18 June 2018
EMA/COMP/316876/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 22-24 May 2018

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

22 May 2018, 09:00-17:30, room 2F

23 May 2018, 08:30-19:30, room 2F

24 May 2018, 08:30-13:00, room 2F

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the COMP plenary session to be held 22-24 May 2018. See May 2018 COMP minutes (to be published post June 2018 COMP meeting).

1.2. Adoption of agenda

The agenda for 22-24 May 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 17-19 April 2018 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/001/18

Treatment of transthyretin-mediated amyloidosis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 27 April 2018, prior to responding to the list of issues.

2.1.2. - EMA/OD/002/18

Treatment of transthyretin-mediated amyloidosis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 27 April 2018, prior to responding to the list of issues.

2.1.3. - EMA/OD/014/18

Treatment of epidermolysis bullosa

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of epidermolysis bullosa, the sponsor should further elaborate on the preliminary clinical results.

- Significant benefit

The sponsor was asked to provide more information on the best standard of care for the target patient population and the authorised products that are used. Subsequently, the sponsor was asked to provide a data driven argumentation of significant benefit over the authorised products that are part of the best standard of care.

In the written response, and during an oral explanation before the Committee on 22 May 2018, the sponsor presented the merits of the preliminary clinical data from an on-going trial. The sponsor tried to justify the design of the trial and the data that can be presented at this point in time. The COMP acknowledged the points that were raised by the sponsor, but noted that interpretation of the meaningfulness of the presented data for the purpose of medical plausibility was difficult. The COMP therefore could not recommend granting an orphan designation at this stage and suggested to the sponsor that they come back when they have completed the study.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 24 May 2018, prior to final opinion.

2.1.4. - EMA/OD/015/18

Treatment of malignant cerebral oedema

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 4 May 2018, prior to responding to the list of issues.

2.1.5. (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride - EMA/OD/003/18

BioCryst UK Ltd; Treatment of hereditary angioedema

COMP coordinator: Martin Možina

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

- Number of people affected

The sponsor has proposed a conservative estimate of 0.15 in 10,000. This is focused on the hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency or HAE Type I. The other two types are not included in the calculation. The sponsor is requested to revise the prevalence calculation to include the other forms of HAE.

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

- Significant benefit

The 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 further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. Of particular

interest is the use of rescue treatment namely plasma-derived C1 inhibitors which was collected.

In the written response, the sponsor provided a revised prevalence calculation taking into consideration the three forms of HAE, and included literature sources spanning from 2000 to 2016, covering a number of European countries. The COMP accepted the revised calculations of the sponsor resulting in a final proposed estimate of prevalence of 0.5 per 10,000. In response to the question on significant benefit further data was submitted from the Phase II trial, to clarify the use of rescue treatment described as a secondary end-point. These results highlight that the optimal does of 125 mg per day is associated with a reduction in the attack rate of 70% as well as an overall reduction in rescue medication of 71%. The sponsor also claimed that a substantial improvement in patient quality of life (QoL), using a validated, HAE-specific QoL instrument, was also demonstrated.

The Committee agreed that the condition, treatment of hereditary angioedema, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride was considered justified based on preliminary clinical data showing a significant reduction in attacks in patients with the condition.

The condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a significant reduction in the number of attacks, the use of intravenous C1 inhibitor replacement therapy and an alternative to using an oral formulation where currently none exists. The Committee considered that this constitutes a clinically relevant advantage and major contribution to patient care.

A positive opinion for (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride, for treatment of treatment of hereditary angioedema, was adopted by consensus.

2.1.6. Efpegsomatropin - EMA/OD/009/18

Hanmi Europe Limited; Treatment of growth hormone deficiency

COMP coordinator: Vallo Tillmann

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

- Prevalence

The applicant is invited to recalculate the prevalence estimate by focusing on European data. Literature used should include recent publications such as Murray PG, Arch Dis Child. 2016 Jan;101(1):96-100.

- Significant benefit

Major contribution to patient care should be discussed in the context of comparable efficacy and safety versus the authorised products. The sponsor was asked to elaborate on the efficacy and safety comparability, before arguing a major contribution to patient care.

In order to justify a major contribution to patient care, the sponsor is invited to provide data with their own product, such as quality of life or adherence to treatment, and discuss this data versus the authorised counterparts.

A data-driven comparison is expected to justify a clinically relevant advantage or major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 23 May 2018, the sponsor provided an updated estimate of 4.67 per 10,000, on the assumption that the duration of paediatric disease may be up to 10 years and the duration of the adult up to 40 years. The COMP accepted the justifications provided and considered the prevalence criterion met.

As for the significant benefit, the sponsor elaborated on the expectation of comparable efficacy and safety. The COMP considered that the assumption of major contribution of patient care may be considered at this point in time based on the pharmacokinetic data, which would be expected to be translated into improved patient outcomes. Some divergent views were voiced, as some members considered that in absence of preliminary clinical observations with the specific product as proposed for designation the assumption of a major contribution to patient care was not justified.

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

The intention to treat the condition with the medicinal product containing efpegsomatropin was considered justified based on nonclinical data showing improvement in weight in a model of the condition, and preliminarily clinical observations showing IGF-1 concentration within a target range.

The condition is life-threatening and chronically debilitating due to the psychosocial impact, the cardiovascular risk, and risk of decreased bone mass and fractures.

The condition was estimated to be affecting approximately 4.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing efpegsomatropin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate significantly improved pharmacokinetics compared to the authorised counterparts that are expected to be translated into improved patient outcomes. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for efpegsomatropin, for treatment of growth hormone deficiency, was adopted by consensus.

2.1.7. L-cystine bis(N'-methylpiperazide) - EMA/OD/012/18

PharmaKrysto Ltd; Treatment of cystinuria

COMP coordinator: Ingeborg Barisic

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

- Significant benefit

The arguments on significant benefit over penicillamine and tiopronin are based on the new mechanism of action and on safety. It is well known that extrapolation from non-clinical studies cannot fully predict the safety of a product in its clinical setting.

The sponsor is requested to expand on the arguments provided for significant benefit engaging in a data driven, comparative discussion.

In the written response, and during an oral explanation before the Committee 23 May 2018, the sponsor provided a comparative discussion between the efficacy results obtained with the product in a valid animal model of cystinuria and efficacy results reported in the literature with the comparators in the same or closely related animal models of the condition. The product was shown to reduce cystine stone formation in a valid animal model of the disease while literature studies showed no significant effect of the comparators in the formation of cystine stones in the same or closely related animal models. The Committee considered this comparative discussion as sufficient to support the significant benefit.

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

The intention to treat the condition with the medicinal product containing L-cystine bis(N'-methylpiperazide) was considered justified based on non-clinical data in a valid *in vivo* model of the disease showing reduction in the formation of cystine stones.

The condition is chronically debilitating due to early onset, persistent renal stone formation which has been associated with a higher risk of developing chronic kidney disease.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing L-cystine bis(N'-methylpiperazide) will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data indicating that the product was more effective than authorised medicinal products in preventing cystine stone formation in the same *in vivo* model of the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for L-cystine bis(N'-methylpiperazide), for treatment of cystinuria, was adopted by consensus.

2.1.8. Carmustine - EMA/OD/007/18

ADIENNE S.r.l.S.U.; Treatment in haematopoietic stem cell transplantation

COMP coordinator: Bożenna Dembowska-Bagińska

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

- Significant benefit

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

The sponsor has however not established how carmustine could be of significant benefit within the context of the treatment of patients who are going to receive haematopoietic stem cell transplantation given that it is considered well-established therapy in this condition. In particular the sponsor needs to elaborate on the contribution of carmustine in the combinations used for the purpose of significant benefit.

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

In the written response, the sponsor referred to 5 recent publications which compare the BEAM (combination of carmustine, etoposide, cytarabine and melphalan) to other conditioning regimes. These publications consistently showed better conditioning response with the BEAM combination highlighting the importance of the role of carmustine in ensuring this response.

The COMP concluded that sufficient evidence had been provided to recommend granting the orphan designation.

Following review of the application by the Committee, it was agreed to rename the indication to treatment in haematopoietic stem cell transplantation.

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

The intention to treat the condition with the medicinal product containing carmustine was considered justified based on clinical bibliographic data supporting the use in conditioning of patients prior to haematopoietic stem cell transplantation.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease.

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing carmustine will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that support the use of carmustine in combination with other products versus available combinations in the conditioning of patients who will receive autologous haematopoietic stem cell transplantation according to the current standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for carmustine, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.9. - EMA/OD/005/18

Treatment of progressive supranuclear palsy

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of progressive supranuclear palsy, the sponsor should:

- justify the choice and further elaborate on the relevance of the non-clinical animal model used in study;
- elaborate on the relevance of the animal model to the orphan condition;
- expand on the interpretation of the results obtained in study and justify the lack of results on functional endpoints.

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources and methodology selected for the calculation of the final prevalence estimate in the EU, given that this is currently based on extrapolation from reported prevalence in one EU country.

In the written response, and during an oral explanation before the Committee on 23 May 2018, the sponsor elaborated on the medical plausibility of the use of the product in the condition and provided an updated prevalence estimate after inclusion of additional sources and age-adjusting the final extrapolated estimate. The Committee considered that the updated prevalence estimate was acceptable.

With regard to the medical plausibility the sponsor further elaborated on the validity of the animal model used and argued that the results of the study on this animal model in combination with the results of the *in vitro* study was enough to support the medical plausibility. The Committee emphasised the lack of results on functional endpoints in a relevant animal model of the condition. The Committee was of the opinion that the evidence provided by the applicant were not sufficient to support the medical plausibility of the use of the product in the orphan condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 May 2018, prior to final opinion.

2.1.10. 20-hydroxyecdysone - EMA/OD/020/18

Biophytis; Treatment of Duchenne muscular dystrophy

COMP coordinator: Elizabeth Penninga

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

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit by providing data to support

a) the potential effects in disease settings without non-sense mutations

b) the claimed improvements in cardiac manifestations *in vivo*

c) the clinical relevance of the pharmacokinetic association with food, for the two compared products.

It is well known that extrapolation from non-clinical or early clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data is required to justify safety arguments in most cases.

The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile of current authorised medicinal products for the same condition.

In the written response, and during an oral explanation before the Committee on 23 May 2018, the sponsor provided non-clinical data pointing to effects outside of the non-sense dystrophin mutations. The data to support such an assumption was based on an improved skeletal function *in vivo* in non-Duchenne settings, further supported as well by myotube differentiation in exon 52 deleted dystrophin cells *in vitro*. The COMP accepted that a potentially broader target population than ataluren would constitute a clinically relevant advantage.

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

The intention to treat the condition with the medicinal product containing 20-hydroxyecdysone was considered justified based on non-clinical data, showing improved muscle force and function in a valid model of the condition.

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

The condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 20-hydroxyecdysone will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data supporting functional effects in subjects with different dystrophin genotypes. In contrast, the authorised product only targets the subset of non-sense mutated patients, and as such the product is expected to target a wider population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 20-hydroxyecdysone, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.1.11. Deferiprone - EMA/OD/006/18

Apotex Europe B.V.; Treatment of neurodegeneration with brain iron accumulation

COMP coordinator: Robert Nistico

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility the sponsor is invited to further elaborate on:

-the generalisability of the results of study, showing an effect on dystonia only in atypical PKAN (pantothenate kinase-associated neurodegeneration), to the whole PKAN and more in general to NBIA (neurodegeneration with brain iron accumulation);

- the lack of response in the co-primary endpoint of Patient Global Impression of Improvement;

- the variability in the results of the secondary endpoints in this study;

- how reduction in brain iron accumulation measured by MRI correlates with clinical outcomes of the condition.

In the written response, the sponsor discussed the results of the clinical study in relation to the different patient populations of typical and atypical PKAN, as requested by the COMP. The main argument of the sponsor to explain the different results in these two patient populations was the different level of iron-induced cell death in typical and atypical forms, with higher cell death in typical forms, usually more severe and with irreversible neuronal damage. This argument was supported by a sub-population analysis in the same study showing that (independently from having a typical or atypical form of PKAN) the therapeutic effects of deperiprone were less pronounced in patients with longer duration of disease as compared to those patients with more recent disease onset.

The sponsor also further discussed the secondary endpoints of the study, showing that even though not all of them were significant, most of them were trending towards a positive outcome. It was also clarified that the chosen secondary endpoints have different sensitivity to detect disease progression. Due to the limited available knowledge on PKAN endpoints, study also helped identifying which endpoints are the most sensitive.

After assessing the written responses, the COMP decided that an oral explanation was not needed and issued a positive opinion to deferiprone for the treatment of neurodegeneration with brain iron accumulation.

The Committee agreed that the condition, neurodegeneration with brain iron accumulation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing deferiprone was considered justified based on preliminary clinical data showing improvement of dystonia and other relevant endpoints measuring motor skills, activities of daily living, quality of sleep, and quality of life in a relevant proportion of patients.

The condition is life-threatening and chronically debilitating due to progressive reduction of neuromotor function that limits the ability to walk, reduces the vision, and significantly reduces life expectancy.

The condition was estimated to be affecting approximately 0.03 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for deferiprone, for treatment of neurodegeneration with brain iron accumulation, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. (2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one) - EMA/OD/004/18

Klinikum der Universität München; Treatment of tuberculosis

COMP coordinator: Nikolaos Sypsas

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

The intention to treat the condition with the medicinal product containing 2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one was considered justified based on non-clinical data showing reduction of the burden of infection in valid models of the condition.

The condition is chronically debilitating and life-threatening due to haemoptysis, bronchiectasis, diffuse pulmonary destruction, and the possibility of extra-pulmonary infection.

The condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the proposed product may have synergic activity with bedaquiline, currently authorised for multidrug resistant tuberculosis, and better activity than isoniazide, currently authorised for first line treatment. In addition 2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one has a novel mode of action, therefore no resistance has been identified in *in vitro* studies, even among multidrug resistant M. tuberculosis strains. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for 2-[(2S)-2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-trifluoromethyl-4H-1,3-benzothiazin-4-one, for treatment of tuberculosis, was adopted by consensus.

2.2.2. - EMA/OD/030/18

Treatment of idiopathic pulmonary fibrosis

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

2.2.3. Argon - EMA/OD/031/18

Air Liquide Santé (International); Treatment of perinatal asphyxia

COMP coordinator: Robert Nistico

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

The intention to treat the condition with the medicinal product containing argon was considered justified based on non-clinical data showing reduction of brain damage measured by histology and by neurological function.

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

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for argon, for treatment of perinatal asphyxia, was adopted by consensus.

2.2.4. Codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles - EMA/OD/022/18

Real Regulatory Limited; Treatment of ornithine transcarbamylase deficiency

COMP coordinator: Martin Možina

Following review of the application by the Committee, it was agreed to rename the active substance to codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles.

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

The intention to treat the condition with the medicinal product containing codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles was considered justified based on studies in a non-clinical model of the condition, showing expression of the impaired enzyme and protection against ammonium challenge.

The condition is life-threatening and chronically debilitating due to the metabolic decompensation that can lead to irreversible neurological damage.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a relevant model of the condition that demonstrate restoration of functional ornithine transcarbamylase in the liver of treated subjects. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for codon-optimised human ornithine transcarbamylase mRNA complexed with lipid-based nanoparticles, for treatment of ornithine transcarbamylase deficiency, was adopted by consensus.

2.2.5. - EMA/OD/036/18

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 June meeting.

2.2.6. - EMA/OD/028/18

Treatment of Duchenne muscular dystrophy

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee June meeting.

2.2.7. - EMA/OD/108/17

Treatment of abdominal aortic aneurysm

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.

2.2.8. - EMA/OD/024/18

Treatment in haematopoietic stem cell transplantation

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.

2.2.9. - EMA/OD/253/17

Treatment of pilonidal sinus disease

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

2.2.10. Omaveloxolone - EMA/OD/033/18

Dr Stefan Blesse; Treatment of Friedreich's ataxia

COMP coordinator: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing omaveloxolone was considered justified based on clinical data demonstrating delayed deterioration of neurological function.

The condition is chronically debilitating and life-threatening due to ataxia, progressive disability that requires the use of wheelchair, and cardiac involvement in the form of hypertrophic cardiomyopathy.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for omaveloxolone, for treatment of Friedreich's ataxia, was adopted by consensus.

2.2.11. Palovarotene - EMA/OD/025/18

PPD Global Ltd; Treatment of multiple osteochondromas

COMP coordinator: Lyubina Racheva Todorova

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

The intention to treat the condition with the medicinal product containing palovarotene was considered justified based on non-clinical data generated in a valid model of the condition showing that treatment was able to reduce the formation of osteochromas.

The condition is chronically debilitating due to the formation of osteochromas resulting in pain and more severe skeletal sequelae like limb-length discrepancies, varus and valgus deformities, impaired range of motion, neurovascular compression, short stature, spinal stenosis, and scoliosis. The condition is life-threatening when osteochromas transform to chondrosarcomas.

The condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for palovarotene, for treatment of multiple osteochondromas, was adopted by consensus.

2.2.12. Recombinant adeno-associated viral vector serotype 9 containing human iduronidase gene - EMA/OD/027/18

REGENXBIO EU Limited; Treatment of mucopolysaccharidosis type I

COMP coordinator: Fernando Méndez Hermida

Following review of the application by the Committee, it was agreed to rename the the active substance to recombinant adeno-associated viral vector serotype 9 containing human iduronidase gene.

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

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector serotype 9 containing human iduronidase gene was considered justified based on non-clinical *in vivo* data in a valid model of the condition showing increased alpha-L-iduronidase activity in the cerebrospinal fluid as well as reversal of central nervous system pathology.

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

The condition was estimated to be affecting approximately 0.03 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant adeno-associated viral vector serotype 9 containing human iduronidase gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate increased alpha-L-iduronidase activity in the cerebrospinal fluid as well as reversal of central nervous system pathology after intrathecal administration of the product. The Committee considered that this constitutes a clinically relevant advantage over the authorised enzyme replacement therapy which is indicated for treatment of the non-neurological manifestations of the disease.

A positive opinion for recombinant adeno-associated viral vector serotype 9 containing human iduronidase gene, for treatment of mucopolysaccharidosis type I, was adopted by consensus.

2.2.13. Recombinant human placental growth factor (rhPlGF) - EMA/OD/035/18

IQVIA RDS Ireland Limited; Treatment of pre-eclampsia

COMP coordinator: Olimpia Neagu

The Committee agreed that the condition, pre-eclampsia, 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 placental growth factor was considered justified based on a non-clinical *in vivo* model of the condition data showing a normalisation of blood pressure and renal function.

The condition is life-threatening due to seizures and risk of maternal death and chronically debilitating due to complications associated with hypertension and reduced renal function.

The condition was estimated to be affecting approximately 4.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human placental growth factor will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate an improvement in renal function which addresses a need for which no authorised treatment is available. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human placental growth factor, for treatment of pre-eclampsia, was adopted by consensus.

2.2.14. - EMA/OD/032/18

Treatment of Duchenne muscular dystrophy

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

2.2.15. - EMA/OD/026/18

Treatment of acute myeloid leukaemia

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

2.2.16. - EMA/OD/034/18

Treatment of epidermolysis bullosa

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.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

2.4.1. Interferon beta – EMA/OD/080/07

Faron Pharmaceuticals Limited; Treatment of acute respiratory distress syndrome

Proposed new indication: Treatment of acute respiratory distress syndrome

COMP coordinator: Kerstin Westermark

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

The intention to treat the amended condition with the medicinal product containing interferon beta was considered justified based on preliminary clinical data showing reduction of mortality with the proposed product in patients affected by the condition.

The condition is life-threatening due to progressive damage of the lungs, with a high fatality rate; in survivors the condition can be chronically debilitating due to sequelae such as lung fibrosis and persistent functional impairment.

The condition was estimated to be affecting approximately 3.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for interferon beta, for treatment of acute respiratory distress syndrome, was adopted by consensus.

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP coordinators

COMP coordinators were appointed for six upcoming applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of acute myeloid leukaemia

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

3.1.2. -

Treatment of pemphigus

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

3.1.3. -

Treatment of small cell lung cancer

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

3.1.4. -

Treatment of tuberous sclerosis

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

3.1.5. -

Treatment of acute myeloid leukaemia

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

3.1.6. -

Treatment of Fabry disease

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

3.1.7. -

Prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy

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

3.1.8. -

Treatment of congenital hyperinsulinism

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

3.1.9. -

Treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome)

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

3.1.10. -

Treatment of multiple myeloma

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

3.2. Finalised letters

3.2.1. -

Treatment of amyotrophic lateral sclerosis

The finalised letter was circulated for information.

3.2.2. -

Treatment of sickle cell disease

The finalised letter was circulated for information.

3.2.3. -

Treatment of soft tissue sarcoma

The finalised letter was circulated for information.

3.2.4. -

Treatment of acute sensorineural hearing loss (acute acoustic trauma, sudden deafness and surgery induced acoustic trauma)

The finalised letter was circulated for information.

3.2.5. -

Treatment of Cushing's syndrome

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of bronchiolitis obliterans syndrome

The new request was noted.

3.3.2. -

Treatment of graft-versus-host disease

The new request was noted.

3.3.3. -

Treatment of hairy cell leukaemia

The new request was noted.

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

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

None

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

4.2.1. – daunorubicin/ cytarabine - EMEA/H/C/004282, EMA/OD/070/11, EU/3/11/942

Jazz Pharmaceuticals Ireland Limited; Treatment of adults with high-risk acute myeloid leukaemia (AML)

The status of the procedure at CHMP was noted.

4.2.2. Tegsedi - inotersen – EMEA/H/C/004782, EMA/OD/098/13, EU/3/14/1250

IONIS USA Ltd; Treatment of ATTR amyloidosis

[*Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting and upon adoption of CHMP opinion.*]

4.2.3. Myalepta - metreleptin – EMEA/H/C/004218

Aegerion Pharmaceuticals Limited;

a) Treatment of familial partial lipodystrophy EMA/OD/033/12, EU/3/12/1022

b) Treatment of Barraquer-Simons syndrome EMA/OD/034/12, EU/3/12/1023

c) Treatment of Lawrence syndrome EMA/OD/035/12, EU/3/12/1024

d) Treatment of Berardinelli-Seip syndrome EMA/OD/036/12, EU/3/12/1025

[*Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting and upon adoption of CHMP opinion.*]

4.2.4. - vonicog alfa – EMA/OD/055/10, EU/3/10/814, EMEA/H/C/004454

Baxalta Innovations GmbH; Treatment of von Willebrand disease

The status of the procedure at CHMP was noted. A question addressed to the applicant has been adopted.

4.2.5. - patisiran – EMEA/H/C/004699, EMA/OD/142/10, EU/3/11/857

Alnylam UK Limited; Treatment of familial amyloid polyneuropathy

The status of the procedure at CHMP was noted.

4.2.6. - tisagenlecleucel – EMEA/H/C/004090

Novartis Europharm Limited;

a) Treatment of diffuse large B-cell lymphoma EMA/OD/087/16, EU/3/16/1745

b) Treatment of B-lymphoblastic leukaemia/lymphoma EMA/OD/187/13, EU/3/14/1266

The status of the procedure at CHMP and CAT was noted. A question addressed to the applicant has been adopted.

4.3. Revision of COMP opinions

4.3.1. Verkazia - ciclosporin – EMEA/H/C/004411, EMEA/OD/106/05, EU/3/06/360

Santen Oy; Treatment of vernal keratoconjunctivitis

Following a second request for clarification from the European Commission (EC) dated 11 April 2018 concerning the revised COMP opinion of 18 January 2018, the COMP adopted a revised final opinion on 31 May 2018.

The COMP re-discussed the assessment in light of the EC's request. The EC provided additional guidance relating to the evidence needed to support magistral and officinal formulas as satisfactory methods of treatment. The COMP, in giving regard to this information from the EC, reflected on its previous opinion regarding ciclosporin formulations and concluded that within this particular context, there was insufficient evidence to support the view that ciclosporin magistral and officinal formulas are satisfactory methods.

The COMP concluded that:

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

The prevalence of vernal keratoconjunctivitis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 3.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating, in particular due to potential visual loss and steroid-induced eye complications.

Magistral/officinal formulations of ciclosporin eye drops could not be regarded as a satisfactory method of treatment and would not have to be considered for the assessment for significant benefit.

The significant benefit of Verkazia over authorised anti-histamines and corticosteroids products was considered justified due to the steroid sparing effect of Verkazia over corticosteroids and the fact that Verkazia can be used on top of anti-histamines, this was considered as a clinically relevant advantage.

An opinion recommending not to remove Verkazia, ciclosporin (EU/3/06/360) for treatment of vernal keratoconjunctivitis from the EC Register of Orphan Medicinal Products was adopted by consensus.

4.4. Appeal

None

4.5. On-going procedures

Action: For information

Document(s) tabled:
Review of orphan designation for OMP for MA - On-going procedures

4.6. Orphan Maintenance Reports

Documents were circulated in MMD.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Adcetris - Brentuximab vedotin – Type II variation – EMEA/H/C/002455/II/0055

Takeda Pharma A/S; Treatment of Hodgkin lymphoma EMEA/OD/073/08, EU/3/08/596

CHMP rapporteur: Paula Boudewina van Hennik; CHMP co-rapporteur: Jan Mueller-Berghaus;

The status of the procedure at CHMP was noted. A question addressed to the applicant has been adopted.

5.2.2. Coagadex - Human coagulation factor X – Type II variation – EMEA/H/C/003855/II/0007, EMEA/OD/044/07, EU/3/07/471

Bio Products Laboratory Limited; Treatment of hereditary factor X deficiency

CHMP rapporteur: Andrea Laslop

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

None

6. Application of Article 8(2) of the Orphan Regulation

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP Strategic Review & Learning meeting, 26-28 March 2018, Amsterdam, The Netherlands

COMP Strategic Review and Learning Meeting Minutes were adopted.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 22 May 2018.

7.1.3. Prevalence Working Group

The working group on Prevalence met on 23 May 2018

7.1.4. Recommendation on criteria for competence and expertise of COMP members / Invitation to propose expert(s) to join the Committee for Orphan Medicinal Products

Action: For information

Recommendation was noted.

7.1.5. Conditions Working Group

The working group on Condition met on 24 May 2018.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes April 2018

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

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

None

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

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

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 5

Action: For discussion

Document tabled:
EC Guideline_REV 5

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. The Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2018

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2018 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

None

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 22-24 May 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Melinda Sobor	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Robert Nistico	Member	Malta	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Mario Ricciardi	Member	Patients' Organisation Representative	No interests declared	
Kerstin Westermark	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*		No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Meeting run with support from relevant EMA staff				

*Experts were only evaluated against the product(s) they have been invited to talk about.

9. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from

the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/