27 February 2017
EMA/COMP/33182/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 17-19 January 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

17 January 2017, 09:00-19:30, room 2F

18 January 2017, 08:30-19:30, room 2F

19 January 2017, 08:30-15:30, room 2F

Disclaimers

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

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

Further information with relevant explanatory notes can be found at the end of this document.

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

COMP agenda for 17-19 January 2017 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 06-08 December 2016 were adopted with amendments and will be published on the EMA website.

[*Post-meeting note: The COMP adopted the minutes by written procedure following its January meeting.*]

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. Fenfluramine hydrochloride - EMA/OD/233/16

Zogenix International Limited; Treatment of Lennox-Gastaut syndrome

COMP coordinator: Giuseppe Capovilla/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:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Lennox-Gastaut syndrome, the sponsor should further

elaborate on the studied population and elaborate on the expected effects of the concomitant pharmacological and non-pharmacological treatments in that population.

- Significant benefit

The applicant argues a clinically relevant advantage on the basis of add-on effects to existing pharmacological therapies.

With regards to the preliminary clinical observations, the sponsor should discuss a) the relevance of the duration of treatment to attribute effects to the proposed product b) the effects and interactions with concomitant treatments and c) the duration of the follow-up in the studied population.

In the written response, the sponsor provided additional clinical data with extended observation periods. Overall, the preliminary clinical data support medical plausibility based on a relevant reduction in seizure rate.

Regarding significant benefit based on add-on efficacy, the sponsor clarified that responses were achieved with increasing doses of the proposed product and stable dosing with concomitant therapies. Furthermore, there is no expectation for drug-interactions. Finally, the length of the observation period compensates for any “honeymoon period” effects.

Based on this supplementary data and justifications, the COMP concluded that there is sufficient evidence to support the assumptions of medical plausibility and significant benefit as add-on therapy. The COMP cancelled the oral explanation and proceeded with the adoption of a positive opinion.

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

The intention to treat the condition with the medicinal product containing fenfluramine hydrochloride was considered justified based on preliminary clinical observations in treated patients who responded with reduced number of epileptic seizures.

The condition is chronically debilitating due to epileptic seizures, psychomotor delay and behavioural symptoms such as hyperactivity, aggressiveness and autistic tendencies.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fenfluramine hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in patients resistant to previous treatments, who responded with reduced numbers of seizures after addition of fenfluramine to their therapeutic regimen. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fenfluramine hydrochloride, for treatment of Lennox-Gastaut syndrome, was adopted by consensus.

2.1.2. 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine - EMA/OD/229/16

Voisin Consulting S.A.R.L.; Treatment of diffuse large B cell lymphoma

COMP coordinator: Jens Ersbøll

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 are based on the novel mechanism of action and the potential improved efficacy in the condition. The sponsor is requested to provide a data-driven discussion of the arguments for significant benefit. Furthermore, it would be useful to obtain more information on the ongoing study and planned development. Without further evidence, significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 17 January 2017, the sponsor presented additional preliminary clinical data from currently ongoing clinical trials. The proposed product was studied in relapsed and refractory patients affected by the condition, who have received the best standard of care including authorised products. The enrolled patients responded to the treatment with the proposed product. The Committee considered that this supports the assumption of significant benefit for the purpose of orphan designation.

The Committee agreed that the condition, diffuse large B-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine was considered justified based on preclinical data in relevant models and preliminary clinical data in patients affected by the condition demonstrating anti-tumour activity.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow, and life-threatening with 5-year survival rates reported as low as approximately one in four patients for the high risk group.

The condition was estimated to be affecting approximately 4.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that relapsed/refractory patients responded to treatment after receiving the best standard of care including authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.1.3. N-(4-(1-cyanocyclopentyl) phenyl)-2-(4-pyridinylmethyl) amino-3-pyridinecarboxamide methanesulfonate - EMA/OD/228/16

Sirius Regulatory Consulting Limited; Treatment of gastric cancer

COMP coordinator: Frauke Naumann-Winter

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 treat

For the purpose of the orphan drug designation, the scope of the gastric cancer orphan indication is including epithelial cancers of the stomach (including gastroesophageal junction tumours). Non-epithelial tumours of the stomach, including mucosa-associated lymphoid tissue lymphoma, other lymphomas of the stomach and gastrointestinal stromal tumours are not included.

- Significant benefit

The sponsor did not discuss the expected benefit of the proposed product over available treatment regimens. In particular, a discussion of significant benefit over ramucirumab, which is authorised in Europe in second line treatment of gastric cancer and shares the same mechanism of action as apatinib, would be expected.

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

In the written response, the sponsor agreed to the suggested definition of gastric cancer for the purpose of the orphan drug designation. This includes epithelial cancers together with gastroesophageal junction tumours.

With regards to the significant benefit, the sponsor provided additional arguments to argue that the product would bring major contribution to patient care over ramucirumab. This is assumed based on the fact that ramucirumab is administered intravenously and the proposed product is an oral formulation. The sponsor discussed the advantages of oral formulation and highlighted the limitations of an IV formulation. The committee accepted these arguments for an assumption of significant benefit at the time of orphan drug designation.

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

The intention to treat the condition with the medicinal product containing N-(4-(1-cyanocyclopentyl)phenyl)-2-(4-pyridinylmethyl)amino-3-pyridinecarboxamide methanesulfonate was considered justified based on clinical data demonstrating improved overall survival of patients with metastatic gastric carcinoma when used in third line treatment.

The condition is life-threatening with a poor overall survival.

The condition was estimated to be affecting approximately 3.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-(4-(1-cyanocyclopentyl)phenyl)-2-(4-pyridinylmethyl)amino-3-pyridinecarboxamide methanesulfonate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with metastatic gastric cancer who have progressed after at least two prior lines of chemotherapy achieved improved progression-free survival and overall survival. In addition, the product is administered orally and thus offers a potential major

contribution to patient care over intravenous products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-(4-(1-cyanocyclopentyl)phenyl)-2-(4-pyridinylmethyl)amino-3-pyridinecarboxamide methanesulfonate, for treatment of gastric cancer, was adopted by consensus.

2.1.4. - EMA/OD/232/16

Treatment of glycogen storage disease type II (Pompe's disease)

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 glycogen storage disease type II (Pompe's disease), the sponsor should further elaborate on the results obtained in the preclinical vivo model. In this context, the sponsor is asked to further discuss and justify the absence of functional outcome data.

- Number of people affected

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

The current proposal is based on unpublished data. The sponsor should provide some more information on how this prevalence has been established and the epidemiological index of this figure. In addition, the sponsor is asked to present a full point prevalence of patients affected by the condition at the time of designation.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit in the absence of functional outcome data from the presented preclinical studies. Furthermore, it would be useful to obtain more information on the planned development.

In the written response, and during an oral explanation before the Committee on 17 January 2017, the sponsor provided arguments to support medical plausibility, prevalence and significant benefit. Regarding medical plausibility, the sponsor argued that the presented data was relevant. The COMP concluded that there was insufficient evidence to support medical plausibility.

Regarding the prevalence, the sponsor resubmitted an updated prevalence calculation that was accepted by the COMP.

Regarding significant benefit, the sponsor claimed that the presented preclinical data would support significant benefit as add-on therapy to currently authorised products. The COMP was of the opinion that in line with the discussion on medical plausibility, further data was necessary to support the assumption of significant benefit for orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 January 2017, prior to final opinion.

2.1.5. - EMA/OD/245/16

Treatment of ovarian cancer

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 15 December 2016, prior to responding to the list of issues.

2.1.6. - EMA/OD/211/16

Treatment of glioma

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 December 2016, prior to responding to the list of issues.

2.1.7. - EMA/OD/249/16

Treatment of glioma

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 December 2016, prior to responding to the list of issues.

2.1.8. - EMA/OD/251/16

Treatment of sickle cell disease

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

- Intention to diagnose, prevent or treat

The presented evidence is considered insufficient to demonstrate medical plausibility. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of sickle cell disease, the sponsor should provide additional data of relevance. In this context, the sponsor should elaborate on the existence of valid preclinical models that could be used to test the product on relevant outcomes including survival.

- Number of people affected

The sponsor should update the prevalence estimate taking into consideration the data from Modell and Darlison, 2007 (Global epidemiology of haemoglobin disorders and derived service indicators, Bulletin of the World Health Organization).

- Significant benefit

Significant benefit cannot be considered unless medical plausibility has been established. Therefore, the sponsor is invited to provide further evidence as outlined above. For the purpose of significant benefit as proposed by the sponsor, specifically further data should be presented to demonstrate significant benefit.

In the written response, and during an oral explanation before the Committee on 18 January 2017, the sponsor presented argumentation as to why the currently available preclinical models of the condition should not be considered useful to study the proposed

product. The COMP acknowledged the argumentation, but was of the opinion that valid models exist and concluded that without additional data with the proposed product medical plausibility could not be assessed.

Regarding the prevalence calculation, the COMP noted that the sponsor has not adequately revised the prevalence calculation to take into consideration the published literature that was proposed by the COMP.

Regarding the significant benefit, the COMP did not agree with the sponsor that the presented evidence could support the positioning of the proposed product into the current clinical treatment paradigm and demonstrate significant benefit in the context of currently authorised products.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2017, prior to final opinion.

2.1.9. Alpha tocopherol and ascorbic acid - EMA/OD/080/15

Advanced Medical Projects; Treatment of fragile X syndrome

COMP coordinator: Vallo Tillmann

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of fragile X syndrome, the sponsor should further elaborate on the results obtained in the clinical studies and provide:

- the full study reports/investigators brochure;
- some further background information on the outcomes, the study methodology and data collection.

In the written response, the sponsor further described the outcomes related to quality of life, behaviour and development in patients affected by the condition. The committee considered these explanations satisfactory to support the assumption of medical plausibility for orphan designation and cancelled the oral hearing.

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

The intention to treat the condition with the medicinal product containing alpha-tocopherol and ascorbic acid was considered justified based on preliminary clinical data showing that treatment led to improvements of patients in clinical rating scales regarding behaviour and development.

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

The condition was estimated to be affecting approximately 2.5 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 alpha-tocopherol and ascorbic acid, for treatment of fragile X syndrome, was adopted by consensus.

2.1.10. Cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl] acetate salt - EMA/OD/244/16

Polyphor UK Ltd; Treatment of primary ciliary dyskinesia

COMP coordinator: Violeta Stoyanova/Armando Magrelli

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

- 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 primary ciliary dyskinesia, the sponsor should further elaborate on:

  - the relevance of the preclinical models used for the treatment of primary ciliary dyskinesia, and the interpretation of the results obtained in the experiments;
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition. From the data provided and the sponsor's arguments it is not well substantiated that the condition can be defined as being life-threatening or chronically debilitating.

In the written response, and during an oral explanation before the Committee on 18 January 2017, the sponsor presented preclinical data, affirming the acceptability of the preclinical models to primary ciliary dyskinesia. In conclusion, the committee considered that in the absence of suitable genetic models of the condition, the presented data was sufficient to support the assumption of medical plausibility for orphan designation.

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

The intention to treat the condition with the medicinal product containing cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl]acetate salt was considered justified based on preclinical data in models of lung inflammation demonstrating that the use of the product leads to a reduction of neutrophil elastase and reduced lung inflammation.

The condition is chronically debilitating due to infertility in men, hearing loss or congenital heart disease and recurrent and chronic infections of the upper and lower respiratory tracts leading to impaired lung function.

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

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

A positive opinion for cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl]acetate salt, for treatment of primary ciliary dyskinesia, was adopted by consensus.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its January meeting.*]

2.1.11. - EMA/OD/239/16

Treatment of pancreatic cancer

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 pancreatic cancer, the sponsor should further elaborate on:

- the proposed mechanism of action of the product and scientific evidence to support this mechanism of action;
- the results obtained in the preclinical studies.

- Significant benefit

The arguments on significant benefit are solely based on the new mechanism of action. The sponsor is invited to present further data and arguments for significant benefit. Without additional data, significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 18 January 2017, the sponsor presented further details on the mechanism of action of the proposed product. Furthermore, the sponsor presented a hypothesis that the product could be used in combination with currently authorised products, which would support significant benefit. The COMP acknowledged this discussion, but concluded that there was insufficient evidence to establish significant benefit in relation to authorised products at the time of application.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 January 2017, prior to final opinion.

2.1.12. - EMA/OD/224/16

Treatment of cystic fibrosis

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 establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of cystic fibrosis, the sponsor should further elaborate on the presented preclinical data and the clinical relevance of the outcomes.

- Significant benefit

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

In the written response, and during an oral explanation before the Committee on 18 January 2017, the sponsor discussed more in details the preclinical experiments supporting the medical plausibility and the significant benefit. The COMP acknowledged the discussion, nevertheless it was concluded that additional data in other preclinical models would be needed to support medical plausibility and significant benefit in relation authorised products.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2017, prior to final opinion.

2.1.13. - EMA/OD/216/16

Treatment of ovarian cancer

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 29 December 2016, prior to responding to the list of issues.

2.1.14. - EMA/OD/246/16

Treatment of non-infectious uveitis

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 the treatment of non-infectious uveitis, the sponsor should further elaborate on the results of the preclinical studies.

- Significant benefit

The sponsor is invited to present any available data supporting the clinical benefit of the proposed product versus all products authorised for the condition.

In addition, the sponsor is invited to further clarify the basis of the claimed major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 18 January 2017, the sponsor further elaborated on the data available to support the medical plausibility and the significant benefit of the proposed product. Overall, the COMP acknowledged that the data may support the medical plausibility at the present stage of development.

Regarding the significant benefit, the COMP questioned the sponsor over potential advantages of the proposed product vs. authorised products. The COMP was of the opinion

that there were not sufficient grounds to support the significant benefit of the proposed product.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 January 2017, prior to final opinion.

2.1.15. 26 base synthetic single-stranded fully phosphorothioated 2'-O-methyl-RNA and DNA mixmer oligonucleotide-based compound - EMA/OD/221/16

Eirgen Pharma Limited; Treatment of Dravet syndrome

COMP coordinator: Giuseppe Capovilla

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

- Significant benefit

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

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

In the written response, the sponsor discussed that the product may address manifestations of the disease that are not amenable by the currently used antiepileptic drugs. This argument was supported by additional data with similar surrogate products, showing a trend in improvement of ataxia as well as anxiety behaviour. The COMP considered that the issues raised were thus resolved and cancelled the oral explanation.

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to 26 base synthetic single-stranded fully phosphorothioated 2'-O-methyl-RNA and DNA mixmer oligonucleotide-based compound.

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

The intention to treat the condition with the medicinal product containing 26 base synthetic single-stranded fully phosphorothioated 2'-O-methyl-RNA and DNA mixmer oligonucleotide-based compound was considered justified based on preclinical data supporting a reduction of seizures in treated subjects affected by the condition.

The condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of convulsive seizures and life-threatening in particular due to generalised tonic-clonic seizures.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 26 base synthetic single-stranded fully phosphorothioated 2'-O-methyl-RNA and DNA mixmer oligonucleotide-based compound will be of significant benefit to those affected by the condition. The sponsor has provided

preclinical data supporting improvements in ataxia, anxiety and cognition, therefore addressing manifestations beyond control of epileptic seizures. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 26 base synthetic single-stranded fully phosphorothioated 2'-O-methyl-RNA and DNA mixmer oligonucleotide-based compound, for treatment of Dravet syndrome, was adopted by consensus.

2.1.16. - EMA/OD/252/16

Treatment of acetaminophen (paracetamol) overdose

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 the view of COMP, paracetamol overdose is an adverse effect of an authorised medicinal product, not an orphan condition, and subsequently not acceptable for an orphan designation. The sponsor's attention is drawn to the fact that adverse effects and effects of overdose of paracetamol are described in warning sections 4.4 and 4.9 of the Summary of Product Characteristics (SmPC). It is irrelevant, whether the drug is misused intentionally or as a result of an accident.

The sponsor is requested to justify paracetamol overdose as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). In addition, the sponsor is requested to clearly specify diagnostic measures of paracetamol overdose.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from preclinical studies to justify the assumption of significant benefit over authorised medicinal product for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 19 January 2017, the sponsor presented further arguments to delineate paracetamol overdose as a distinct medical entity. The sponsor used an ICD10 code T39.1 and discussed past decisions by the COMP with similar wording, e.g. mercury of lead poisoning. The committee explained that ICD-10 codes serve solely as supportive evidence. Additionally, the committee outlined that mercury and lead are environmental pollutants and thus poisoning by these substances is very different to that caused by an authorised medicinal product. The committee concluded that the proposed population lies on a spectrum of paracetamol side effects defined in the summary of product's characteristics. As such the population was not defined though distinct pathophysiology, histopathology and clinical characteristics and was deemed unacceptable for an orphan drug designation.

In the view of this outcome, the significant benefit was not discussed in detail.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 January 2017, prior to final opinion

2.1.17. Recombinant human club cell 10 KDa protein - EMA/OD/247/16

EUDRAC Limited; Treatment of bronchiolitis obliterans syndrome

COMP coordinator: Armando Magrelli

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

- Intention to diagnose, prevent or treat

In the view of COMP, bronchiolitis obliterans syndrome (BOS) includes both BOS post lung transplantation and BOS post haematopoietic stem cell transplantation. It should be noted that this is for the purpose of orphan medicinal product designation. The sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

The sponsor is invited to recalculate the prevalence estimate in line with the amended inclusion criteria for bronchiolitis obliterans syndrome.

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

In the written response, the sponsor agreed to the inclusion of bronchiolitis obliterans syndrome post hematopoietic stem cell transplantation patients in the definition of the condition. This resulted in a small increase of overall bronchiolitis obliterans syndrome prevalence. The committee found the new prevalence of 0.9 in 10,000 acceptable and adopted a positive opinion with the prevalence "less than 1".

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

The intention to treat the condition with the medicinal product containing recombinant human club cell 10 KDa protein was considered justified based on pre-clinical data demonstrating reduced bronchiolar obstruction, reduced inflammatory cells counts and improved survival.

The condition is chronically debilitating due to bronchiolar obstruction and fibrosis of bronchioles and life threatening due to progressive nature of the condition leading to death due to pulmonary insufficiency.

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

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

A positive opinion for recombinant human club cell 10 KDa protein, for treatment of bronchiolitis obliterans syndrome, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor - EMA/OD/156/16

Vertex Pharmaceuticals (Europe) Limited; Treatment of cystic fibrosis

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor was considered justified based on preclinical data showing increased chloride transport across membranes of lung epithelial cells harbouring cystic fibrosis relevant mutations, and on preliminary clinical data showing improvement of lung function in patients affected by the condition.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improvement of lung function in patients heterozygous for the F508del and G5551D mutations with the proposed product. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor, for treatment of cystic fibrosis, was adopted by consensus.

2.2.2. - EMA/OD/285/16

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 February meeting.

2.2.3. 505 amino acid protein, corresponding to amino acids 2-506 of the wild type human histidyl-tRNA synthetase - EMA/OD/279/16

Voisin Consulting S.A.R.L.; Treatment of Limb-Girdle muscular dystrophy

COMP coordinator: Armando Magrelli

Following review of the application by the Committee, it was agreed to broaden/rename the indication from treatment of Limb-Girdle muscular dystrophy type 2B, to treatment of Limb-Girdle muscular dystrophy.

The Committee agreed that the condition, Limb-Girdle 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 505 amino acid protein, corresponding to amino acids 2-506 of the wild-type human histidyl-tRNA synthetase was considered justified based on early clinical data demonstrating improvement in muscle function in patients affected by Limb-Girdle muscular dystrophy type 2B.

The condition is chronically debilitating due to muscle wasting, consequent reduced mobility and debilitating fatigue.

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.

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 505 amino acid protein, corresponding to amino acids 2-506 of the wild-type human histidyl-tRNA synthetase, for treatment of Limb-Girdle muscular dystrophy, was adopted by consensus.

2.2.4. - EMA/OD/276/16

Treatment of Niemann-Pick disease type C

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. - EMA/OD/280/16

Treatment of retinitis pigmentosa

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.

2.2.6. - EMA/OD/227/16

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 February meeting.

2.2.7. Autologous T-cells transduced with lentiviral vector encoding an anti-SLAMF7 CD28/CD3-zeta chimeric antigen receptor - EMA/OD/274/16

Dr. Michael Hudecek; Treatment of plasma cell myeloma

COMP coordinator: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing autologous T-cells transduced with lentiviral vector encoding an anti-SLAMF7 CD28/CD3-zeta chimeric antigen receptor was considered justified based on in vivo models showing reduction of myeloma cells from peripheral blood, spleen and bone marrow, as well as improved survival compared to untreated subjects.

The condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a median survival of approximately 6 years.

The condition was estimated to be affecting less than 4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T-cells transduced with lentiviral vector encoding an anti-SLAMF7 CD28/CD3-zeta chimeric antigen receptor will be of significant benefit to those affected by the condition. The sponsor has provided data in in vivo models showing elimination of myeloma cells in peripheral blood, spleen and bone marrow, as well as improved survival compared to untreated subjects. This compares favourably to the effects of other authorised products in similar models, as discussed in literature. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T-cells transduced with lentiviral vector encoding an anti-SLAMF7 CD28/CD3-zeta chimeric antigen receptor, for treatment of plasma cell myeloma, was adopted by consensus.

2.2.8. - EMA/OD/275/16

Treatment of Lennox-Gastaut syndrome

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

2.2.9. - EMA/OD/284/16

Treatment of amyotrophic lateral sclerosis

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.

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its January meeting.*]

2.2.10. - EMA/OD/278/16

Treatment of short bowel syndrome

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

2.2.11. Ex-vivo-expanded autologous keratinocytes transduced with retroviral vector containing the COL7A1 gene - EMA/OD/283/16

Ser-mes Planificación SL; Treatment of epidermolysis bullosa

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing ex-vivo-expanded autologous keratinocytes transduced with retroviral vector containing the COL7A1 gene was considered justified based on clinical data demonstrating successful graft transplantation, improved would healing and the establishment of normal dermal-epidermal junctions in patients with recessive dystrophic epidermolysis bullosa.

The condition is life-threatening and chronically debilitating due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

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 ex-vivo-expanded autologous keratinocytes transduced with retroviral vector containing the *COL7A1* gene, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.12. Humanised IgG4 monoclonal antibody to the human toll-like receptor type 2 - EMA/OD/273/16

Opsona Therapeutics Ltd; Treatment of pancreatic cancer

COMP coordinator: Ingrid Wang

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

The intention to treat the condition with the medicinal product containing humanised IgG4 monoclonal antibody to the human toll-like receptor type 2 was considered justified based on preclinical in vivo data in a valid model of the condition demonstrating that treatment was able to reduce tumour growth.

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

The condition was estimated to be affecting less than 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG4 monoclonal antibody to

the human toll-like receptor type 2 will be of significant benefit to those affected by the condition/to the population at risk of developing the condition. The sponsor has provided preclinical data that demonstrate that the proposed product has an additive anti-tumour effect when given in combination with gemcitabine and nab-paclitaxel, which are currently authorised for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG4 monoclonal antibody to the human toll-like receptor type 2, for treatment of pancreatic cancer, was adopted by consensus.

2.2.13. Humanised IgG4 monoclonal antibody to the human toll-like receptor type 2 - EMA/OD/272/16

Opsona Therapeutics Ltd; Treatment of myelodysplastic syndromes

COMP coordinator: Karri Penttila

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

The intention to treat the condition with the medicinal product containing humanised IgG4 monoclonal antibody to the human toll-like receptor type 2 was considered justified based on preliminary clinical data from patients affected by the condition demonstrating that treatment was able to improve cytopenia.

The condition is life-threatening and chronically debilitating due to the development of anaemia, thrombocytopenia, neutropenia and progression to acute myelogenous leukaemia.

The condition was estimated to be affecting less than 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG_4 monoclonal antibody to the human toll-like receptor type 2 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product improved cytopenia in patients with lower-risk (low and intermediate-1) myelodysplastic syndromes patients, who have failed or are not candidates for erythroid-stimulating agents and/or azacitidine or decitabine, and who are not candidates for lenalidomide. There are currently no authorised treatment options for these patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG_4 monoclonal antibody to the human toll-like receptor type 2, for treatment of myelodysplastic syndromes, was adopted by consensus.

2.2.14. - EMA/OD/267/16

Treatment of Neuromyelitis Optica Spectrum Disorders (NMOSD)

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.

2.2.15. Iodine (131I) murine IgG1 monoclonal antibody against CD276 - EMA/OD/271/16

Y-mAbs Therapeutics A/S; Treatment of neuroblastoma

COMP coordinator: Bożenna Dembowska-Bagińska

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

The intention to treat the condition with the medicinal product containing Iodine (131I) murine IgG1 monoclonal antibody against CD276 was considered justified based on clinical data in paediatric patients with refractory and metastatic neuroblastoma where it was shown that there was an improvement in survival.

The condition is life-threatening due to an overall survival of 1year following diagnosis and chronically debilitating due to growth reduction, thyroid function disorders, learning difficulties, and greater risk of secondary cancers in survivors of high-risk disease.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Iodine (^{131}I) murine IgG1 monoclonal antibody against CD276 will be of significant benefit to those affected by the condition/to the population at risk of developing the condition. The sponsor has provided clinical data that demonstrate improved survival in patients with refractory and metastatic forms of the condition for which there are no authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Iodine (^{131}I) murine IgG1 monoclonal antibody against CD276, for treatment of neuroblastoma, was adopted by consensus.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its January meeting.*]

2.2.16. - EMA/OD/234/16

Treatment of granulosa cell tumors

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 at the February meeting.

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its January meeting.*]

2.2.17. - EMA/OD/236/16

Treatment of granulosa cell tumors

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 at the February meeting.

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its January meeting.*]

2.2.18. - EMA/OD/288/16

Treatment of short bowel syndrome

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

2.2.19. - EMA/OD/289/16

Treatment of cystic fibrosis

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

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its January meeting.*]

2.2.20. - EMA/OD/255/16

Treatment of pancreatic cancer

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

2.2.21. - EMA/OD/217/16

Treatment of cystic fibrosis

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

2.2.22. - EMA/OD/219/16

Treatment of invasive aspergillosis

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.

2.2.23. Propranolol hydrochloride - EMA/OD/256/16

Consejo Superior de Investigaciones Cientificas (CSIC); Treatment of Von Hippel Lindau Disease

COMP coordinator: Pauline Evers

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

The intention to treat the condition with the medicinal product containing propranolol hydrochloride was considered justified based on preliminary clinical data showing a stabilisation of retino-haemangioblastomas in patients with the condition and who were refractory to laser therapy.

The condition is life-threatening due to the high incidence of patients with clear cell renal cell carcinoma which leads to reduced life expectancy. It is chronically debilitating due to

associated conditions including angiomatosis, retinal and central nervous system haemangioblastomas, pheochromocytoma, renal cell carcinoma, pancreatic cysts, endolymphatic sac tumour, and bilateral papillary cystadenomas of the epididymis or broad ligament of the uterus.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made; thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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

A positive opinion for propranolol hydrochloride, for treatment of von Hippel-Lindau disease, was adopted by consensus.

2.2.24. - EMA/OD/262/16

Treatment of pancreatic cancer

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

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its January meeting.*]

2.2.25. Recombinant human fibroblast growth factor receptor 3 - EMA/OD/269/16

TherAchon SAS; Treatment of achondroplasia

COMP coordinator: Irena Bradinova/Aušra Matulevičienė

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to soluble recombinant human fibroblast growth factor receptor 3.

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

The intention to treat the condition with the medicinal product containing soluble recombinant human fibroblast growth factor receptor was considered justified based on improvement in survival and bone growth in an in vivo model of the condition.

The condition is chronically debilitating due to manifestations such as otolaryngeal system dysfunction, and rhizomelic short stature, thoracolumbar kyphosis, spinal stenosis, and foramen magnum stenosis and life-threatening with approximately 10 years shorter life expectancy compared to the general population.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

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 soluble recombinant human fibroblast growth factor receptor 3, for treatment of achondroplasia, was adopted by consensus.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its January meeting.*]

2.2.26. - EMA/OD/261/16

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 February meeting.

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its January meeting.*]

2.2.27. - EMA/OD/266/16

Treatment of pancreatic cancer

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

2.2.28. Tauroursodeoxycholic acid - EMA/OD/242/16

Bruschettini s.r.l.; Treatment of amyotrophic lateral sclerosis

COMP coordinator: Violeta Stoyanova

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

The intention to treat the condition with the medicinal product containing tauroursodeoxycholic acid was considered justified based on preliminary clinical observations supporting a slower deterioration of function when the proposed product was added to riluzole treatment.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tauroursodeoxycholic acid will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients receiving currently authorised product riluzole, who exhibited slower deterioration of function when the proposed product was added on to their treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tauroursodeoxycholic acid, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its January meeting.*]

2.2.29. Thalidomide - EMA/OD/268/16

PlumeStars s.r.l.; Treatment of hereditary haemorrhagic telangiectasia

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing thalidomide was considered justified based on preliminary clinical data showing reduction of frequency, intensity and duration of nasal epistaxis and improvement of haemoglobin levels in patients affected by the condition.

The condition is life-threatening and chronically debilitating due to arteriovenous malformations in different organs, leading to recurrent bleeding from the nasal mucosa with development of severe anaemia, and to potentially fatal bleeding in the stomach, gut, brain, liver and lungs.

The condition was estimated to be affecting not more than 2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for thalidomide, for treatment of hereditary haemorrhagic telangiectasia, was adopted by consensus.

2.2.30. Vemurafenib - EMA/OD/281/16

Groupe d'étude des histiocytoses; Treatment of Erdheim chester disease

COMP coordinator: Katerina Kopečková

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

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

The condition is life-threatening with 5-year survival of less than 30% in the absence of treatment, and chronically debilitating due to pericardial heart lesions leading to myocardial infarction, diabetes insipidus, urological and nephrological infiltrations, and neurological involvement leading to severe functional disability, seizures, headaches, neuropsychiatric signs or cognitive impairment, sensory disturbances, and cranial nerve paralysis.

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

A positive opinion for vemurafenib, for treatment of Erdheim-Chester disease, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

2.4.1. Synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA– EMA/OD/142/10, EU/3/11/857

Alnylam UK Limited - United Kingdom; Treatment of familial amyloid polyneuropathy; proposed new indication: Treatment of transthyretin-mediated amyloidosis (ATTR amyloidosis)

COMP coordinator: Kerstin Westermark

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

- Intention to diagnose, prevent or treat

It appears that the sponsor already has a designation for the treatment of ATTR amyloidosis for "synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues" from 2014.

In order to justify the medical plausibility of the proposed product, the sponsor is invited to discuss the similarity of the proposed product *vis a vis* the siRNA oligonucleotide designated in 2014.

In the written response, the sponsor informed the COMP that the development of the product designated in 2014 under the name "synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues" (designation EU/3/14/1267) was stopped. Consequently, the sponsor sent a withdrawal request to the European Commission for EU/3/14/1267. In view of the withdrawal of the EU/3/14/1267, the COMP decided that an oral explanation was not needed and granted a positive opinion to the amendment.

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

The intention to treat the amended condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA was considered justified based on preliminary clinical data showing sustained reduction of transthyretin serum levels over 24 months of treatment and stabilisation of parameters of neurologic and cardiac damage.

The condition is life-threatening and chronically debilitating due to the development of neuropathy and cardiomyopathy. Life expectancy is 3 to 15 years from symptom onset, depending on the transthyretin mutation.

The condition was estimated to be affecting less than 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the

assumption that the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing an effect of the proposed product on the cardiac manifestations of the condition, which are not targeted by the currently authorized treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA, for treatment of transthyretin-mediated amyloidosis, 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 16 applications submitted.

2.7. Evaluation on-going

Thirty three applications for orphan designation will not be discussed as evaluation is on-going.

Action: For information

Notes:
See 7.8.1. Table 6. Evaluation on-going.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of paroxysmal nocturnal haemoglobinuria

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

[*Post-meeting note: The COMP adopted the proposed answers by written procedure following its January meeting.*]

3.1.2. -

Treatment of autosomal dominant polycystic kidney disease

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

[*Post-meeting note: The COMP adopted the proposed answers by written procedure following its January meeting.*]

3.2. Finalised letters

None

3.3. New requests

3.3.1. -

Treatment of Gaucher disease

The new request was noted.

3.3.2. -

Treatment of amyotrophic lateral sclerosis

The new request was noted**.**

3.3.3. -

Treatment of narcolepsy

The new request was noted.

3.3.4. -

Treatment of Langerhans cell histiocytosis

The new request was noted.

3.3.5. -

Treatment of glioma

The new request was noted.

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

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

4.1.1. Ledaga - chlormethine – EMA/OD/112/11, EU/3/12/963, EMEA/H/C/002826

Actelion Registration Ltd.; Treatment of cutaneous T-cell lymphoma

COMP coordinator: Jens Ersbøll / Daniel O'Connor

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

- Prevalence

The sponsor is asked to describe and justify the methodology used for the prevalence calculation with respect to:

- the appropriateness of the epidemiological index used, based on the characteristics of the disease;
- the inclusion/choice of the sources selected for the estimation of the prevalence of the condition.

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

- Significant benefit:

The sponsor has not provided sufficient evidence for justification of significant benefit. The sponsor is asked to provide evidence regarding the potential for major contribution to patient care, particularly in terms of evidence of patient harm due to the current lack of supply of chlormethine in the European Union, and what the meaningful advantages for patients are with improved availability.

In its written response, the sponsor provided a revised prevalence calculation that marginally increased the prevalence to 2.7 in 10,000. This was based on an updated literature. The COMP accepted the revised prevalence calculation.

The COMP then discussed the concerns associated with significant benefit. Current available products or medical devices used in the treatment of the condition are topical corticosteroids, psoralens + PUVA A, narrow-band ultraviolet B medicinal products. The current ESMO guideline also recommends the use of cytostatics such as mechlorethamine or carmustine. The COMP noted that there have been no authorised forms of chlormethine in Europe since the French nationally authorised product Caryolysine was commercially withdrawn in 2006. The COMP acknowledged that there could be hospital formulations of chlormethine and carmustine which are used in one or several EU member states, however these are not currently available in all member states. In conclusion, the COMP considered that the treatment options recommended by ESMO could not be fully implemented currently and that patients were as a consequence not treated optimally. Therefore, the licencing of this product as the only standard topical gel formulation available in Europe was considered a major contribution to patient care. It is expected to improve the patients' ease of use at home and to improve accessibility to patients by reducing the need to import the product on special requests or to get preparations from pharmacy hospital with potentially variable formulations.

The COMP concluded that:

The proposed therapeutic indication, mycosis fungoides-type cutaneous T-cell lymphoma (MF type CTCL) falls entirely within the scope of the orphan indication of the designated orphan medicinal product, cutaneous T-cell lymphoma.

The prevalence of cutaneous T-cell lymphoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 2.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, and lymphadenopathy. Ulceration of tumours, with secondary bacterial infections, is linked to morbidity and death. The overall five-year survival rates vary between 24% and 68% according to the subtype of cutaneous T-cell lymphoma.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Ledaga may be of significant benefit to those affected by the orphan condition still holds. The availability of a chlormethine gel product in Europe offers the possibility for topical treatment of these patients, for whom currently no chlormethine formulation is authorised in the EU. This has prevented patients from receiving one of the therapeutic options in current European Guidelines. The COMP considered that this offered a major contribution to patient care and is therefore of significant benefit within the context of how these patients with cutaneous T-cell lymphoma are treated.

An opinion not recommending the removal of Ledaga, chlormethine (EU/3/12/963) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

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

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

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

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.

4.2.2. - parathyroid hormone – EMA/OD/102/13, EU/3/13/1210, EMEA/H/C/003861

NPS Pharma Holdings Limited; Treatment of hypoparathyroidism

The status of the procedure at CHMP was noted.

4.2.3. - pentosan polysulfate sodium – EMA/OD/179/14, EU/3/14/1411, EMEA/H/C/004246

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.

4.2.4. Raxone – idebenone - type II variation – EMEA/OD/077/06, EU/3/07/437, EMEA/H/C/003834/II/0003

Santhera Pharmaceuticals (Deutschland) GmbH; Treatment of Duchenne muscular dystrophy

CHMP rapporteur: John Joseph Borg; CHMP co-rapporteur: Andrea Laslop

The status of the procedure at CHMP was noted.

4.2.5. – nusinersen - EMEA/H/C/004312, EMA/OD/141/11, EU/3/12/976

Biogen Idec Ltd; Treatment of 5q spinal muscular atrophy

The status of the procedure at CHMP was noted.

4.3. Appeal

4.3.1. Chenodeoxycholic acid sigma-tau - chenodeoxycholic acid – EMA/OD/196/14, EU/3/14/1406, EMEA/H/C/004061

Sigma-tau Arzneimittel GmbH; Treatment of inborn errors of primary bile acid synthesis

COMP coordinator: Frauke Naumann-Winter / Daniel O'Connor

In its grounds for appeal, and during an oral explanation before the Committee on 17 January 2017, the sponsor presented three main arguments in support of orphan maintenance as follows:

1. Given that the initial designation application had already been evaluated on the basis of clinical evidence and vis-a-vis the already authorised cholic acid (CA), and that the circumstances have not essentially changed since the designation stage, the significant benefit should still hold. However, the COMP considered that the opinion at the time of the initial designation was based on an assumption of significant benefit in the broader orphan indication which also included a number of other inborn errors of primary bile acid synthesis diseases besides inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX).

2. The sponsor also argued that chenodeoxycholic acid (CDCA) downregulates two important rate-limiting enzymes in the pathway of bile acid synthesis (namely HMG CoA reductase and CYP7A1), which was not the case for CA. Moreover, endogenous levels of the latter may be elevated in the proposed condition, and this fact would contradict an intention to substitute CA with the authorised product. The COMP considered that notwithstanding that different mechanisms of action between CDCA and CA can be acknowledged, especially with reference to HMG CoA reductase inhibition by CDCA, the different mechanism of action would not provide per se the basis for a comparative discussion of clinical outcomes, as the latter have to be confirmed by clinical observations.

3. The sponsor maintained that CDCA exerts beneficial effects in extrahepatic and in particular neurological manifestations of CTX patients, while CA addresses different aspects of the disease. To support this claim the applicant further elaborated on the available data from i) the literature ii) the marketing authorisation studies and iii) expert statements. This argument was considered acceptable by the COMP. It was considered that based on the pivotal trial, the published literature and expert statements, CDCA improves or stabilises neurological endpoints relevant in cerebrotendinous xanthomatosis, such as epilepsy, polyneuropathy, pyramidal dysfunction, cerebellar dysfunction, neurological disability, cognitive and psychiatric outcomes. These are different aspects of the condition with regards to the authorised CA, which has been shown to improve other endpoints, such as

liver biochemistry and urinary bile acid concentrations. The committee considered that this constitutes a clinically relevant advantage over cholic acid.

The COMP concluded that:

The proposed therapeutic indication, treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment inborn errors of primary bile acid synthesis.

The prevalence of inborn errors of primary bile acid synthesis (hereinafter referred to as "the condition") is estimated to remain below 5 in 10,000 and was concluded in to be 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to progressive neurological decline, fat malabsorption and fat-soluble vitamin deficiencies and life-threatening in particular due to the development of liver cirrhosis and liver failure.

The sponsor has established that chenodeoxycholic acid will be of significant benefit to those affected by the orphan condition. Based on the pivotal trial, published literature and expert statements, chenodeoxycholic acid has been demonstrated to improve or stabilize neurological endpoints in cerebrotendinous xanthomatosis, such as epilepsy, polyneuropathy, pyramidal dysfunction, cerebellar dysfunction, neurological disability, cognitive and psychiatric outcomes .Therefore cholic acid and chenodeoxycholic acid address different aspects of the condition. The committee considered that this constitutes a clinically relevant advantage.

An opinion not recommending the removal of Chenodeoxycholic acid sigma-tau, chenodeoxycholic acid (EU/3/14/1406) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

4.4. On-going procedures

COMP co-ordinators were appointed for 5 applications submitted.

4.5. Public Summary of Opinions

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

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. Nplate - recombinant megakaryopoiesis-stimulating protein – EMEA/OD/008/05, EU/3/05/283

Amgen Europe BV - The Netherlands; Treatment of idiopathic thrombocytopenic purpura

COMP co-ordinators were appointed.

5.2.2. Soliris – eculizumab - EMA/OD/062/14; EU/3/14/1304

Alexion Europe SAS; Treatment of myasthenia gravis

COMP co-ordinators were appointed.

5.3. Appeal

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. Protocol Assistance Working Group

The working group on Protocol Assistance met on 17 January 2017.

7.1.2. Recommendations on eligibility to PRIME – report from CHMP

An update on PRIME was presented to the committee. Clarifications on the role of COMP representatives at PRIME kick-off meetings and feedback on experience to date were provided.

7.1.3. Timing of COMP vs CHMP opinions

Update on measures to be taken to meet EC requirements to speed up the timing between CHMP and COMP opinions.

EMA presented the proposed case-by-case approach to speed up the time between CHMP and COMP opinion:

For the following situations the COMP will discuss and adopt draft grounds before the CHMP final opinion:

- products without significant benefit;
- products under accelerated assessment;
- products for which there is a CHMP opinion before a long break (in July or December).

The COMP will adopt the final grounds in a written procedure after the CHMP final opinion.

7.1.4. Strategic Review & Learning meetings

COMP Strategy Review & Learning meetings, 19-20 March 2017, Valletta, Malta

The presentation from the Malta Medicines Authority was displayed to the COMP for information.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. PDCO/COMP Working Group

The PDCO/COMP working group took place on 18 January 2017 by teleconference.

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

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

The COMP noted the PCWP work plan 2017.
Agendas from PCWP latest meetings were circulated for information.

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

The COMP noted the HCPWP Work plan 2017.

7.3.3. Working Party with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP)

The joint report of the PCWP/HCPWP workshop on social media and the minutes of the PCWP/HCPWP joint meeting held on 20 September 2016 were circulated for information.

7.4. Cooperation within the EU regulatory network

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

The draft agenda of the monthly teleconference with FDA held on 13 December 2016 was circulated via MMD for information.

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

7.7.1. COMP Work Plan 2017

The COMP Work Plan 2017 was tabled in MMD for information.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

None

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 17-19 January 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	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	
Melinda Sobor	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Dan Henrohn	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 participation in final deliberations and voting on:	2.2.14.
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*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Expert - in person*	Patients' Organisation Representative	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.

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/