6 February 2013
EMA/COMP/790271/2012
Human Medicines Development and Evaluation

# Committee for Orphan Medicinal Products (COMP)

Minutes of the 8 - 9 January 2013 meeting

## Note on access to documents

Documents under points 1.1 and 2 to 7 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).

## Contents




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# 1. Introduction

**1.1** Adoption of the agenda, EMA/COMP/789439/2012

The agenda was adopted with no amendments.

**1.2** Adoption of the minutes of the previous meeting held on 5 - 6 December 2012 EMA/COMP/722237/2012

The minutes were adopted with minor corrections to point 2.1.1.

**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:

- EURORDIS receives funding from the sponsor who have submitted dossier to be considered for orphan designation at the current meeting (2.2.5). Nevertheless, no direct conflicts of interest have been identified for L. Greene and B. Byskov Holm, who are the volunteer patient representatives for EURORDIS.

# 2. Applications for orphan medicinal product designation[1]

## 2.1. For opinion

**2.1.1** For treatment of haemophilia A - EMA/OD/152/12
*[Co-ordinators: L. Gramstad / 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 justification of significant benefit. The arguments on significant benefit are based on the potential for improved efficacy and a less frequent dosing scheme in haemophilia patients requiring treatment with bypassing agents. The sponsor is basing this assumption on improved catalytic activity and pharmacological potency, and on claimed extended duration of the pharmacodynamic effect.

The sponsor was requested to elaborate on these claims by any available data in relevant preclinical or preliminary clinical settings, and to provide a comparative discussion based on data vis a vis bypassing agents, in order to justify a clinically relevant advantage or major contribution to patient care.

In its written response and during the oral explanation before the Committee on 8 January 2013 the sponsor argued that the product may have a prolonged duration of effect based on a more favourable volume distribution and clearance relative to an authorised counterpart. The sponsor supported this notion on the grounds that roughly equipotent doses have different duration of effect in preclinical models as shown by thromboelastography. It was claimed that this may result in a less frequent dosing scheme which could represent a major contribution to patient care.

[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 COMP considered that even though the pharmacological profile of the proposed product may be different to an authorised counterpart, the assumption of a major contribution to patient care could not be considered justified. This was based on the one hand on the paucity of data which did not defined a specific dosing scheme for the product under evaluation, and on the other hand on the fact that as not all patients require daily administration, alleviating the need for a less frequent administration in the terms presented by the sponsor would not automatically justify a 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 9 January 2013, prior to final opinion.

### **2.1.2** For treatment of haemophilia B - EMA/OD/151/12

*[Co-ordinators: L. Gramstad / 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 justification of significant benefit. The arguments on significant benefit are based on the potential for improved efficacy and a less frequent dosing scheme in haemophilia patients requiring treatment with bypassing agents. The sponsor is basing this assumption on improved catalytic activity and pharmacological potency, and on claimed extended duration of the pharmacodynamic effect.

The sponsor was requested to elaborate on these claims by any available data in relevant preclinical or preliminary clinical settings, and to provide a comparative discussion based on data vis a vis other bypassing agents, in order to justify a clinically relevant advantage or major contribution to patient care.

In its written responses and during the oral explanation before the Committee on 8 January 2013 the sponsor argued that the product may have a prolonged duration of effect based on a more favourable volume distribution and clearance relative to an authorised counterpart. The sponsor supported this notion on the grounds that roughly equipotent doses have different duration of effect in preclinical models as shown by thromboelastography. It was claimed that this may result in a less frequent dosing scheme which could represent a major contribution to patient care.

The COMP considered that even though the pharmacological profile of the proposed product may be different to an authorised counterpart, the assumption of a major contribution to patient care could not be considered justified. This was based on the one hand on the paucity of data which did not establish a specific dosing scheme for the product under evaluation, and on the other hand on the fact that as not all patients require daily administration, alleviating the need for a less frequent administration in the terms presented by the sponsor would not automatically justify a 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 9 January 2013, prior to final opinion.

### **2.1.3** **Cyclo-Cys-Gly-Gln-Arg-Glu-Thr-Pro-Glu-Gly-Ala-Glu-Ala-Lys-Pro-Trp-Tyr-Cys** for treatment of high altitude pulmonary oedema, Apeptico Forschung und Entwicklung GmbH - EMA/OD/144/12

*[Co-ordinators: M. Možina / L. Fregonese]*

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was invited to justify high altitude pulmonary oedema (HAPE) as a distinct condition, in

particular in relation to a potential overlap with acute lung injury, for which the sponsor already holds and orphan designation, taking into account the pathophysiology of the two conditions and the mechanism of action of the product in the two conditions.

In the written response, and during an oral explanation before the Committee on 8 January 2013, the sponsor further elaborated on the differences between acute lung injury and high altitude pulmonary oedema with respect to aetiology, pathogenesis, and clinical manifestations.

It was discussed that HAPE is defined by occurring in high altitude (more than 3,000 m), being this is the only recognized cause of this condition. From a pathogenetic point of view HAPE is mainly driven by the physiologic response to the hypoxia of high altitude combined with exercise. The main pathogenetic events as far as known include excessive rise in pulmonary artery pressure and an abnormally brisk vasoconstrictor response to hypoxia and exercise. Hypersympathetic activity is also involved, and in fact HAPE is traditionally considered a neurogenic oedema. These mechanisms result in stress failure of the lung capillary circulation leading to leakage of macromolecules in the interstitium and the alveoli.

On the other hand, ALI is driven by the direct damage to the lung alveolar surface due to e.g. toxic gases, aspiration of gastric material, infectious agents, or by indirect damage through systemic inflammation (e.g. sepsis, polytrauma), or both. Oedema in this case occurs as consequence of the alveolar damage and the disruption of the alveolar-capillary membrane, and increasing vascular permeability due to inflammatory mediators, among other pathogenetic events. The Committee agreed that the condition, high altitude pulmonary oedema, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat with the proposed product was supported by several relevant pre-clinical studies, including high altitude pulmonary oedema models. In these models, which accurately represent the physiopathology of the condition, treatment with the product significantly increased alveolar fluid clearance, and induced progressive recovery of relevant functional parameters such as dynamic lung compliance and airway resistance. High altitude pulmonary oedema was estimated to be affecting less than 0.03 in 10,000 people in the European Union, at the time the application was made. Incidence is acceptable as epidemiologic measure of the disease due to its short duration. The sponsor based the calculations on an extensive literature search; the calculations were also supported by expert opinions. The condition is life-threatening, with mortality rates estimated between 24 and 44%. The condition can appear with mild symptoms which rapidly worsen in absence of treatment, leading to progressive hypoxemia, respiratory muscle fatigue, lethargy, coma, and death from respiratory arrest. There is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for Cyclo-Cys-Gly-Gln-Arg-Glu-Thr-Pro-Glu-Gly-Ala-Glu-Ala-Lys-Pro-Trp-Tyr-Cys, for treatment of high altitude pulmonary oedema, was adopted by consensus.

### 2.1.4 **Treprostinil sodium** for treatment of inoperable chronic thromboembolic pulmonary hypertension, SciPharm S.a.r.L - EMA/OD/154/12

*[Co-ordinators: V. Saano / S. Tsigkos][Expert: A. Alonso]*

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:

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

- Proposed indication and medical plausibility

The sponsor is proposing a subset of chronic thromboembolic pulmonary hypertension (CTEPH), focusing on inoperable patients. The sponsor's attention is drawn to the updated guideline ENTR 6283/00, which provisions against using stages of severity or degrees to define a valid condition for designation. Unless the sponsor would be in a position to justify that there would be no pharmacodynamic effects in the excluded patients the proposed indication as applied for cannot be accepted. The sponsor was asked hence to revise the proposed indication.

- Significant benefit

In light of an amended indication, the sponsor should position the product in the current management of these patients. The sponsor was also requested to provide a comparative discussion versus authorised counterparts for the broader indication of pulmonary hypertension, including products containing the same active substance authorised in several Member States authorised for pulmonary arterial hypertension.

In the written response, and during the oral explanation before the Committee on 8 January 2013, the sponsor accepted to remove the restriction to "inoperable" patients from the proposed orphan indication in line with the Committee suggestion and stressed that no medicinal products are authorised for CTEPH. The Committee considered that "CTEPH" was a distinct medical entity and different from PAH, based on the "Guidelines for the diagnosis and treatment of pulmonary hypertension" published in 2009 by the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT).

Following review of the application by the Committee, it was agreed to rename the indication to "treatment of chronic thromboembolic pulmonary hypertension".

Supported by the arguments and justifications presented on the treatment of the condition the Committee also accepted that no satisfactory methods exist for the treatment of the proposed condition.

The Committee agreed that the condition, chronic thromboembolic pulmonary hypertension is a distinct medical entity based on the "Guidelines for the diagnosis and treatment of pulmonary hypertension" published in 2009 by the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT).

It was acknowledged that in the past the Committee adopted opinions encompassing PAH and CTEPH based on the similarities between these forms of pulmonary hypertension, supported by expert views that distal CTEPH presents some hemodynamic and histologic similarities to those of primary arterial hypertension. In that conclusion it was also previously considered that grouping both entities would stimulate research and development in CTEPH, the rarer of the two. The Committee has revisited the principle of grouping the conditions in view of the abovementioned latest PH classification and the current knowledge.

The intention to threat the proposed condition with the product as applied for designation was considered justified in the basis of published clinical data in patients with the proposed condition that showed improved survival and physical activity for treated patients. Based on literature data the condition was estimated to be affecting between 0.1 and 0.52 in 10,000 people in the European Union, at the time the application. The condition is life-threatening and chronically debilitating due to impairment of physical activity with symptoms including dyspnoea and fatigue and a 5-year survival

rate as low as 16% for untreated patients with CTEPH. There is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for treprostinil sodium, for treatment of chronic thromboembolic pulmonary hypertension, was adopted by consensus.

**2.1.5 Progesterone** for treatment of moderate and severe traumatic brain injury, BHR Pharma Belgium - EMA/OD/141/12
*[Co-ordinators: D. Krievins / L. Fregonese]*

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 was invited to elaborate on the justifications for excluding the use of the product in mild forms of traumatic brain injury, taking into account: the mechanism of action of the proposed product, its potential efficacy in the mild forms, and the pharmacological and clinical arguments for restricting the therapeutic use to moderate and severe traumatic brain injury.

If it is medically plausible to include the mild form, the incidence calculation and the significant benefit discussion would have to be updated to the broadened condition.

- Prevalence

The sponsor should provide a final acceptable value of the incidence of the condition. The sponsor states that, based on the consulted literature sources, the incidence ranges from 0.95 to 6.6 per 10,000 population. The sponsor did not explain the scientific reasons for discarding in the final calculations the studies where incidence was above 5 in 10,000.

In addition the sponsor was invited to clarify whether the currently presented incidence data include also pre-hospital incidence.

In the written response, and during the oral explanation before the Committee on 8 January 2013, the sponsor stressed that there is no need for treating mild forms of traumatic brain injury supplemented by a complete uncertainty regarding possible clinical benefits of progesterone in this form of the disease.

The COMP noted that the benefit of treating mild brain injury in order to prevent long-term consequences such as e.g. dementia or psychiatric disorders is under discussion in the scientific community and that studies were on-going on this subject. The Committee accepted the justification of the sponsor about the lack of need and unproven efficacy of progesterone in the treatment of mild forms, but at the same time cautioned the sponsor towards possible changes in the management of the disease between this designation stage and the moment of marketing authorization. The COMP strongly recommended the sponsor to take into account this point during the protocol assistance procedure.

Regarding the question on prevalence, the sponsor explained the reasons for excluding studies where high incidence was reported. It was agreed by the Committee that pre-hospital incidence is extremely difficult to assess and it would by large majority include mild forms, which have been at the end excluded by the present application. As such the reasoning and final calculations from the sponsor were considered acceptable. The Committee agreed that the condition, moderate and severe traumatic brain injury, is a distinct medical entity and meets the criteria for orphan designation.

Moderate and severe traumatic brain injury was estimated to be affecting approximately 4 in 10,000 people in the European Union, at the time the application was made. The incidence estimate has been based on relevant literature. The intention to treat the product is supported by preclinical studies published in the literature showing the neuro-protective action of progesterone, and by clinical results showing survival and functional benefit in most patients treated with progesterone. The condition is life-threatening, with high fatality rates due to direct brain damage and cerebral oedema in the days immediately post-trauma. The condition is chronically debilitating due to the possible development of long-term complications including neurological deficits with motor and cognitive disorders, psychiatric disorders, and dementia.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that progesterone may be of significant benefit to those affected by the condition. The significant benefit assumption at the present stage is based on the results of a non-sponsor generated phase II randomized placebo-controlled clinical trial of intravenous progesterone *versus* placebo on top of standard of care, showing improvement of survival in a subgroup of patients with severe traumatic brain injury treated with intravenous progesterone.

A positive opinion for progesterone, for treatment of moderate and severe traumatic brain injury, was adopted by consensus.

### **2.1.6** For treatment of beta-thalassemia intermedia and major - EMA/OD/138/12

*[Co-ordinators: R. Elbers / 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 beta-thalassemia intermedia and major, the sponsor is invited to further elaborate on:

- the relevance of the results of the single preclinical study used to support the medical plausibility of the product for the treatment of beta-thalassemia intermedia and major. It is not clear how the results seen on erythrocytes are applicable considering the underlying causes of the condition.

In the written response, and during the oral explanation via teleconference on 8 January 2013, the sponsor elaborated on the mechanism of action and discussed that even though the product did not target the underlying cause of beta thalassaemia, multiple downstream pathologies arising from unbalanced globin chain synthesis are affected. With regards to the preclinical dossier, it was discussed that theTh1 and Th3 models of beta-thalassemia are widely accepted. The sponsor argued that the product shows comparable activity in the two preclinical models and that early data in healthy volunteers support the activity of the product in the disease.

The Committee discussed that an effect may be accepted with regards to late-stage maturation of erythrocytes. Nevertheless the fact that central aspects of the disease such as the defects in globin synthesis and related consequences such as precipitation of globin chains are not addressed makes the Committee to conclude that there are no sufficient data at the moment to justify the intention to treat beta-thalassemia.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2013, prior to final opinion.

**2.1.7** For treatment of myelodysplastic syndromes - EMA/OD/139/12
*[Co-ordinators: R. Elbers / 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 justification of significant benefit. The justification of significant benefit is based on a novel mechanism of action, which may allow the product to treat the anaemia as a prominent symptom of the proposed condition. It is postulated by the sponsor that the mechanism of action is independent from that of epoietins, as it involves the maturation phase of red blood cell development.

The sponsor however does not translate this new mechanism into a clinically relevant advantage or a major contribution to patient care. The sponsor was requested to further elaborate on the justification of significant benefit by discussing any available data and providing any comparative discussion vis a vis the standard of care for the proposed condition as applied for designation, including epoietins.

In the written response, and during the oral explanation via teleconference on 8 January 2013, the sponsor reiterated the different mechanism of action, namely the inhibition of the negative regulation of the late-stage erythroid progenitor differentiation. The sponsor argued on significant benefit based on the delineation of a population with limited response to erythropoiesis stimulating agents, for whom the product may have a beneficial effect.

The Committee considered that significant benefit should be argued on the basis of data in either relevant preclinical models or preliminary clinical settings. Simply stating that the proposed product has a different mechanism of action would not suffice for the justification of significant benefit unless translated into a clinically relevant advantage (e.g. the potential for improved efficacy) or major contribution to patient care. Therefore the justification of significant benefit cannot be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2013, prior to final opinion.

## 2.2. For discussion / preparation for an opinion

**2.2.1** For treatment of hepatocellular carcinoma - EMA/OD/159/12
*[Co-ordinators: R. Elbers / 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 hepatocellular carcinoma, the sponsor is invited to discuss the relevance of the in vitro studies on migration and aggregation of hepatocarcinoma cells to the proposed anti-tumour activity of the product, with particular regard to invasiveness and formation of metastasis.

In addition the sponsor is invited to further discuss the results of the clinical study Phase II in patients with hepatocellular carcinoma who have had disease progression on sorafenib or are not eligible to receive sorafenib, and in particular:

- the demographics, methodology and up to date results of this study including, among others, the number of cycles that the patients received up to date, the baseline levels of alpha fetoprotein and its

changes in the whole patient population, the results with respect to the primary endpoint of this study (time to progression).

- Justification of significant benefit

The sponsor is requested to further elaborate on the results from the clinical study phase II in order to explain how such results would support the claim of significant benefit over authorised medicinal products, e.g. sorafenib.

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 February meeting.

**2.2.2** For treatment of glioma - EMA/OD/157/12
*[Co-ordinators: K. Kubáčková / S. Mariz]*

The Committee considered that the medical plausibility requires clarification by the sponsor:

- to establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of glioma, the sponsor is invited to further elaborate on:

- the relevance and the applicability of the results obtained from the preclinical models used with the sponsors' product for the treatment of glioma.

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

**2.2.3** For treatment of emphysema secondary to congenital alpha-1 antitrypsin deficiency - EMA/OD/166/12
*[Co-ordinators: V. Saano / S. Tsigkos]*

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

The proposed indication is a subset of congenital alpha-1 antitrypsin deficiency. In line with the updated guideline on the format and content of the applications ENTR6283/00 Rev 03, the restriction of the proposed indication should be justified.

- Proposed indication

The sponsor is invited to broaden the proposed indication to "treatment of congenital alpha-1 antitrypsin deficiency".

- Prevalence

In light of an amended indication, an updated prevalence calculation should be submitted to the Committee.

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

**2.2.4** For treatment of chronic non-infectious uveitis - EMA/OD/161/12
*[Co-ordinators: J. Torrent-Farnell / S. Mariz]*

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 chronic non-infectious uveitis, the sponsor is invited to further elaborate on:

- all the studies with the product described in the dossier are designed exclusively in patients with Behçet's disease uveitis. Nonetheless, chronic non-infectious uveitis is associated with a lot of different conditions and not only with Behçet's disease.

- the sponsor is requested to show how the data in Behçet's patients can be extrapolated in uveitis associated with other conditions.

- Prevalence

The sponsor is invited to re-calculate the proposed prevalence of the condition in view of the different subsets that exist under this condition including uveitis associated with Behçet's.

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 February meeting.

### 2.2.5 **Humanized anti-myostatin monoclonal antibody** for treatment of Duchenne muscular dystrophy, Pfizer Limited - EMA/OD/164/12

*[Co-ordinators: P. Evers / S. Tsigkos]*

For the purpose of orphan designation the COMP considered that the active substance should be renamed as "humanised monoclonal antibody against myostatin";

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

The intention to threat the condition can be considered justified based on preclinical models of the condition that show increased lean mass and grip strength after treatment with the proposed product as applied for designation. The condition was estimated to be affecting approximately 0.5 in 10,000 people in the European Union, at the time the application was made; this was based on several publications on the condition in Europe; this is not more than 5 in 10,000 people as established in Article 3(1) (a) of Regulation (EC) 141/2000. The sponsor has provided satisfactory argumentation to establish that the condition is chronically debilitating and life-threatening, mainly due to progressive muscle weakness with loss of function of voluntary muscles and involvement of cardiac muscle. Most children affected by the condition will need a wheel chair before 12 years of age, while respiratory muscle deterioration results in reduced forced vital capacity of the lungs, requiring ventilation support. Death occurs at median age of 25 years, usually due to respiratory or cardiac failure.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for humanised monoclonal antibody against myostatin, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

### 2.2.6 **Humanized IgG1 kappa antibody against serum amyloid A and AL amyloid** for treatment of amyloid light chain AL amyloidosis, Onclave Therapeutics Limited - EMA/OD/129/12

*[Co-ordinators: K. Westermark / S. Mariz]*

The Committee agreed that the condition, amyloid light-chain amyloidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to threat the condition can be considered justified based on a preclinical model of the condition that shows a reduction in volume and weight of an induced amyloidoma after treatment with the proposed product as applied for designation. Amyloid light-chain amyloidosis was estimated to be affecting approximately 1.1 in 10,000 people in the European Union, at the time the application was made; the sponsor has based their prevalence calculation on an extensive literature search. The condition is chronically debilitating due to the accumulation of extracellular amyloidogenic fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues. The disease carries a poor prognosis, predominantly influenced by the patient's performance status and extent of organ involvement, particularly cardiac involvement, at diagnosis. As such, the majority of patients with AL amyloidosis die from cardiac death, which is often sudden.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for humanised IgG1 kappa antibody against serum amyloid A and AL amyloid, for treatment of amyloid light-chain amyloidosis, was adopted by consensus.

**2.2.7 L-asparaginase encapsulated in Erythrocytes** for treatment of acute myeloid leukemia, ERYtech Pharma S.A. - EMA/OD/167/12
*[Co-ordinators: R. Elbers / S. Tsigkos]*

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 acute myeloid leukaemia was considered justified based on clinical studies on relapsed AML patients treated with asparaginase in combination to cytarabine, that showed increased complete remission rates compared to patients treated with cytarabine alone. The condition was estimated to be affecting not more than 1.2 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating and 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 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%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that the product may be of significant benefit to those affected by the condition. This appears justified in particular with regards to the clinically relevant advantage of improved efficacy. This is based on clinical studies on relapsed AML patients treated with asparaginase in combination to cytarabine that showed increased complete remission rates compared to patients treated with cytarabine alone.

A positive opinion for l-asparaginase encapsulated in erythrocytes, for treatment of acute myeloid leukaemia, was adopted by consensus.

**2.2.8** For prevention of graft rejection following solid organ transplant - EMA/OD/165/12
*[Co-ordinators: K. Westermark / S. Mariz]*

The Committee considered that the justification of significant benefit issues requires clarification by the sponsor. The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is requested to clarify whether the product would be used for the prevention and/or for the treatment of the condition, taking into account the current protocols for the management of acute graft rejection of solid organ transplantation in Europe. In addition the sponsor is invited to clarify whether the product is intended to replace the current regimens or to be used as add-on. In this respect, the sponsor is invited to discuss the clinical added value of using the proposed product in relation to the currently authorized medicinal products, including standard immunosuppressive regimens.

As they refer to literature data using previous similar products, the sponsor should also discuss the potential difference between those products and their product, i.e. if it is possible to extrapolate the results. The sponsor is also invited to discuss the risk of developing antibodies to the 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 February meeting.

**2.2.9** For treatment of sickle cell disease - EMA/OD/162/12
*[Co-ordinators: L. Gramstad / L. Fregonese]*

The Committee considered that the medical plausibility requires clarification by the sponsor. To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of sickle cell disease, the sponsor is invited to further elaborate on the mechanism of action of the product, and in particular on the events happening at cell membrane level. The sponsor is also invited to elaborate on possible additional pharmacologic mechanisms of action of the product in the proposed condition, such as e.g. at endothelial level.

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 February meeting.

**2.2.10 Recombinant adeno-associated viral vector expressing a human CNGB3 gene** for treatment of achromatopsia caused by mutations in the CNGB3 gene, TMC Pharma Services Ltd - EMA/OD/109/12
*[Co-ordinators: A. Magrelli/ K. Westermark / L.Fregonese]*

For the purpose of orphan designation, the COMP considered that the active ingredient should be renamed as "recombinant adeno-associated viral vector containing the human *CNGB3* gene".

The Committee agreed that achromatopsia caused by mutations in the *CNGB3* gene, is a valid subset of achromatopsia based on the fact that the proposed treatment is exclusively targeting achromatopsia caused by mutations in the CNGB3 gene and meets the criteria for orphan designation.

Achromatopsia caused by mutations in the *CNGB3* gene was estimated to be affecting approximately 0.15 in 10,000 people in the European Union, at the time the application was made. The prevalence was estimated based on relevant literature. The intention to treat the condition with the proposed product is supported by pre-clinical studies showing rescue of the cones in treated eyes, which remained stable for at least six months. The condition is chronically debilitating due to the serious impairment of visual acuity in daylight, which is associated with limitations in normal day activities. Lack of visual acuity can be accompanied by severe photophobia, nistagmus, small central scotoma, eccentric fixation and reduced or complete loss of colour discrimination.

There is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for recombinant adeno-associated viral vector containing the human *CNGB3* gene, for treatment of achromatopsia caused by mutations in the *CNGB3* gene, was adopted by consensus.

**2.2.11** For treatment of X-linked juvenile retinoschisis (XLRS) - EMA/OD/108/12
*[Co-ordinators: A. Magrelli/ K. Westermark / L.Fregonese]*

The Committee considered that the medical plausibility requires clarification by the sponsor. The sponsor presented literature data on a model and stated that they replicated such data. In order to justify the medical plausibility of the product in the proposed condition the sponsor is invited to provide their own generated proof-of-concept pre-clinical data in the model.

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

**2.2.12** For treatment of Niemann-Pick's disease, type C - EMA/OD/160/12
*[Co-ordinators: P. Evers / S. Tsigkos]*

The Committee considered that the justification of significant benefit requires clarification by the sponsor. The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition when used in combination with miglustat or as a monotherapy. The sponsor is requested to further discuss these points by presenting any available data in preclinical models or preliminary clinical settings that support this position.

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 February meeting.

**2.2.13 Terguride** for treatment of systemic sclerosis, High Tech Participations GmbH - EMA/OD/156/12
*[Co-ordinators: A. Moraiti/ N. Sypsas / S. Mariz]*

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

The intention to treat the condition with the product was considered justified on the grounds of the pre-clinical data. In this model, treatment with terguride showed an effect in the condition. Systemic sclerosis was estimated to be affecting approximately 1.6 in 10,000 people in the European Union, at the time the application was made; the sponsor has used the results of a literature search to establish the prevalence. The condition is chronically debilitating due to the deposition of collagen in the skin and, less commonly, in the kidneys, heart, lungs and stomach. This deposition presents in two forms: diffuse scleroderma which affects the skin as well as the heart, lungs, gastrointestinal tract and kidneys and localized scleroderma which affects the skin of the face, neck, elbows and knees and late in the disease causes isolated pulmonary hypertension. Common complications seen with the diffuse form are pulmonary hypertension, reflux esophagitis and dysphagia, as well as the appearance of sclerodermal renal crisis. Symptoms of scleroderma renal crisis are malignant hypertension, hyperreninaemia, azotaemia and microangiopathic haemolytic anaemia. Renal involvement is associated with poor prognosis and is frequently associated with mortality. It is also life-threatening

due to a 5-year survival which has been reported to lie between 34% and 73%. Frequent causes of mortality are pulmonary arterial hypertension and sclerodermal renal crisis.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that terguride, may be of significant benefit to those affected by the condition. The current approved therapy in Europe is bosentan which targets pulmonary hypertension a consequence of diffuse scleroderma and not the underlying cause. Terguride offers the possibility of targeting an alternative aspect of the condition which is driven by a systemic autoimmune process. The sponsor has provided pre-clinical data supporting the potential effectiveness of terguride on the fibrotic process in systemic sclerosis. This would offer significant benefit since the therapy offers the possibility of reducing the fibrotic process which is directly associated with the condition not targeted by the current approved therapy.

A positive opinion for terguride, for treatment of systemic sclerosis, was adopted by consensus.

**2.2.14** For treatment of autosomal dominant polycystic kidney disease - EMA/OD/163/12
*[Co-ordinators: A. Corrêa Nunes / S. Tsigkos]*

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

- Description of the condition

The applicant is requested to further discuss why apart from autosomal dominant polycystic kidney disease, autosomal recessive and unspecified forms cannot be part of the proposed indication.

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the product for treatment of autosomal dominant polycystic kidney disease, the sponsor is invited to further elaborate on:

- the results from the rat and murine models of the proposed condition as applied for;

- the available clinical efficacy studies in the proposed indication as applied for.

- Prevalence

The sponsor is invited to re-calculate the prevalence calculation based on full and not partial prevalence, 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 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 February meeting.

## 2.3. Appeal procedure

**2.3.1 Zoledronic acid** for treatment of complex regional pain syndrome, Axsome Therapeutics Limited - EMA/OD/125/12
(active time: day 88)

The grounds for appeal to the COMP negative opinion adopted on 6 December 2012 are expected by 19 March 2013. The Committee noted the coordinators for the appeal procedure, K. Westermak and S. Tsigkos.

## 2.4. Evaluation on-going

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

## 2.5. Validation on-going

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

# 3. Requests for protocol assistance

**3.1** For treatment of pouchitis [Co-ordinator: R. Elbers]

The Committee was briefed on the significant benefit issues. The protocol assistance letter was adopted.

**3.2** For treatment of acute myeloid leukaemia [Co-ordinator: R. Elbers]

The Committee was briefed on the significant benefit issues. The protocol assistance letter was adopted.

# 4. Overview of applications

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

COMP co-ordinators were appointed for one application submitted and twenty one 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 Exjade** (4-(3,5-bis(hydroxy-phenyl)-1,2,4) triazol-1-yl) benzoic acid) for treatment of chronic iron overload requiring chelation therapy; Novartis Europharm Limited (OD/061/01, EU/3/02/092) [Co-odinators: M. Mozina/ S. Mariz]
Positive CHMP opinion on Type II variation adopted in November 2012 for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

The Committee noted that following the consultation with the CHMP Rapporteur it has been confirmed that the proposed for the Type II variation indication falls within the orphan indication.

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

**5.2.1 Bosulif** (Bosutinib) for treatment of chronic myeloid leukaemia; Pfizer Limited (OD/160/09, EU/3/10/762) [Co-ordinators: R. Elbers / S. Tsigkos].

**5.2.2 Defitelio** (Defibrotide); Gentium S.p.A. [Co-ordinators: J. Torrent-Farnell / S. Mariz]

- prevention of hepatic veno-occlusive disease (OD/025/04, EU/3/04/211)
- treatment of hepatic veno-occlusive disease (OD/026/04, EU/3/04/212)

**5.2.3 Raxone** (previously SAN Idebenone; Idebenone) for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (OD/076/06, EU/3/07/434) [Co-ordinators: J. Torrent-Farnell / S. Mariz].

## 5.3. On-going procedures

**5.3.1 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. (OD/024/05 , EU/3/05/314 , EMA/H/C/002614) [Co-ordinators: N. Sypsas / L. Fregonese].

**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 (OD/080/09, EU/3/09/683,) [Co-ordinators: A. Magrelli / S. Tsigkos].

**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 (OD/088/08, EU/3/08/610) [Co-ordinators: B. Bloech-Daum / TBC].

**5.3.4 Cysteamine bitartrate** [Cysteamine bitartrate (gastroresistant)] for treatment of cystinosis; Raptor Pharmaceuticals Europe B.V. (OD/034/10, EU/3/10/778) [Co-ordinators: V. Saano / S. Mariz].

**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 (OD/094/07, EU/3/07/524); Otsuka Novel Products GmbH [Co-ordinators: V. Stoyanova / L. Fregonese].

**5.3.6 Exjade** (4-(3,5-bis(hydroxy-phenyl)-1,2,4) triazol-1-yl) benzoic acid) for treatment of chronic iron overload requiring chelation therapy; Novartis Europharm Limited (OD/061/01, EU/3/02/092) [Co-odinators: M. Mozina/ S. Mariz]
Type II variation - for the treatment of chronic iron overload due to blood transfusions in patients with beta thalassaemia major aged 6 years and older.

**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. (OD/055/12, EU/3/12/1043) [Co-ordinators: B. Bloech-Daum / TBC].

**5.3.8 Iclusig** (benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-); ARIAD Pharma Ltd (EMA/H/C/002695) [Co-ordinators: K. Kubackova / L. Fregonese].

- treatment of chronic myeloid leukaemia (OD/121/09, EU/3/09/716)

- treatment of acute lymphoblastic leukaemia (OD/122/09, EU/3/09/715).

**5.3.9 Kinaction** (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (OD/063/09, EU/3/09/684) [Co-ordinators: B. Bloech-Daum / S. Tsigkos].

**5.3.10 Loulla** (Mercaptopurine) for treatment of acute lymphatic leukaemia, Only For Children Pharmaceuticals (OD/065/07, EU/3/07/496) [Co-ordinators: D. O'Connor / S. Tsigkos].

**5.3.11 Masican** N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (OD/061/04, EU/3/04/251) [Co-ordinators: D. O'Connor / S. Mariz].

**5.3.12 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. (OD/056/12, EU/3/12/1044) [Co-ordinators: B. Bloech-Daum / TBC].

**5.3.13 Opsumit** (Macitentan) for treatment of pulmonary arterial hypertension; Actelion Registration Ltd. (OD/023/11, EU/3/11/909), [Co-ordinators: V. Saano / L. Fregonese].

**5.3.14 PAS-GR** (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (OD/072/10, EU/3/10/826) [Co-ordinators: V. Stoyanova / S. Mariz].

**5.3.15 Pheburane** (Sodium phenylbutyrate) for treatment of carbamoyl-phosphate synthase-1 deficiency; Lucane Pharma SA (OD/098/11, EU/3/12/951) [Co-ordinators: J. Torrent-Farnell / L. Fregonese].

**5.3.16 Pomalidomide Celgene** (Pomalidomide) for treatment of multiple myeloma, Celgene Europe Ltd. (OD/053/09, EU/3/09/672) [Co-ordinators: R. Elbers/ S. Mariz]
CHMP LoQ adopted in October 2012.

**5.3.17 Revlimid** (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) for treatment of myelodysplastic syndromes; Celgene Europe Limited – UK (OD/083/03, EU/3/04/192) [Co-ordinators: L. Gramstad / S. Tsigkos]
Type II variation - for the 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.

**5.3.18 Scenesse** ([Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide) for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (OD/108/07, EU/3/08/541) [Co-ordinators: L. Gramstad / S. Mariz].

**5.3.19 Translarna** (3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid) for treatment of Duchenne muscular dystrophy; PTC Therapeutics Ltd (OD/106/04, EU/3/05/278) [Co-ordinators: P. Evers / TBC].

**5.3.20 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. (OD/094/11, EU/3/12/959) [Co-ordinators: B. Bloechl-Daum / TBC].

**5.3.21 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 (OD/020/02, EU/3/02/115) [Co-ordinators: S. Thorsteinsson / S. Mariz].

**5.3.22 Vantobra,** Tobramycin (inhalation use) for treatment of Pseudomonas Aeruginosa lung infection in cystic fibrosis; PARI Pharma GmbH (OD/094/08, EU/3/09/613) [Co-ordinators: J. Eggenhofer, V. Stoyanova / L. Fregonese].

# 6. Procedural aspects

**6.1** Appointment of the COMP representatives to the EMA Scientific Advice Working Party (SAWP)

The COMP re-nominated B. Bloechl-Daum and nominated K. Westermark as the COMP representatives in the SAWP.

**6.2** Proposal for new wording of the grounds for the COMP opinions

The new grounds for the COMP opinions/summary reports were agreed on by the COMP. The new text will be implemented in the revised summary report and opinion templates.

# 7. Any other business

**7.1** COMP Informal meeting held on 22-23 November 2012 in Rome

The adoption of the draft minutes of the meeting was postponed to the next meeting.

**7.2** COMP Informal meeting to be held on 28 February - 1 March 2013 in Dublin

The draft agenda will be circulated before the next meeting for comments.

**7.3** COMP Work Programme 2013-2015

The proposal document EMA/COMP/600966/2012 with comments was circulated for preparation for a discussion at the next meeting.

The Committee thanked warmly Prof. Rembert Elbers (COMP member representing Germany), who has left the COMP, for his contribution to the work of the Committee. Prof. Elbers contributed very significantly to the assessment of applications for orphan designation during his membership. He also developed a very fruitful collaboration with the Scientific Advice Working Party, being the COMP representative at this working party and developing the implementation of significant benefit in the advice given to sponsors.

# Date of next COMP meeting: 5 - 6 February 2013

# List of participants

**Chair:**

Bruno Sepodes

**Vice-Chair:**

| | |
|---|---|
| Lesley Greene | Volunteer patient representative for Eurordis |

**COMP Members:**

| | |
|---|---|
| André Lhoir | België/Belgique/Belgien |
| 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 |
| Aušra Matulevičienė | Lietuva |
| Henri Metz | Luxembourg |
| Judit Eggenhofer | Magyarország |
| Albert Vincenti | Malta |
| Violeta Stoyanova-Beninska | Nederland |
| Lars Gramstad | Norway |
| Brigitte Blöchl-Daum | Österreich |
| Bożenna Dembowska-Bagińska | Polska |
| Ana Corrêa-Nunes | Portugal |
| Flavia Saleh | Romãnia |
| 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 |
| János Borvendég | CHMP Representative |
| Vacant | EMA Representative |

**Observers:**

| | |
|---|---|
| Maria Mavris | Eurordis |

**EMA:**

| | |
|---|---|
| Jordi Llinares Garcia | Head of Orphan Medicines |
| Stiina Aarum | Scientific Administrator |
| Laura Fregonese | Scientific Administrator |
| Segundo Mariz | Scientific Administrator |
| Stylianos Tsigkos | Scientific Administrator |
| Carla Paganin | EMA Expert |
| Agnieszka Wilk-Kachlicka | Assistant |
| Frederique Dubois | Assistant |

# Apologies

**Members:**

| | |
|---|---|
| Pauline Evers | Patient representative representing the European Genetic Alliances Network |
| Aikaterini Moraiti | CHMP Representative |

**Observers:**

| | |
|---|---|
| Antonio Blazquez | Agencia Española de Medicamentos y Productos Sanitarios |
| Ivana Martinovic | Croatia |
| Vesna Osrecki | Croatia |