7 December 2017
EMA/COMP/708746/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 30-31 October 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

30 October 2017, 08:30-19:30, room 2F

31 October 2017, 08:30-16:30, 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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

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 30-31 October 2017 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 03-05 October 2017 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. 2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione - EMA/OD/132/17

NeuroVive Pharmaceutical AB; Treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

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:

- 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 mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, it is noted that the neurological symptoms are more relevant than the muscular symptoms. The sponsor should further elaborate on:

– the relevance of the preclinical model used for the treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, and the interpretation of the results obtained in the experiments.

In the written response, and during an oral explanation before the Committee on 30 October 2017, the sponsor further elaborated on the data presented from their non-clinical *in vivo* study to support the feasibility of the use of their product in this mitochondrial condition. The COMP discussed the representability of the non-clinical *in vivo* model used by the sponsor, and the sponsor noted that there are no specific models of the condition. The functional outcomes on that model were particularly discussed and grip strength was considered a clinically relevant outcome.

The Committee agreed that the condition, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione was considered justified based on non-clinical *in vivo* data showing an improvement in the muscle function as highlighted by an improvement in grip function.

The condition is life-threatening due to reduced life-expectancy and chronically debilitating due to recurrence of seizures, vomiting and headaches, anorexia, exercise intolerance, proximal limb weakness, sensorineural hearing loss and stroke-like episodes of transient hemiparesis or cortical blindness with the onset between the ages of 2 and 10 years.

The condition was estimated to be affecting approximately 0.06 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 2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione, for treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, was adopted by consensus.

2.1.2. - EMA/OD/143/17

Treatment of myotonic disorders

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 proposed through testimonials that the reduced availability of the product in Europe could be causing patient harm in the member states.

The sponsor is requested to demonstrate that patient harm is caused across Europe due to the limited availability they are indicating. The current submission only provided information for assessment in three member states making it difficult to establish the seriousness and extent of the patient harm. Data would be expected from experts treating the condition, including therapeutic guidelines on how these patients are managed in all EU member states.

In the absence of data demonstrating that patient harm is caused, significant benefit based on availability cannot be accepted.

In the written response, and during an oral explanation before the Committee on 30 October 2017, the sponsor discussed the raised issue, and patient experts were involved in the discussion on both the side of the sponsor as well as from the EMA/COMP. The COMP could not establish how difficult it was for patients across Europe to obtain mexiletine, nor was made aware of documented patient harm as requested in the list of issues. Therefore, the application for orphan designation was not considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 31 October 2017, prior to final opinion.

2.1.3. 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl - EMA/OD/135/17

Premier Research Group Limited; Treatment of familial cerebral cavernous malformation

COMP coordinator: Michel Hoffmann

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 COMP requests to change the condition to “familial cerebral cavernous malformation”.

The sponsor’s attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

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

  - the time of initiation of treatment in the context of the progression of disease pathology in the model. It seems that treatment started very close to the induction of the knock-out, while the main pathology findings can only be observed at 2 months of age. In general, the 2 month time point would be considered as most relevant to study a treatment option;
  - the results regarding reduction of lesions; it seems that the positive effect is statistically significant only for reducing the number and the size of small or mid-size lesions;
  - the absence of data on incidence of haemorrhage or micro-haemorrhage in familial cerebral cavernous malformation.

- 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 current prevalence calculation should be revised to take into account the change of condition.

In the written response, the sponsor agreed with the request of the COMP to change the condition to “familial cerebral cavernous malformation”. In line with this change, a new and

updated prevalence estimate was submitted, which was based on published epidemiological literature. The estimate of less than 3 per 10,000 was accepted by the COMP.

Regarding medical plausibility, the sponsor has provided more background information on the non-clinical model justifying the start of treatment prior to the major pathological manifestations. Furthermore, the sponsor confirmed that overall treatment led to a statistically significant reduction in cerebrovascular lesions. While it was acknowledged that the observed effect size regarding larger lesions was less pronounced compared to the small and mid-sized lesions, the non-clinical model is characterised by small and medium sized lesion and there is currently no evidence that disease severity is linked with lesion size. The COMP accepted these written justifications and agreed that the presented evidence was sufficient for establishing medical plausibility for orphan designation. The oral explanation was cancelled.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of familial cerebral cavernous malformation.

The Committee agreed that the condition, familial cerebral cavernous malformation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl was considered justified based on preclinical data from a valid model demonstrating that treatment was able to reduce cerebrovascular lesions.

The condition is chronically debilitating due to focal seizures and neurological deficits determined by the localisation of the lesion, such as weakness of arms or legs, headache, vision impairment, memory and attention problems, and life-threatening due to severe brain haemorrhage.

The condition was estimated to be affecting not more than 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 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, for treatment of familial cerebral cavernous malformation, was adopted by consensus.

2.1.4. Pegunigalsidase alfa - EMA/OD/138/17

Protalix B.V.; Treatment of Fabry disease

COMP coordinator: Pauline Evers

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 claims significant benefit based on data from a non-clinical model of the condition demonstrating the product's comparative efficacy in decreasing peripheral neuroinflammation and clinical data to claim improved efficacy based on reduced immunogenicity, improved control of the kidney damage and improved dosing scheme due to improved stability of the product. The arguments on significant benefit are based on increased stability of the product 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 non-clinical and clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. In particular, the sponsor is requested to elaborate on detailed comparison between historical studies using authorised products and the clinical study using Pegunigalsidase alpha (studied populations, duration of studies etc.).

In the written response, the sponsor provided additional non-clinical data in the model of the condition demonstrating that the product reduced temperature hypersensitivity in comparison to the existing enzyme replacement therapies (ERTs). This would support the assumption of improved efficacy of the product in management of peripheral neuropathy. In addition, the sponsor provided detailed explanation of clinical data, which suggest a significantly reduced immunogenicity of the product compared to that of the two authorised ERTs. The committee did not accept the additional arguments of the sponsor regarding improved stabilisation of kidney function in patients treated with pegunigalsidase alpha compared to other products, because the study populations were not comparable.

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

The intention to treat the condition with the medicinal product containing pegunigalsidase alfa was considered justified based on non-clinical data showing reduced accumulation of toxic metabolites in relevant tissues and on clinical data demonstrating the stabilisation of kidney function.

The condition is chronically debilitating due to recurrent episodes of severe pain that do not respond to standard analgesics, and life-threatening due to renal failure, cardiovascular and cerebrovascular complications.

The condition was estimated to be affecting approximately 2.2 in 10,000 persons in the European Union, at the time the application was made.

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 pegunigalsidase alfa will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a model of the condition that demonstrate that the product reduced peripheral neuropathy, which is an improvement over the authorised products. Clinical data also demonstrate reduced immunogenicity of the product compared to other authorised treatments. In addition, the product can be used in a wider patient population than miglustat. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pegunigalsidase alfa, for treatment of Fabry disease, was adopted by consensus.

2.1.5. - EMA/OD/139/17

Treatment of spinal cord injury

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

- Number of people affected

For the calculation and presentation of the prevalence estimate 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 further elaborate on the incidence data identified for non-traumatic spinal cord injury. There is data to suggest a higher incidence, *e.g*. Spain (11.4 per million; van den Berg *et al* Arch Phys Med Rehabil 2012 (93:2):325-31). In the absence of data in Europe, maybe further data outside of Europe might be considered useful to contextualise, *e.g.* Australia (New *et al*, Spinal Cord. 2013 Feb;51(2):99-102).

Furthermore, the sponsor should justify the proposed disease durations of 25 and 12 years for traumatic and non-traumatic spinal cord injury respectively. The sponsor should also take into considerations reports on longer disease durations of the non-traumatic SCI part of the sponsor's bibliography (median survival of 24 years; New *et al*. 2014a)

- Significant benefit

The sponsor is requested to provide a data driven justification of significant benefit. In this context, the sponsor should discuss the reliability of the non-clinical model for testing products with BBB score outcome, and if the generated results can be considered sufficiently robust to allow indirect comparisons.

In the written response, and during an oral explanation before the Committee on 31 October 2017, the sponsor addressed the raised issues. For the prevalence, the sponsor provided further epidemiological data on the incidence of non-traumatic spinal cord injury and on the disease duration of non-traumatic spinal cord injury. The COMP acknowledged that even the most conservative prevalence estimate that was presented (4.8 per 10,000) would still fall below the threshold of 5 per 10,000.

Regarding significant benefit, the sponsor argued that methylprednisolone treatment would be envisaged immediately after injury and prior to the treatment with the proposed product. The COMP sought non-clinical or preliminary clinical evidence to support the effects of the product administered after methylprednisolone treatment. The sponsor could not provide such confirmation, because proof of concept with the proposed product has been studied without taking into consideration methylprednisolone. Therefore the COMP considered that at this point in time there was insufficient evidence to fully substantiate 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 31 October 2017, prior to final opinion.

2.1.6. - EMA/OD/130/17

Treatment of hepatocellular carcinoma

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 10 October 2017, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidine-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridine-2-yl)-4-fluoropyrrolidine-2-carboxamide - EMA/OD/156/17

FGK Representative Service GmbH; Treatment of paroxysmal nocturnal hemoglobinuria

COMP coordinator: Martin Možina

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

The intention to treat the condition with the medicinal product containing (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidine-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridine-2-yl)-4-fluoropyrrolidine-2-carboxamide was considered justified based on preliminary clinical data supporting an improvement in haemoglobin levels in patients with the condition.

The condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications in the central nervous system are the most common cause of death.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidine-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridine-2-yl)-4-fluoropyrrolidine-2-carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that supports a reduction in the number of transfusions needed in patients with aplastic anaemic paroxysmal nocturnal haemoglobinuria where eculizumab is not recommended. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidine-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridine-2-yl)-4-fluoropyrrolidine-2-carboxamide, for treatment of paroxysmal nocturnal haemoglobinuria, was adopted by consensus.

2.2.2. Acetylleucine - EMA/OD/158/17

IntraBio Ltd; Treatment of GM2 Gangliosidosis

COMP coordinator: Ingeborg Barisic

The Committee agreed that the condition, GM2 gangliosidosis , is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing acetylleucine was considered justified based on non-clinical and preliminary clinical data demonstrating that treatment improved motor function.

The condition is life-threatening with a reduced life expectancy of 3 to 15 years in infantile and juvenile onset patients, and chronically debilitating due to ataxia, muscle weakness, loss of motor function, sight, hearing and development of seizures and dementia.

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.

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 acetylleucine, for treatment of GM2 gangliosidosis, was adopted by consensus.

2.2.3. - EMA/OD/151/17

Treatment of Huntington's 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 December 2017 meeting.

2.2.4. - EMA/OD/167/17

Treatment of mucopolysaccharidosis type I

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 December 2017 meeting.

2.2.5. - EMA/OD/168/17

Treatment of mucopolysaccharidosis type II

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 December 2017 meeting.

2.2.6. Adenovirus associated viral vector serotype 8 containing the human *AIPL1* gene - EMA/OD/162/17

MeiraGTx UK II Limited; Treatment of Leber congenital amaurosis

COMP coordinator: Fernando Méndez Hermida

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

The intention to treat the condition with the medicinal product containing adenovirus associated viral vector serotype 8 containing the human *AIPL1* gene was considered justified based on non-clinical data in a model of the condition demonstrating improved electroretinograms compared to controls which is indicative of preserved visual function.

The condition is chronically debilitating due to progressive loss of vision and blindness.

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 in the European Union for patients affected by the condition.

A positive opinion for adenovirus associated viral vector serotype 8 containing the human *AIPL1* gene, for treatment of Leber's congenital amaurosis, was adopted by consensus.

2.2.7. Agammaglobulinaemia tyrosine kinase - EMA/OD/157/17

Clinical Network Services (UK) Ltd; Treatment of pemphigus

COMP coordinator: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing agammaglobulinaemia tyrosine kinase was considered justified based on preliminary clinical data showing control of the disease with the proposed product.

The condition is chronically debilitating and potentially life-threatening due to chronic blistering associated with dehydration and secondary infection which can lead to premature death.

The condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

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 agammaglobulinaemia tyrosine kinase will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that treatment with the proposed product reduced the need of corticosteroids in some of the patients. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition as it could help reducing the side-effects of long term treatment with high doses of corticosteroids.

A positive opinion for agammaglobulinaemia tyrosine kinase, for treatment of pemphigus, was adopted by consensus.

2.2.8. - EMA/OD/144/17

Treatment of oculopharyngeal muscular dystrophy (OPMD)

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 December 2017 meeting.

2.2.9. - EMA/OD/095/17

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 December 2017 meeting.

2.2.10. - EMA/OD/161/17

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 December 2017 meeting.

2.2.11. - EMA/OD/160/17

Treatment of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy

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 December 2017 meeting.

2.2.12. - EMA/OD/152/17

Treatment of atypical haemolytic uremic 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 December 2017 meeting.

2.2.13. - EMA/OD/155/17

Treatment of Immunoglobulin G4-Related 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 December 2017 meeting.

2.2.14. - EMA/OD/159/17

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 December 2017 meeting.

2.2.15. Modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles - EMA/OD/153/17

PhaseRx Ireland, Ltd; Treatment of argininosuccinic aciduria

COMP coordinator: Annie Lorence

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

The intention to treat the condition with the medicinal product containing modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles was considered justified based on non-clinical data showing reduction of ammonemia in valid models of the condition.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

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

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 modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles will be of significant

benefit to those affected by the condition. The sponsor has provided non-clinical data showing reduction of ammonemia when modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles was used in addition to ammonia scavenger products, currently authorized for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles, for treatment of argininosuccinic aciduria, was adopted by consensus.

2.2.16. - EMA/OD/166/17

Treatment of small cell lung 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 December 2017 meeting.

2.2.17. - EMA/OD/164/17

Treatment of congenital adrenal hyperplasia

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 December 2017 meeting.

2.2.18. - EMA/OD/096/17

Treatment of adult-onset Still's 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 December 2017 meeting.

2.2.19. - EMA/OD/129/17

Treatment of systemic juvenile idiopathic arthritis

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 December 2017 meeting.

2.2.20. Venetoclax - EMA/OD/131/17

Abbvie Ltd.; Treatment of mantle cell lymphoma

COMP coordinator: Karri Penttila

The Committee agreed that the condition, mantle 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 venetoclax was considered justified based on preliminary clinical data in relapsed/refractory patients who responded to treatment with the proposed product.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss. Median survival is 3 to 5 years.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing venetoclax will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations supporting improved clinical responses in relapsed/refractory patients when venetoclax was combined with ibrutinib, as well as an indirect comparison that favours the proposed product when used as monotherapy in relapsed/refractory patients compared to other treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for venetoclax, for treatment of mantle cell lymphoma, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

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 25 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 28 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of spinal muscular atrophy

The Committee was briefed on the significant benefit issues.

3.1.2. -

Treatment of plasma cell myeloma

The Committee was briefed on the significant benefit issues.

3.1.3. -

Treatment of sickle cell disease

The Committee was briefed on the significant benefit issues.

3.1.4. -

Treatment of chronic lymphocytic leukaemia

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 idiopathic pulmonary fibrosis

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 small cell lung cancer

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

3.1.7. -

Treatment of ornithine transcarbamylase deficiency

The Committee was briefed on the significant benefit issues.

3.2. Finalised letters

None

3.3. New requests

3.3.1. -

Treatment of Lennox-Gastaut syndrome

The new request was noted.

3.3.2. -

Treatment of mantle cell lymphoma

The new request was noted.

3.3.3. -

Treatment of acute myeloid leukaemia

The new request was noted.

3.3.4. -

Treatment of myelodysplastic syndromes

The new request was noted.

3.3.5. -

Treatment of Leber's hereditary optic neuropathy

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. Prevymis - letermovir - S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid - EMEA/H/C/004536, EMA/OD/090/10, EU/3/11/849

Merck Sharp & Dohme Limited; Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk

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 issues identified in the application.

Upon assessing the sponsor's written response and upon listening to the oral explanation on 30 October 2017, the Committee confirmed that all the issues previously identified in this application had been addressed.

An opinion recommending not to remove Prevymis, (S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid, letermovir, EU/3/11/849 for prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its 30-31 October meeting and upon adoption of CHMP opinion.*]

4.2.2. - plitidepsin – EMEA/H/C/004354, EMEA/OD/044/04, EU/3/04/245

Pharma Mar SA; Treatment of multiple myeloma

The status of the procedure at CHMP was noted.

4.2.3. - rucaparib - EMEA/H/C/004272, EMA/OD/085/12, EU/3/12/1049

Clovis Oncology UK Ltd; Treatment of ovarian 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.

4.2.4. Lenvima - Lenvatinib – Type II variation - EMEA/H/C/003727/II/0011/G, EMA/OD/287/14, EU/3/15/1460

Eisai Ltd; Treatment of hepatocellular carcinoma

CHMP rapporteur: Bart Van der Schueren; CHMP co-rapporteur: Robert James Hemmings

The status of the procedure at CHMP was noted.

4.2.5. - budesonide - EMEA/H/C/004655, EMA/OD/078/13, EU/3/13/1181

Dr. Falk Pharma GmbH; Treatment of eosinophilic esophagitis

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 December 2017 meeting.

4.2.6. - velmanase alfa - EMEA/H/C/003922, EMEA/OD/074/04, EU/3/04/260,

Chiesi Farmaceutici S.p.A.; Treatment of alpha-Mannosidosis

The status of the procedure at CHMP was noted.

4.2.7. - glibenclamide - EMEA/H/C/004379, EMA/OD/149/15, EU/3/15/1589

Ammtek; Treatment of neonatal diabetes

The status of the procedure at CHMP was noted.

4.2.8. - burosumab - EMEA/H/C/004275, EMEA/H/C/004275, EU/3/14/1351

Kyowa Kirin Limited; Treatment of X-linked hypophosphataemia

The status of the procedure at CHMP was noted.

4.3. Appeal

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

Santen Oy; Treatment of vernal keratoconjunctivitis

A COMP opinion was adopted on 28 July 2017, recommending the removal of the orphan medicinal product designation from the Community Register of Orphan Medicinal Products.

On 13 October 2017, the sponsor submitted detailed grounds for appeal. An oral explanation was given by the sponsor on 30 October 2017.

Based on the assessment of the detailed grounds for appeal and the argumentations presented by the sponsor during the oral explanation on 30 October 2017, 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.

The data provided for Verkazia does not justify significant benefit that their product would offer a clinically relevant advantage based on better safety when compared with magistral/officinal formulations. The sponsor has highlighted an argumentation indicating that there has been a reduction in the production of officinal formulations due to safety concerns associated with manufacturing practice in particular concerns associated with bacterial load and excipients which cause topical irritation. However, this view was not supported by sufficient evidence. The assumption of major contribution to patient care due to improved availability of the product was also not accepted due to widespread use of magistral/officinal preparations of ciclosporin in the vast majority of EU member states. Thus, the assumption that Verkazia may be of potential significant benefit to those affected by the orphan condition does not hold.

Therefore, the sponsor has not established that Verkazia is still of significant benefit to those affected by the condition.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, was of the opinion that:

The criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied.

The criteria for designation as set out in Article 3(1)(b) are not satisfied.

The COMP recommended, by a majority of 26 out of 28 votes, that Verkazia, ciclosporin (EU/3/06/360) for treatment of vernal keratoconjunctivitis is removed from the Community Register of Orphan Medicinal Products.

The Icelandic and the Norwegian COMP members agreed with the above-mentioned recommendation of the COMP.

The divergent positions (Jens Ersbøll and Dan Henrohn) were appended to this opinion.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its 30-31 October meeting and upon adoption of CHMP opinion.*]

4.4. On-going procedures

Action: For information

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

4.5. Public Summary of Opinions

Action: For information

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. Bosulif (Bosutinib) - Type II variation – EMEA/H/C/002373/II/0025/G, EMEA/OD/160/09, EU/3/10/762

Pfizer Limited - UK; Treatment of chronic myeloid leukaemia

CHMP rapporteur: Harald Enzmann

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.

5.2.2. Lynparza - (Olaparib) – EMEA/H/C/003726/X/0016/G, EMEA/OD/063/07, EU/3/07/501

AstraZeneca AB - Sweden; Treatment of ovarian cancer

CHMP rapporteur: Alexandre Moreau

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

Action: For information

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

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. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 30 October 2017.

7.1.3. Non-Clinical Working Group

None

7.1.4. Condition Working Group

The working group on Condition met on 27 October 2017.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes October 2017.

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

7.3.3. Scientific Advice Working Party (SAWP)

Re-examination of SAWP composition and Committee representatives at SAWP

Document(s) tabled:
List of volunteers

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

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

COMP Work Plan 2018 was adopted.

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

8.1. Preparedness of the system and capacity increase

8.2. S-REPS: a new way of supporting COMP procedures with a CRM (Customer Relationship Management software)

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 30-31 October 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	
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	
Ioannis Kkolos	Member	Cyprus	No interests declared	
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	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Dan Henrohn	Member	Sweden	No interests declared	
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	
Kerstin Westermark	Member	Expert recommended by EMA	No participation in final deliberations and voting on:	5.2.2.
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Monika Skočovská	Patient Expert - in person*	Patient expert		
Jeanette Charlton	Patient Expert - in person*	Patient expert		
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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/