Committee on 14 May 2013, the sponsor further elaborated on the medical plausibility by discussing the product in the context of broader management for neuroendocrine tumours, without focusing on the specific product as applied for designation. The sponsor also provided further prevalence justifications based on RARECARE and argued that the product might be of significant benefit compared to other authorised medicines due to improved tumour-targeted activity. Given that these arguments were not supported by specific data with the product as proposed for designations, the Committee considered that the intention to treat and significant benefit were not adequately justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 May 2013, prior to final opinion.

2.1.2 For diagnosis of neuroendocrine tumours - EMA/OD/001/13

[Co-ordinators: K. Kubáčková / S. Aarum]

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:

- Medical plausibility

The sponsor has based their medical plausibility for the proposed product for the diagnosis of neuroendocrine tumours on an hypothesis but has not supported this with any data of their own or bibliographical data. The sponsor was invited to present supporting data either non-clinical and/or, if available clinical data with their product showing the plausibility of using it in the diagnosis of neuroendocrine tumours.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

The sponsor should indicate on which population the prevalence calculation is based on. In this case the COMP would need to see all forms of neuroendocrine tumours as currently defined in current publications. The sponsor was invited to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition; in this case the diagnosis of neuroendocrine tumours.

- Justification of significant benefit

The sponsor has not established the significant benefit for using of the product in question as diagnostic for neuroendocrine tumours over OctreoScan® which is a kit for radiopharmaceutical preparation of ^{111}In-Pentetreotide and is approved in Europe for this purpose. The sponsor was invited to further elaborate on the sensitivity and specificity of the product over the currently approved diagnostic methods in Europe.

- Development of medicinal products

The sponsor should clarify if the product applied for will be developed, and provide detailed information and update the Committee on the current stage of development of the product.

The sponsor informed the Committee of their intention to withdraw the application prior to it being discussed at the oral explanation on 14 May 2013 and formally withdrew the application for orphan designation, on 15 May 2013, prior to final opinion.

2.1.3 For treatment of Alagille syndrome - EMA/OD/007/13

[Co-ordinators: A. Corrêa Nunes / S. Tsigkos]

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:

- Medical plausibility

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

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed.

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Prevalence

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.

The sponsor should justify in detail the grounds on which the proposed prevalence has been calculated.

In the written response and during an oral explanation before the Committee on 14 May 2013, the sponsor discussed the position of pruritus in the symptomatology of the condition as applied for designation by referring to literature. It was pointed out that more than 75% of patients affected by the condition have pruritus, which causes skin lesions and sleep issues. The use of serum bile acid levels as a clinical surrogate for pruritus in the condition was defended mainly based on literature data on the effects of partial external biliary diversion in the symptom of pruritus, bile acid concentration and the hepatic biochemistry. The sponsor also provided further data from preclinical studies, most of which had been performed not with the product under evaluation but another product with a similar mechanism of action. In particular, the discussion focused on a partial bile duct ligation experimental

model of cholestasis, which the sponsor used to study the effects of another product with a similar structure and the mechanism of action. With this surrogate product in the experimental partial ligation model, the sponsor reported that treatment improved serum liver biochemistry and bile acids.

With regards to prevalence, the sponsor provided a recalculated estimate based on literature data on bith prevalence, corrected to account for subsequent genetic testing that might have increased the diagnosis. The sponsor provided a conclusion of birth prevalence of 3.16 per 100,000. This was further corrected by the reduced life expectancy of these patients based on two references. The final prevalence estimate proposed was between 0.22 and 0.26 people in 10,000.

The Committee considered that the available preclinical data to support the intention to treat, as presented by the applicant, pertained mainly to another surrogate product which could not be easily extrapolated to draw conclusions for the specific product under evaluation. In the absence data on relevant preclinical models or clinical settings in the condition as proposed for designation and with the specific product as applied for, the COMP does not consider justified the intention to treat the condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 May 2013, prior to final opinion.

2.1.4 For treatment of primary sclerosing cholangitis - EMA/OD/008/13

[Co-ordinators: A. Corrêa Nunes / S. Tsigkos]

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:

- Medical plausibility

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Justification of significant benefit

The sponsor is requested to provide a comparative discussion vis a vis any authorised counterparts for the proposed condition as applied for designation in the EU, including ursodeoxycholic acid.

In the written response and during an oral explanation before the Committee on 14 May 2013, the sponsor provided a discussion on the presence of pruritus in different conditions. The use of serum bile acid levels as a clinical surrogate for pruritus in the condition scope of the application was also defended on the grounds of literature discussing the effects of partial external biliary diversion in the symptom of pruritus, bile acid concentration and the hepatic biochemistry in cholestasis patients. The sponsor also provided further data from preclinical studies, most of which had been performed not with the product under evaluation but another product with a similar mechanism of action. In particular, the discussion focused on a partial bile duct ligation experimental model of cholestasis, which the

sponsor used to study the effects of another product with a similar structure and the mechanism of action. With this surrogate product in the experimental partial ligation model, the sponsor reported that treatment improved serum liver biochemistry and bile acid concentration.

With regards to significant benefit, the sponsor did not confirm that authorised medicines existed, which was contrary to the knowledge of the COMP. The sponsor also pointed out the limitations of using ursodeoxycholic acid in patients affected by the condition, based on literature data and US guidelines.

The Committee considered that the available preclinical data to support the intention to treat, as presented by the applicant, pertained mainly to another surrogate product which could not be easily extrapolated to draw conclusions for the specific product under evaluation. In the absence data on relevant preclinical models or clinical settings in the condition as proposed for designation and with the specific product as applied for, the COMP does not consider justified the intention to treat the condition. In addition, with regards to significant benefit, there no a comparative discussion of the product versus authorised treatments was presented. This would be needed to justify a potential clinically relevant advantage or major contribution to patient care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 May 2013, prior to final opinion.

2.1.5 For treatment of primary biliary cirrhosis - EMA/OD/010/13

[Co-ordinators: A. Corrêa Nunes / S. Tsigkos]

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:

- Medical plausibility

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

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Justification of significant benefit

The sponsor was requested to provide a comparative discussion in particular with regards to the authorised medicines for the proposed condition as applied for designation.

In the written response and during an oral explanation before the Committee on 14 May 2013, the sponsor discussed pruritus as a symptom of the condition as applied for designation by referring to literature. It was argued that up to 69% of patients affected by the condition have pruritus and that this reutls in skin lesions from scratching and sleep disroders. The use of serum bile acid levels as a

clinical surrogate for pruritus in the condition was supported by literature data discussing the effects of partial external biliary diversion, bile acid concentration and the hepatic biochemistry in cholestasis patients. The sponsor also provided further data from preclinical studies, most of which had been performed not with the product under evaluation but another product with a similar mechanism of action. In particular, the discussion focused on a partial bile duct ligation model of cholestasis, which the sponsor used to study the effects of another product with a similar structure and the mechanism of action. The sponsor reported that treatment improved serum liver biochemistry and bile acid concentration in the partial ligation model.

With regards to significant benefit, the sponsor acknowledged that ursodeoxycholic acid and cholestyramine are authorised treatments for the condition, and argued on a potentially improved efficacy based on the novel mechanism of action that may act complementarily and produce additional effects in combination with the proposed products. However no data was supports any such assumptions, and the only data discussed pertained to the limitations of the authorised products in some subsets of the treated population.

The Committee considered that the available preclinical data to support the intention to treat the condition, as presented by the applicant, refers to another product. These results cannot be extrapolated to draw conclusions for the specific product under evaluation. In the absence of data on relevant preclinical models or clinical settings in the condition as proposed for designation with the product as applied for, the COMP does not consider justified the intention to treat the condition. In addition, with regards to significant benefit, the sponsor did not provide a comparative discussion versus authorised treatments, which would be necessary to justify a potential clinically relevant advantage or major contribution to patient care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 May 2013, prior to final opinion.

2.1.6 For treatment of progressive familial intrahepatic cholestasis - EMA/OD/009/13

[Co-ordinators: A. Corrêa Nunes / S. Tsigkos]

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:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development the proposed product for treatment of progressive familial intrahepatic cholestasis, the sponsor should further elaborate on:

- the relevance of pruritus in the clinical presentation of patients affected by the proposed condition

- the use of serum bile acid levels as a clinical surrogate for cholestatic pruritus

- the absence of any data in either preclinical models or clinical settings in the condition as proposed for designation

- the extent of the clinical effect in the serum concentration by providing further data, as so far there is only a trend of reduction and an absence of a dose-response effect in the data discussed

- the relevance of the observed effects in serum concentration of bile acids in healthy volunteers for the treatment of pruritus in patients with the proposed condition as applied for designation.

- Prevalence

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. The sponsor should justify in detail the grounds on which the proposed prevalence has been calculated.

In the written response and during an oral explanation before the Committee on 14 May 2013, the sponsor discussed pruritus as a symptom of the condition as applied for designation by referring to literature. It was argued that pruritus is a salient feature of progressive familial intrahepatic cholestasis and particularly type 1. Based on a sponsor's study that includes patients and caregivers, itching is reported at least in 85% of patients. Skin damages, sleep disturbances and social impact were described based on this survey. The use of serum bile acid levels as a clinical surrogate for pruritus in the condition was also discussed based on literature data on the effects of partial external biliary diversion in cholestasis patients, bile acid concentration and the hepatic biochemistry. To support the medical plausibility, the sponsor also provided data from preclinical studies, most of which had been performed not with the product under evaluation but another product with a similar mechanism of action. In particular, the discussion focused on a partial bile duct ligation experimental model of cholestasis, which the sponsor used to study the effects of another product with a similar structure and the mechanism of action. The sponsor reports that treatment with this product improved serum liver biochemistry and bile acid concentration in the experimental partial ligation model.

For the issue of prevalence, the sponsor submitted an updated estimatebased on birth prevalence reported in one publication. The estimate was calculated taking into account the duration of the condition. The final amended estimate is "less than 0.1/10,000".

The Committee considered that the available preclinical data to support the intention to treat the conditionrefers to another product that cannot be extrapolated to draw conclusions for the specific product under evaluation. In the absence data on relevant preclinical models or clinical settings in the condition as proposed for designation and with the specific product as applied for, the COMP does not consider justified the intention to treat the condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 May 2013, prior to final opinion.

2.1.7 For treatment of Stargardt's disease - EMA/OD/004/13

[Co-ordinators: I. Bradinova/ A. Magrelli / S. Tsigkos]

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:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Stargardt's disease, the sponsor should further elaborate on:

- the proposed mechanism of action for the product as applied for designation

- the absence of any model of the proposed condition as applied for designation

- the pre-clinical studies and the results from these studies and their relevance for the development of the product in the condition as proposed for designation.

- Prevalence

The sponsor should justify the sources selected for the estimation of the prevalence of the condition and recalculate the prevalence in line with the abovementioned guideline.

In the written response and during an oral explanation before the Committee on 14 May 2013, the sponsor discussed the absence of data from experimental models relevant to the proposed condition. The sponsor also further elaborated on the validity of lipofuscin accumulation as an endpoint for the proposed condition. It is claimed that accumulation in retinal pigment epithelial cells compromises their lysosomal function and reduces rod phagocytosis, as well as it causes increased phototoxicity and reduced antioxidant capacities.

The prevalence estimate was estiatmed according to the request from the list of questions. The sponsor concludes on a prevalence of 1.25 in 10,000 people.

The Committee considered that relevant models exist for the proposed condition and these should have been used to justify the intention to treat the condition. In the absence of data with the product in the specific condition in either relevant preclinical models or preliminary clinical studies, the Committee considers that the medical plausibility is not justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 May 2013, prior to final opinion.

2.1.8 For treatment of Schnitzler Syndrome - EMA/OD/006/13
[Co-ordinators: A. Corrêa Nunes / S. Mariz]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the medical plausibility. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Schnitzler *s*yndrome, the sponsor should present and discuss the data of their own investigations with the product, in a pre-clinical model or in a preliminary clinical setting in the condition.

The sponsor formally withdrew the applications prior to responding to the COMP list of questions.

2.2. For discussion / preparation for an opinion

2.2.1 For treatment of narcolepsy - EMA/OD/029/13
[Co-ordinators: L. Gramstad / S. Mariz]

The Committee considered that the prevalence requires clarification by the sponsor.

The estimated prevalence by the sponsor is close to the 5/10,000 threshold. Since the absence of cataplexy requires polysomnography for proper narcolepsy diagnosis, this subgroup is often omitted in the reported data, even though this subgroup accounts for about 30% of narcolepsy patients. It is also noted that much of the reported incidence/prevalence data were published about 10-20 years ago or more. The age of the data is even more important if it is considered that in more recent years there has been an increasing interest in sleep disturbances as well as developments of sleep clinics, this could affect the prevalence estimate of the condition and should be taken into account for the calculations.

The sponsor should re-calculate the prevalence estimate based on the most current 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. The sponsor should refer for further guidance to "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

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 June meeting.

2.2.2 4,6,4'-trymethylangelicin for treatment of cystic fibrosis, Rare Partners srl Impresa Sociale - EMA/OD/017/13
[Co-ordinators: J. Eggenhofer / L. Fregonese]

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

The intention to treat the condition with the medicinal product containing 4,6,4'–trimethylangelicin was considered justified based on preclinical data showing inhibition of the synthesis of interleukin 8, and correction and potentiation of the activity of the Cystic Fibrosis Transmembrane conductance Regulator.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure. The condition was estimated to be affecting approximately 0.8 in 10,000 people in the European Union, at the time the application was made, based on data from the literature and from national and European registries and databases.

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 4,6,4'–trimethylangelicin may be of significant benefit to those affected by the condition. The sponsor provided preclinical data that demonstrate significantly increased chloride transport across epithelial cell membranes, an endpoint that reflects the improvement of function of the Cystic Fibrosis Transmembrane conductance Regulator protein that is defective in cystic fibrosis. The clinical translation of these data is assumed to result in the potential to treat the disease long-term, as the proposed product would act downstream of the mutation rather than on the symptoms of the disease, and therefore differently from the currently authorized products. The only authorized product with a similar mechanism of action, Ivacaftor, is active on the G551Del mutated CFTR, while the proposed product 4,6,4'–trimethylangelicin targets the F508Del mutation, therefore covering a different part of the cystic fibrosis patient population. The Committee considered that this constitutes a clinically relevant advantage based on an assumption of improved efficacy.

A positive opinion for 4,6,4'-trymethylangelicin, for treatment of cystic fibrosis, was adopted by consensus.

2.2.3 Adenovirus associated viral vector serotype 5 containing the human *pde6β* gene for treatment of retinitis pigmentosa, Centre Hospitalier Universitaire de Nantes - EMA/OD/031/13
[Co-ordinators: A. Magrelli / S. Mariz]

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 5 containing the human *pde6ß* gene was considered justified based on non-clinical in vivo data showing improved vision in the treated eye vs the non-treated eye.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progress to total blindness. The condition was estimated to be affecting less than 3.7 in 10,000 people in the European Union, at the time the application was made; this was based on a literature search the sponsor has conducted.

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 5 containing the human *pde6β* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.4 For treatment of renal cell carcinoma in patients with remaining primary tumour or presence of at least one metastasis - EMA/OD/172/12
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

Renal cell carcinoma in patients with remaining primary tumour or presence of at least one metastasis should be justified as a distinct medical entity or a valid subset for the purpose of orphan designation.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of renal cell carcinoma in patients with remaining primary tumour or presence of at least one metastasis, the sponsor should further elaborate on:

1. the proposed mechanism of action, as it is not supported by data showing elicitation of immune responses as assumed by the sponsor;
2. the absence of data to investigate if any systemic effects are obtained if the activated cells were to be injected outside or near the tumour;
3. the validity of the preclinical model used for the purpose of proof of concept, since breast cancer cells are used;
4. the appropriateness of the product tested in the preclinical model as a surrogate for the product proposed for designation;
5. the absence of any data with the proposed product in the specific condition as applied for designation. Any available data from the on-going preliminary clinical studies should be included and discussed.

- Prevalence

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 epidemiological index used, and provide a sensitivity analysis of the assumptions used for the calculation of prevalence.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit by positioning the product in the management of the condition versus authorised treatments.

The sponsor should also present any data to justify the claims for significant benefit in either preclinical or preliminary clinical settings pertaining to the condition as applied for.

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 June meeting.

2.2.5 For prevention of graft versus host disease - EMA/OD/026/13
[Co-ordinators: D. Meyer / L. Fregonese]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

It is understood that a variable rate of non-apoptotic cells, up to 60%, are also contained in the proposed product. As such the final product is a mixture of apoptotic and non-apoptotic cells.

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of graft-versus-host disease, the sponsor should further elaborate on:

- the implications and possible consequences related to the presence of non-apoptotic cells in the final product

- the sponsor is also invited to better clarify the methodology and results of the clinical study on 13 subjects including e.g. additional treatments administered to the patients of the study in the event of acute GvHD.

The sponsor is invited to further discuss:

- the characteristics of the mononuclear cells other than apoptotic cells in the final product;

- the methodology used to define the cell state as "early" apoptotic besides staining with Annexin V.

Post-meeting note:

Due to lack of the quorum on 15 May 2013, the list of issues was adopted formally via written procedure on 21 May 2013. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.6 For treatment of amyotrophic lateral sclerosis - EMA/OD/011/13
[Co-ordinators: V. Stoyanova / S. Mariz]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

With reference to the mechanism of action of the product the sponsor elaborates on assumptions based on published literature about retrograde transport of molecules along axons.

The sponsor is invited to:

- discuss data of the cell survival and function after injection

- elaborate on the role of the transplantation of the cells used, in the ALS situation and its translation into clinically meaningful effects.

- Justification of significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the on-going Phase I/II study to justify the assumption of significant benefit over riluzole or in combination with it for the proposed orphan indication. Data involving compassionate use patients should be further elaborated.

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 June meeting.

2.2.7 Copper meso-5,15-Bis[3-[(1,2-Dicarba-closo-dodecaboranyl)methoxy]phenyl]-meso-12,20-dinitroporphyrin

Copper meso-5,15-Bis[3-[(1,2-Dicarba-closo-dodecaboranyl)methoxy]phenyl]-meso-12,20-dinitroporphyrin for treatment of squamous cell carcinoma of the head and neck in patients undergoing radiotherapy, MorEx Development Partners LLP - EMA/OD/022/13
[Co-ordinators: K. Kubáčková / S. Mariz]

The Committee agreed that the condition, squamous cell carcinoma of the head and neck in patients undergoing radiotherapy, is a valid subset and meets the criteria for orphan designation.

The intention to treat the subset with the medicinal product containing copper meso-5,15-Bis[3-[(1,2-Dicarba-closo-dodecaboranyl)methoxy]phenyl]-meso-12,20-dinitroporphyrin was considered justified based on non-clinical in vivo data showing tumour control in 50% of the treated group.

The subset is life-threatening due to a reduction in life expectancy. The effect of age on survival is marked. Survival at 5 years was 54% for the youngest age group (15 - 45 years) and 35% in the oldest group of patients. The subset was estimated to be affecting 3.7 in 10,000 people in the European Union, at the time the application was made; the sponsor has based this on registers and a literature search.

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 copper meso-5,15-bis[3-[(1,2-dicarba-closo-dodecaboranyl)methoxy]phenyl]-meso-12,20-dinitroporphyrin may be of significant benefit to those affected by squamous cell carcinoma of the head and neck in patients undergoing radiotherapy. The sponsor has provided pre-clinical data that demonstrate that when their product is used in conjunction with radiotherapy there is a 50% control of tumours when compared to controls.

Post-meeting note:

Due to lack of the quorum a positive opinion for copper meso-5,15-bis[3-[(1,2-dicarba-closo-dodecaboranyl)methoxy]phenyl]-meso-12,20-dinitroporphyrin, for treatment of squamous cell carcinoma of the head and neck in patients undergoing radiotherapy, was adopted formally via written procedure on 21 May 2013.

2.2.8 For treatment of renal cell carcinoma - EMA/OD/030/13
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of renal cell carcinoma, the sponsor should further elaborate on the reported phase I/II study pertaining to 67 heavily pretreated patients with RCC. The design, population, previous treatments in detail and results should be discussed.

- Prevalence

With reference to the published minutes of the COMP plenary meeting of July 2012 (EMA EMA/COMP/404711/2012 Rev.1), "the Committee pointed out that as per the published results of the RARECARE project, the complete prevalence for RCC was 6.718 per 10,000 people. Thus, the Committee was not convinced that the prevalence of the condition remained below the threshold provisioned in the orphan regulation".

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 further justify:

- the inclusion/choice of the sources selected for the estimation of the prevalence of the condition;
- the exclusion of Rarecare data;
- the choice of the 5-year partial prevalence adjusted by age and gender as a valid epidemiological index for the purpose of orphan designation.

The sponsor should also provide further data with regards to:

- a ***currently applicable incidence*** of the condition in the EU at the time the application is made, and discuss how this impacts on the prevalence of the condition;
- an ***updated duration*** of the condition in the EU in light of the currently available authorised products for the condition is question, and discuss how this impacts on the prevalence of the condition in 2013;
- a ***recalculation of the prevalence*** of the condition taking into consideration the updated incidence and duration, including a ***sensitivity analysis***.
- Significant benefit

As also requested for the purpose of establishing medical plausibility, the sponsor should further elaborate on the reported phase I/II study pertaining to 67 heavily pretreated patients with RCC. The design, population, previous treatments in detail and results should be discussed.

Post-meeting note:

Due to lack of the quorum on 15 May 2013, the list of issues was adopted formally via written procedure on 21 May 2013. The list of issues will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June meeting.

2.2.9 Expanded human allogeneic neural retinal progenitor cells extracted from neural retina for treatment of retinitis pigmentosa, ReNeuron Ltd - EMA/OD/025/13

[Co-ordinators: V. Saano / S. Aarum]

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

The intention to treat the condition with the medicinal product containing expanded human allogeneic neural retinal progenitor cells extracted from neural retina was considered justified based on the preclinical results presented.

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 approximately 3.7 in 10,000 people 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 expanded human allogeneic neural retinal progenitor cells extracted from neural retina, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.10 Genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor for treatment of soft tissue sarcoma, Oncos Therapeutics Ltd - EMA/OD/041/13

[Co-ordinators: D. O'Connor / S. Mariz]

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

The intention to treat the condition with the medicinal product containing genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor was considered justified based on non-clinical in vivo models which demonstrated tumour regression.

The condition is life-threatening due to reduced life expectancy. The condition was estimated to be affecting approximately 3 in 10,000 people in the European Union, at the time the application was made; this was based on cancer registries and an extensive literature search conducted by the sponsor.

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 genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor may be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data where combination of their product with doxorubicin showed improved antitumor activity over doxorubicin. The Committee considered that this could translate into a clinically relevant advantage.

A positive opinion for genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.11 For treatment of pulmonary alveolar proteinosis - EMA/OD/106/12
[Co-ordinators: V. Saano / L. Fregonese]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

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

- the mechanism of action of the product in the proposed condition;

- the bibliographic clinical studies presented to support the medical plausibility. The studies reported by the sponsor are a mixture of safety studies and efficacy studies on different populations and with different endpoints. The sponsor is invited to provide a critical review of the studies containing data on the efficacy of the product, including drawing clear conclusions on the type of data and magnitude of the effects supporting the medical plausibility.

- Justification of significant benefit

The sponsor is invited to discuss the significant benefit of the proposed product in relation to whole lung lavage (WLL).

- Development of the product

The sponsor is invited to clarify on the current state of the product as applied for. In addition the sponsor is invited to provide some more details on the planned formulation for inhalation and planned studies (clinical and/or preclinical) with the proposed product.

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 June meeting.

2.2.12 For treatment of Hunter syndrome (mucopolysaccharidosis type II) - EMA/OD/021/13
[Co-ordinators: V. Saano / S. Aarum]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of significant benefit

The arguments on significant benefit are mainly based on the potentially improved efficacy and safety over Elaprase in the condition.

The sponsor is requested to further discuss the molecular and structural features (e.g. glycosylation, FGly content, tertiary structure) of the applied product that are claimed to justify the clinically relevant advantage over Elaprase. In particular, the sponsor is invited to elaborate on how these biologic differences are expected to translate to improved PK/PD profile of the applied product versus Elaprase.

Further, the sponsor is asked to provide more details (such as a clinical trial report) of the clinical trial performed and to clarify the clinical results especially with regards to the 6MWT taking into account any possible bias that may have affected the results.

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 June meeting.

2.2.13 Immortalised human C3A hepatoblastoma cells for treatment of acute liver failure, Vital Therapies Limited - EMA/OD/032/13
[Co-ordinators: A. Corrêa Nunes/ A. Lorence / L. Fregonese]

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

The intention to treat the condition with the medicinal product containing immortalised human C3A hepatoblastoma cells was considered justified based on early clinical data showing improvement of the encephalopathy due to liver failure in some patients and suggesting the possibility of the product of delaying the need for liver transplantation.

The condition is life threatening in particular due to the development of encephalopathy with intracranial hypertension, multi-organ failure and sepsis. The condition was estimated to be affecting less than 1 in 10,000 people per year 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 immortalised human C3A hepatoblastoma cells may be of significant benefit to those affected by the condition. This is supported by early clinical data suggesting the possibility of the product of delaying the need for liver transplantation.

A positive opinion for immortalised human C3A hepatoblastoma cells, for treatment of acute liver failure, was adopted by consensus.

Post-meeting note:

Due to lack of the quorum a positive opinion for immortalised human C3A hepatoblastoma cells, for treatment of acute liver failure, was adopted formally via written procedure on 21 May 2013.

2.2.14 For treatment of acute lymphoblastic leukaemia - EMA/OD/024/13
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

The Committee considered that the condition originally proposed by the sponsor should be renamed as "B-lymphoblastic leukaemia/lymphoma" according to the 2008 WHO classification of haematological malignancies.

The sponsor is therefore invited to provide an estimate of the prevalence of B-lymphocytic leukaemia/lymphoma.

Post-meeting note:

Due to lack of the quorum on 15 May 2013, the list of issues was adopted formally via written procedure on 21 May 2013. The list of issues will be sent to the sponsor a written response.

2.2.15 Recombinant Human Alpha-N-acetylglucosaminidase for treatment of mucopolysaccharidosis type IIIB (Sanfilippo B syndrome), Synageva BioPharma Ltd - EMA/OD/035/13
[Co-ordinators: P. Evers / S. Aarum]

The Committee agreed that the condition, mucopolysaccharidosis type IIIB (Sanfilippo B syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human alpha-N-acetylglucosaminidase was considered justified based on the *in vitro* results and preclinical results presented. In the animal model of the disease, the product increased the enzymatic activity of alpha-N-acetylglucosaminidase and decreased the heparin sulfate in the liver and the brain.

The condition is life-threatening and chronically debilitating due to frequent infections and neurocognitive delay that progress to profound mental disability and vegetative state. The survival of the patients is limited to 20-30 years. The condition was estimated to be affecting approximately 0.02 in 10,000 people 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 recombinant human alpha-N-acetylglucosaminidase, for treatment of mucopolysaccharidosis type IIIB (Sanfilippo B syndrome), was adopted by consensus.

2.2.16 For treatment of lymphoblastic lymphoma - EMA/OD/027/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Indication

The sponsor is invited to apply for a) treatment of B lymphoblastic leukaemia/lymphoma, and b) treatment of T lymphoblastic leukaemia/lymphoma, in line with the 2008 WHO classification of haematopoietic and lymphoid malignancies.

- Prevalence

In case of an amended indication(s) the sponsor should provide recalculated prevalence figures.

- Significant benefit

The sponsor is arguing significant benefit on two points, the first being reduced risk of causing hypersensitivity compared to other similar products and the second being increased availability in case of a shortage of supply of non-recombinant counterparts.

The sponsor is invited to:

a) document the relative safety issues of other similar products and substantiate the claim of improved safety of the current product based on data

b) document any serious lack of supply of asparaginase in Europe for patients affected by the condition by providing data.

c) position the product in the treatment of T-ALL/LBL and B-ALL/LBL

d) discuss the significant benefit against all authorised products for the condition without limiting the discussion to asparaginase.

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 June meeting.

2.2.17 Sodium chlorite for treatment of amyotrophic lateral sclerosis, Shore Limited - EMA/OD/023/13
[Co-ordinators: V. Saano / S. Aarum]

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 sodium chlorite was considered justified based on the preclinical data and clinical experience presented.

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 less than 1 in 10,000 people 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 sodium chlorite may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data supporting the assumption that the product delays the disease progression.

A positive opinion for sodium chlorite, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.18 Synthetic double-stranded siRNA oligonucleotide directed against the keratin 6a N171K mutation for treatment of pachyonychia congenita, Alan Irvine - EMA/OD/028/13
[Co-ordinators: V. Tillmann / S. Tsigkos]

The Committee agreed that the condition, pachyonychia congenita, 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 siRNA oligonucleotide directed against the keratin 6a N171K mutation was considered justified based on preclinical data showing restoration of the organisation of keratin filaments in treated cells transfected with mutant keratin 6a, as well as preliminary clinical data showing a reduction in the size of lesions in a treated patient affected by the condition.

The condition is chronically debilitating due to impaired ambulation. The condition was estimated to be affecting less than 0.02 in 10,000 people 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.

Post-meeting note:

Due to lack of the quorum a positive opinion for synthetic double-stranded siRNA oligonucleotide directed against the keratin 6a N171K mutation, for treatment of pachyonychia congenita, was adopted formally via written procedure on 21 May 2013.

2.2.19 Unoprostone isopropyl for treatment of retinitis pigmentosa, Sucampo Pharma Europe Ltd - EMA/OD/067/13
[Co-ordinators: V. Saano / S. Tsigkos]

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

The intention to treat the condition with the medicinal product containing unoprostone isopropyl was considered justified based on preliminary clinical studies showing improvements in the retinal sensitivity of treated patients.

The condition was estimated to be affecting less than 3.7 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to the development of nyctalopia (night blindness) and tunnel vision that progress to total blindness.

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 unoprostone isopropyl, for treatment of retinitis pigmentosa, was adopted by consensus.

2.3. COMP opinions adopted via written procedure following previous meeting

2.3.1 Maribavir for treatment of cytomegalovirus disease, ViroPharma SPRL - EMA/OD/013/13 [Co-ordinators: K. Kubáčková / L. Fregonese]

2.4. Evaluation on-going

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

2.5. Validation on-going

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

3. Requests for protocol assistance

The Committee was briefed on the significant benefit issues for two products with the following indications:

- treatment of neovascular glaucoma;
- treatment peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated).

Post-meeting note:

Due to lack of the quorum the protocol assistance letters were adopted formally via written procedure on 21 May 2013.

4. Overview of applications

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

COMP co-ordinators were appointed for 17 upcoming applications. 1 Expert was appointed for an on-going application.

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 Revlimid (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) for treatment of myelodysplastic syndromes; Celgene Europe Limited – UK (EU/3/04/192) [Co-ordinators: L. Gramstad / J. Llinares Garcia]

The CHMP adopted their positive opinion on a Type II variation at their April 2013 meeting. The variation refers to an extension of indication nfor the following therapeutic indication: "treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities".

The COMP reviewed the maintenance of the criteria for orphan designation prior to marketing authroisation and concluded that:

The proposed therapeutic indication "treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities " falls entirely within the scope of the orphan indication of the designated orphan medicinal product for treatment of myelodysplastic syndromes.

The prevalence of myelodysplastic syndromes is estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. Available data indicates that the point estimate is below 3 in 10,000. The condition is life-threatening with a median survival of less than 2 years. Patients affected by the condition have their quality of life severely compromised by haemorrhagic episodes, infections requiring in-patient hospitalisation and the need for frequent transfusions of blood.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Revlimid is of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication is confirmed.

The significant benefit of the product is supported by the effect of the product as shown during the clinical development. The study results from a randomised open label placebo controlled study show achievement of transfusion independence in a significant larger proportion of patients with myelodysplastic syndromes treated with lenalidomide compared to placebo (55% versus 6%) and a clinically relevant increase in haemoglobin from baseline was achieved (6.4 g/dL).

The assumption at the time of orphan designation that Revlimid is of significant benefit to those affected by the orphan condition is now confirmed based on a clinically relevant advantage based on the achievement of transfusion independence and increase in haemoglobin levels in a subgroup of patients with low risk myelodysplastic syndromes where no other products are authorised. The achievement of transfusion independence is of significant benefit over transfusion therapy.

An opinion not recommending the removal of Revlimid (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) (EU/3/04/192) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion (EMA/COMP/288804/2013) was adopted for publication on the EMA website.

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

5.2.1 Procysbi (former name: cysteamine bitartrate) [Cysteamine bitartrate (gastroresistant)] for treatment of cystinosis; Raptor Pharmaceuticals Europe B.V. (EU/3/10/778) [Co-ordinators: V. Saano / S. Mariz]

The Committee considered that the sponsor should clarify the significant benefit.

The sponsor should further support with data justify the potential significant benefit of Cysteamine bitartrate (gastroresistant) (Procysbi) over Cystagon for treatment of cystinosis regarding major contribution to patient.

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 June meeting.

5.2.2 Pomalidomide Celgene (Pomalidomide) for treatment of multiple myeloma; Celgene Europe Ltd. (EU/3/09/672) [Co-ordinators: K. Kubackova / S. Mariz]

Following the initial discussion the review of the orphan designation, the Committee expressed a positive trend on the maintenance of the designation. A formal opinion to be adopted by the COMP in June 2013.

5.3. On-going procedures

5.3.1 Adempas (Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate) for treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension; Bayer Pharma AG (EU/3/07/518)

5.3.2 Cholic Acid FGK for treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid; FGK Representative Service GmbH (EU/3/09/683)

5.3.3 Cometriq [Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt] for treatment of medullary thyroid carcinoma; TMC Pharma Services Ltd (EMA/H/C/002640)

5.3.4 Defitelio (Defibrotide); Gentium S.p.A.
Re-examination requested in April 2013.

- prevention of hepatic veno-occlusive disease (EU/3/04/211)

- treatment of hepatic veno-occlusive disease (EU/3/04/212)

5.3.5 Delamanid ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis; Otsuka Novel Products GmbH (EU/3/07/524)

5.3.6 Dexamethasone (40 mg tablet) for treatment of multiple myeloma; Laboratoires CTRS (Cell Therapies Research & Services) (EU/3/10/745)

5.3.7 Folcepri (N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine to be used with folic acid) for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1043)

5.3.8 Holoclar (former name: GPLSCD01) (substance to be reviewed) (Ex vivo expanded autologous human corneal epithelium containing stem cells) for treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns; Chiesi Farmaceutici S.p.A. (EU/3/08/579)

5.3.9 Kinaction (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (EU/3/09/684)

5.3.10 Masican N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (EU/3/04/251)

5.3.11 Neocepri (Folic acid to be used with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine) for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1044)

5.3.12 Opsumit (Macitentan) for treatment of pulmonary arterial hypertension; Actelion Registration Ltd. (EU/3/11/909)

5.3.13 PAS-GR (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826)

5.3.14 Sirturo (former name: Bedaquiline) ((1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethano) for treatment of tuberculosis; Janssen-Cilag International N.V. (EU/3/05/314)

5.3.15 Scenesse ([Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide) for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (EU/3/08/541)

5.3.16 Translarna (3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid) for treatment of Duchenne muscular dystrophy; PTC Therapeutics Ltd (EU/3/05/278)

5.3.17 Vantobra, Tobramycin (inhalation use) for treatment of Pseudomonas Aeruginosa lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613)

5.3.18 Vynfinit (Vincaleukoblastin-23-oic acid, O4-deacetyl-2-[(2-mercaptoethoxy)carbonyl]hydrazide, disulfide with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-gamma-glutamyl-L-alpha-aspartyl-L-arginyl-L-alpha-aspartyl-L-alpha-aspartyl-L-cysteine) for treatment of ovarian cancer; Endocyte Europe, B.V. (EU/3/12/959)

5.3.19 Winfuran (-)-17(cyclopropylmethyl)-1,14 ß-dihydroxy-4,5 alpha-epoxy-6ß-[N-methyl-trans-3-(3-furyl) acrylamido] morphinan hydrochloride for treatment of uremic pruritus; Toray International U.K. Limited (EU/3/02/115)

5.4. Appeal procedure

5.4.1 Following adoption of the COMP negative opinions at the 16-17 April 2013 meeting, the grounds for appeal are expected by 5 August 2013

6. Procedural aspects

6.1 Report on fee reductions for orphan medicines

A report on the use of the special EU contribution for fee reductions was provided for information.

6.2 European Medicines Agency Human Scientific Committees' Working Party with Healthcare Professionals' Organisations (HCPWP)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000032.jsp&mid=WC0b01ac0580028dd3

The HCWP mandate EMA/36437/2013 was adopted by the COMP. The COMP representative in the HCPWP to be appointed at the June meeting. Draft agenda of the HCPWP meeting to be held on 5 June 2013 EMA/228646/2013 was circulated for information.

6.3 European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP)

The draft agenda EMA/228739/2013 for the joint PCWP-HCPWP meeting to be held on 5 June 2013 and the draft agenda EMA/248075/2013 for the PCWP meeting to be held on 6 June 2013 were circulated for information.

Post-meeting note:

The PCWP Mandate, objectives and rules of procedure EMA/369907/2010 Rev. 2 was adopted via written procedure on 21 May 2013.

6.4 Proposed revision of the EC *Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another* ENTR/6283/00 Rev. 4

The Committee discussed the proposed revision of the EC guideline.

Date of next COMP meeting: 11-13 June 2013

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

Irena Bradinova	България
Kateřina Kubáčková	Česká Republika
Dorthe Meyer	Danmark
Rembert Elbers	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Annie Lorence	France
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος
Dainis Krievins	Latvija
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Lars Gramstad	Norway
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Martin Možina	Slovenija
Vacant	Slovensko
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Volunteer patient representative for Eurordis
Pauline Evers	Patient representative representing the European Genetic Alliances Network
János Borvendég	CHMP Representative
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative

Observers:

Ingeborg Barisic	Croatia

Maria Mavris	Eurordis
Frauke Naumann-Winter	Germany

European Commission:

Agnes Mathieu	DG Health and Consumers

EMA:

Jordi Llinares Garcia	Head of Orphan Medicines
Stiina Aarum	Scientific Administrator
Laura Fregonese	Scientific Administrator
Segundo Mariz	Scientific Administrator
Stylianos Tsigkos	Scientific Administrator
Federica Castellani	Scientific Administrator (for 5.1.1)
Agnieszka Wilk-Kachlicka	Assistant
Cinzia N'Diamoi	Assistant

Apologies

Members:

André Lhoir	België/Belgique/Belgien
Aušra Matulevičienė	Lietuva
Henri Metz	Luxembourg
Brigitte Blöchl-Daum	Österreich
Flavia Saleh	Romãnia

Observers:

Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios
Vesna Osrecki	Croatia