12 June 2017
EMA/COMP/238488/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 10-11 April 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

10 April 2017, 09:00-19:00, room 2F

11 April 2017, 08:30-17:00, 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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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 that no restriction in the involvement of meeting participants in upcoming discussions was identified 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

The COMP agenda for 10-11 April 2017 was adopted with amendments.

1.3. Adoption of the minutes

The COMP minutes for 14-15 March 2017 were adopted with amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. ^{225}Ac-lintuzumab - EMA/OD/319/16

Voisin Consulting S.A.R.L.; Treatment of acute myeloid leukaemia

COMP coordinator: Irena Rogovska

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 new mechanism of action and the potential improved efficacy in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the partial results of the phase I/II study to justify the assumption of significant benefit over approved products for the proposed orphan indication.

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, and during an oral explanation before the Committee on 10 April 2017, the sponsor provided arguments to support the assumption of significant benefit. The sponsor argued that patients enrolled in the phase I/II study were at baseline older and more difficult to treat compared to baseline characteristics of patients in published phase III trials of decitabine and azacitidine, currently authorised products for acute myeloid leukaemia patients who are not eligible for induction therapy.

The sponsor reported promising complete response rates in patients without previous hypomethylating exposure and in patients with previous hypomethylating exposure (including decitabine and azacitidine). The COMP considered that those patients, who are non-eligible for induction therapy and mostly patients with secondary acute myeloid leukaemia derived from myelodysplastic syndromes previously treated by the hypomethylating agents could benefit from the product which may provide a clinically relevant advantage. Therefore, the product may be of significant benefit over currently authorised products.

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

The intention to treat the condition with the medicinal product containing ^{225}Ac-lintuzumab was considered justified based on preliminary clinical data showing improvements in progression free survival.

The condition is life-threatening due to haematologic malignancy characterized by a rapid degradation into a fatal outcome without intensive medical care, with limited treatment options, in particular for patients non eligible for intensive therapy with poor prognostic genetic features. The 1-year survival rate for patients $\geq$ 65 years is less than 20% compared to 60% for younger patients and up to 64% of acute myeloid leukaemia patients $\geq$ 65 years go untreated, other than with supportive care. The median survival in those patients is 1.7 months.

The condition was estimated to be affecting approximately 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 ^{225}Ac-lintuzumab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate an improvement in outcomes in acute myeloid leukaemia patients who are not eligible for induction therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ^{225}Ac-lintuzumab, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.2. - EMA/OD/260/16

Treatment of glioma

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

- Number of people affected

The sponsor presented a prevalence calculation based on literature and registry data including references until the year 2007. Recent sources of epidemiological data were not included, which makes the calculation potentially outdated.

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

The sponsor should re-calculate the prevalence estimate based on relevant most recent epidemiological studies and registers for the proposed orphan condition.

- Significant benefit

The sponsor submitted preliminary *in vitro* data to demonstrate improved efficacy of the product compared to temolozomide and an indirect comparison to historical data with the comparator. No head-to-head *in vivo* comparison data to support significant benefit was presented in the application. The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

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

The sponsor should detail the intended use of the product in the context of the current standard of care.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 10 April 2017, the sponsor provided several additional citations to support stable glioma incidence and survival over the years. Although some sources cited were representing global and USA statistics rather than European, the values given also included some European countries. The committee accepted this response.

In reference to the question on significant benefit, the sponsor did not present any new data and the arguments were based on limitations of non-clinical models in representing the full clinical practise (which includes also surgery and radiotherapy). The COMP insisted that comparative data to pharmacological agents registered for treatment of glioma (i.e. temolozomide) is required and that *in vitro* data or indirect comparison vs. historical non-clinical data is not sufficient.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 April 2017, prior to final opinion.

2.1.3. - EMA/OD/323/16

Treatment of Herpes simplex encephalitis

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

Herpes simplex encephalitis should be justified as a distinct medical entity or a valid subset. Note 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).

It appears that from the point of view of aetiology and pathogenesis, herpes simplex encephalitis is a subset of herpes virus (usually HSV-1) infection. In general the committee would consider a subset valid when it has different aetiology, pathophysiology and clinical characteristics from the broader condition and when there is a justification as to why the proposed product would work only in the subset and not in the broader condition.

The sponsor should therefore elaborate on any aetiology and pathophysiological characteristics that would support Herpes simplex encephalitis as distinct medical entity or valid subset.

In addition, to establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of Herpes simplex encephalitis, data in the proposed condition are needed. To this purpose the sponsor should further elaborate on:

– the clinical relevance of reducing pain and swelling, and accelerating healing in herpes labialis to the intended clinical use in herpes virus encephalitis;

– the extrapolation of data from the oral formulation of the product, as used in the herpes labialis study, to the intravenous formulation and use as foreseen for the treatment of herpes virus encephalitis.

In the written response, and during an oral explanation before the Committee on 10 April 2017, the sponsor clarified his views in relation to all pathophysiologic mechanisms involved in Herpes simplex encephalitis, including the involvement of nitric oxide-activated pathways, other oxidative mechanisms, immunologic mechanisms, and the role of kynurenine pathways. The sponsor also discussed with the COMP mechanisms of actions and effects of the product that could be relevant to their intended use in Herpes simplex encephalitis. The Committee, however, questioned the lack of any proof of concept data in Herpes simplex encephalitis or in valid models of Herpes simplex encephalitis, as the sponsor did not present any additional data to the small study on herpes labialis that had been submitted with the initial application. This was considered not adequate to support the medical plausibility and significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 April 2017, prior to final opinion.

2.1.4. Ursodeoxycholic acid - EMA/OD/316/16

IntraBio Ltd; Treatment of Niemann-Pick disease

COMP coordinator: Ingeborg Barisic/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:

- Condition

The sponsor is invited to revise the proposed indication to “treatment of Niemann-Pick disease” and recalculate the prevalence accordingly.

- Significant benefit

The arguments on significant benefit are based on the potential for improved safety and possible combination with miglustat.

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

In the written response, and during an oral explanation before the Committee on 10 April 2017, the sponsor accepted to broaden the indication to covering all types of Niemann-Pick disease. With regards to the prevalence calculation the sponsor asserted that the statutory threshold is still respected, and the COMP relied also on previous considerations of other procedures to consider a 0.1 per 10,000 figure.

In addition the sponsor further elaborated on the available data from four Niemann-Pick disease patients who have received the proposed product. Importantly, the product was used in combination with miglustat regimen in three patients enrolled. In the treated patients, improvements in liver biochemistry were noted, and that improvement is also in line with the authorised uses of the product in cholestatic diseases. Miglustat is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease. Therefore an improvement in liver function would address a different aspect of the condition from the neurological manifestations covered by the authorised product. Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of Niemann-Pick disease.

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

The intention to treat the condition with the medicinal product containing ursodeoxycholic acid was considered justified based on preclinical data showing improvements in neurological endpoints in a model of the proposed condition and preliminary clinical observations in affected patients supporting improvements in liver function.

The condition is chronically debilitating and life-threatening in particular due to complications such as neurological degeneration, splenomegaly, and hepatomegaly. The majority of patients with Niemann-Pick disease type A die before two years of age, while patients with other forms usually die in their twenties.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ursodeoxycholic acid will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in affected patients supporting improvements in liver function, while the

authorised product is indicated for the treatment of neurological manifestations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ursodeoxycholic acid, for treatment of Niemann-Pick disease, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/017/17

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 May meeting.

2.2.2. - EMA/OD/005/17

Treatment of glioma

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

2.2.3. - EMA/OD/324/16

Treatment of spinal cord Injury

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 May meeting.

2.2.4. Chimeric locked nucleic acid deoxynucleoside phosphorothioate-linked oligonucleotide inhibitor directed against microRNA-155-5p - EMA/OD/011/17

Miragen Therapeutics Europe Ltd; Treatment of cutaneous T-cell lymphoma

COMP coordinator: Frauke Naumann-Winter

The Committee agreed that the condition, cutaneous T-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 chimeric locked nucleic acid deoxynucleoside phosphorothioate-linked oligonucleotide inhibitor directed against microRNA-155-5p was considered justified based on preliminary clinical data in patients with condition showing a reduction in skin tumour size.

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.

The condition was estimated to be affecting approximately 2.6 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing chimeric locked nucleic acid

deoxynucleoside phosphorothioate-linked oligonucleotide inhibitor directed against microRNA-155-5p will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in cutaneous tumour size when used as add-on and in patients who could be considered refractory to current treatments used. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for chimeric locked nucleic acid deoxynucleoside phosphorothioate-linked oligonucleotide inhibitor directed against microRNA-155-5p, for treatment of cutaneous T-cell lymphoma, was adopted by consensus.

2.2.5. - EMA/OD/008/17

Treatment of sickle cell disease

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 May meeting.

2.2.6. - EMA/OD/248/16

Prevention of arteriovenous access dysfunction in haemodialysis patients

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 May meeting.

2.2.7. - EMA/OD/013/17

Treatment of growth hormone deficiency

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 May meeting.

2.2.8. - EMA/OD/311/16

Treatment of neonatal abstinence 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 May meeting.

2.2.9. Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain - EMA/OD/004/17

Best Regulatory Consulting Ltd; Treatment of paroxysmal nocturnal haemoglobinuria

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 Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain was considered justified based on preliminary clinical data showing improvement of parameters of haemolysis.

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 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that the proposed product improved haemoglobin levels in patients in whom haemolysis was not controlled by the currently authorised treatment for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain, for treatment of paroxysmal nocturnal haemoglobinuria, was adopted by consensus.

2.2.10. Recombinant adeno-associated viral vector serotype 6 encoding the B-domain-deleted human factor VIII - EMA/OD/019/17

Coté Orphan Consulting UK Limited; Treatment of haemophilia A

COMP coordinator: Fernando Méndez Hermida

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to recombinant adeno-associated viral vector serotype 6 encoding the B-domain-deleted human factor VIII.

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

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector serotype 6 encoding the B-domain-deleted human factor VIII was considered justified based on pre-clinical *in vivo* data that show a reduction in bleeding time.

The condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or in surgery, which may also be life-threatening.

The condition was estimated to be affecting 1.3 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 recombinant adeno-associated viral vector serotype 6 encoding the B-domain-deleted human factor VIII will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate reduced bleeding times through an alternative mechanism. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant adeno-associated viral vector serotype 6 encoding the B-domain-deleted human factor VIII, for treatment of haemophilia A, was adopted by consensus.

2.2.11. - EMA/OD/018/17

Treatment of haemophilia B

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 May meeting.

2.2.12. Recombinant human interleukin-7 fused to a hybrid crystallisable fragment region of a human antibody - EMA/OD/321/16

NeoImmuneTech, INC., Spółka Akcyjna, Oddział w Polsce; Treatment of idiopathic CD4 lymphocytopenia

COMP coordinator: Frauke Naumann-Winter

The Committee agreed that the condition, idiopathic CD4 lymphocytopenia, 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 interleukin-7 fused to a hybrid crystallisable fragment region of a human antibody was considered justified based on clinical data demonstrating clinically relevant increase of circulating CD4+ lymphocytes.

The condition is life-threatening and chronically debilitating due to the impairment of immune system leading to reoccurring opportunistic infections.

The condition was estimated to be affecting less than 0.01 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 recombinant human interleukin-7 fused to a hybrid crystallisable fragment region of a human antibody, for treatment of idiopathic CD4 lymphocytopenia, was adopted by consensus.

2.2.13. - EMA/OD/014/17

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 at the May meeting.

2.2.14. - EMA/OD/304/16

Prevention of arterial pulmonary hypertension

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 May meeting.

2.2.15. - EMA/OD/001/17

Prevention of rejection following solid organ 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 May meeting.

2.2.16. - EMA/OD/007/17

Treatment of tuberous 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 May meeting.

2.2.17. Sodium (1R,3R,4R,5S)-3-({2-N-acetylamino-2-deoxy-3-O-[(1S)-1-carboxylato-2-cyclohexylethyl]-beta-D-galactopyranosyl}oxy)-4-({6-deoxy-alpha-L-galactopyranosyl}oxy)-5-ethyl-cyclohexan-1-yl-(38-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-azahentetracontan-41-yl)carboxamide - EMA/OD/010/17

TMC Pharma Services Ltd; Treatment of acute myeloid leukaemia

COMP coordinator: Jens Ersbøll

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to sodium (1R,3R,4R,5S)-3-({2-N-acetylamino-2-deoxy-3-O-[(1S)-1-carboxylato-2-cyclohexylethyl]-beta-D-galactopyranosyl}oxy)-4-({6-deoxy-alpha-L-galactopyranosyl}oxy)-5-ethyl-cyclohexan-1-yl-(38-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-azahentetracontan-41-yl)carboxamide.

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

The intention to treat the condition with the medicinal product containing sodium (1R,3R,4R,5S)-3-({2-N-acetylamino-2-deoxy-3-O-[(1S)-1-carboxylato-2-cyclohexylethyl]-beta-D-galactopyranosyl}oxy)-4-({6-deoxy-alpha-L-galactopyranosyl}oxy)-5-ethyl-

cyclohexan-1-yl-(38-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-azahentetracontan-41-yl)carboxamide was considered justified based on pre-clinical *in vivo* and preliminary clinical data showing an improvement in survival.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

The condition was estimated to be affecting approximately 1.3 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 sodium (1R,3R,4R,5S)-3-({2-N-acetylamino-2-deoxy-3-O-[(1S)-1-carboxylato-2-cyclohexylethyl]-beta-D-galactopyranosyl}oxy)-4-({6-deoxy-alpha-L-galactopyranosyl}oxy)-5-ethyl-cyclohexan-1-yl-(38-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-azahentetracontan-41-yl)carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in complete remission in relapsed/refractory acute myeloid leukaemia patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium (1R,3R,4R,5S)-3-({2-N-acetylamino-2-deoxy-3-O-[(1S)-1-carboxylato-2-cyclohexylethyl]-beta-D-galactopyranosyl}oxy)-4-({6-deoxy-alpha-L-galactopyranosyl}oxy)-5-ethyl-cyclohexan-1-yl-(38-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-azahentetracontan-41-yl)carboxamide, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.18. - EMA/OD/020/17

Treatment of subarachnoid haemorrhage (SAH)

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 May meeting.

2.2.19. - EMA/OD/002/17

Treatment of congenital hyperinsulinism

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 May meeting.

2.2.20. Tamoxifen citrate - EMA/OD/006/17

GB Pharma Srl; Treatment of cystic fibrosis

COMP coordinator: Ingeborg Barisic/Melinda Sobor

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 tamoxifen citrate was considered justified based on preclinical data showing increased transport of chloride across cystic fibrosis airway epithelial cells.

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 tamoxifen citrate will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing that the proposed product increases chloride transport in models of F508del cystic fibrosis to a higher extent than the recently authorised combination of ivacaftor and lumacaftor. Due its mechanism of action it is expected that the effects of the product will not be limited to the CFTR F508del mutation. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for tamoxifen citrate, for treatment of cystic fibrosis, was adopted by consensus.

2.2.21. - EMA/OD/016/17

Treatment of distal renal tubular acidosis

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 May meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

2.4.1. Ciclosporin – EMA/OD/022/04, EU/3/04/210

PARI Pharma GmbH - Germany; Treatment of graft rejection after lung transplantation; Proposed new indication: Treatment of bronchiolitis obliterans syndrome

COMP coordinator: Martin Mozina

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 amended condition with the medicinal product containing ciclosporin (inhalation use) was considered justified based on clinical data showing increased survival with the proposed product.

The condition is life-threatening and chronically debilitating due to progressive airway fibrosis and loss of lung function, leading to death in approximately 80% of patients within 5 years from the diagnosis.

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 ciclosporin, for treatment of bronchiolitis obliterans syndrome, was adopted by consensus.

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

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 24 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 13 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of Wolfram syndrome

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

3.1.2. -

Treatment of Wolfram syndrome

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

3.1.3. -

Treatment of soft tissue sarcoma

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

3.1.4. -

Treatment of haemophilia A

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

3.1.5. -

Treatment of beta-thalassemia intermedia and major

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

3.2. Finalised letters

3.2.1. -

Treatment of Gaucher disease

The finalised letter was circulated for information.

3.2.2. -

Treatment of narcolepsy

The finalised letter was circulated for information.

3.2.3. –

Treatment of Langerhans cell histiocytosis

The finalised letter was circulated for information.

3.2.4. -

Treatment of paroxysmal nocturnal haemoglobinuria

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of myasthenia gravis

The new request was noted.

3.3.2. -

Prevention of graft-versus-host disease

The new request was noted.

3.3.3. -

Treatment of mercury toxicity

The new request was noted.

4. Review of orphan designation for orphan medicinal products for marketing authorisation

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

4.1.1. Refixia - nonacog beta pegol – EMEA/OD/005/09, EU/3/09/640, EMEA/H/C/004178

Novo Nordisk A/S; Treatment of haemophilia B

COMP coordinator: Vallo Tillmann / Karri Penttilä

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

The sponsor is invited to discuss the significant benefit of the proposed product in relation to existing products with longer half-life than BeneFIX and Rixubis, namely Alprolix and Idelvion.

In this respect the sponsor should highlight any clinically relevant advantage or major contribution to patient care that can be supported by clinical data. Any advantage claimed on grounds of major contribution to patients care should be built on the demonstration of an at least comparable clinical efficacy and safety of Refixia to those of the currently authorised products.

In the written response, and during an oral explanation before the Committee on 10 April 2017, the sponsor further discussed potential advantages of Refixia in relation to the existing treatments for Haemophlia B. The discussion was mainly centred on Alprolix and Idelvion, as they have similar half-life and dosing schedule as Refixia.

Regarding efficacy, the sponsor states that 40 IU/kg Refixia provides significant benefit in adolescents and adults that are better than, or comparable to, those of Alprolix and Idelvion as demonstrated in their open and uncontrolled trials. All three long-acting products with once weekly (or even once every 10-14 days) are effective in reducing bleeding events which is highlighted in very low or median annualized bleeding rates (ABRs) (0 – 2.95) in the pivotal studies supporting the MA of these products.

Similar efficacy is relevant for a benefit/risk assessment in the context of the marketing authorisation, but demonstration of significant benefit requires that a product provides some quantifiable advantage over authorised products. In this respect, the sponsor discussed the fact that 40 IU/kg Refixia provides and maintains higher FIX activity levels

(trough levels) than those delivered by the current non-modified and extended half-life products, including Alprolix and Idelvion. The COMP questioned the clinical relevance of such levels, as the optimal target level to avoid joint bleeds has not been established, and there is no evidence from the clinical studies so far that it may lead to a better control of the disease. The results presented by the sponsor in relation to the reduction of target joint during the treatment are so far too preliminary for being considered as a demonstrated advantage over the existing long-life products. The COMP also took into account the fact that the indication of Refixia is restricted to adults and children older than 12 years due to potential safety issues related to the accumulation of PEG in tissues in preclinical studies.

Additional arguments in relation to quality of life (QoL) were also not considered sufficient, because there were no differences compared to the QoL results of the studies of Idelvion and Alprolix.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 10 April 2017, prior to final opinion.

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

Bene-Arzneimittel GmbH; Treatment of interstitial cystitis

COMP coordinator: Annie Lorence / Ingrid Wang

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

- Prevalence:

The COMP is of the view that the broader term for this condition within the current understanding in this therapeutic area is bladder pain syndrome. The sponsor is requested to further elaborate and provide a prevalence calculation for this broader condition.

- Condition:

The sponsor is invited to further elaborate on the specificity of the treatment of patients within the context of the proposed indication as defined by CHMP rather than a broader population of patients. The sponsor should submit any available data that could support that the product is only effective in the subset corresponding to BPS Type 2 and 3. Alternatively, any additional clinical data available regarding the use of this product in the broader condition should be submitted such as named patient use or compassionate use programmes.

In the written response, and during an oral explanation before the Committee on 10 April 2017, the sponsor attempted to reopen the debate on the condition, which was previously discussed by the COMP in March 2017. The COMP informed the sponsor that a re-discussion of the condition and its reclassification was not acceptable. The sponsor then discussed the specificity of pentosan polysulfate sodium in treatment of Type 2 and 3 Bladder Pain Syndrome. The discussion was focused on the specificity of the treatment of GAG deficiency. Non-clinical *in vivo* data were used as well as anecdotal evidence from publications to support the sponsor's claim that pentosan polysulfate sodium was specific for this specific subset of bladder pain syndrome. The sponsor could not clearly establish that GAG deficiency was only limited to this subset of bladder pain syndrome. The COMP could not

establish with the data submitted or the information available in the public domain if the product was indeed specific. It was noted that the product has been reported to be used off-label in patients with bladder pain syndrome Type 1. The COMP could not therefore conclude on the specificity of the product for Type 2 and 3 bladder pain syndrome and therefore could not recommend the maintenance of the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 10 April 2017, prior to final opinion.

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

4.2.1. - cenegermin - EMEA/H/C/004209, EMA/OD/143/15, EU/3/15/1586

Dompe farmaceutici s.p.a.; Treatment of neurotrophic keratitis

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 May meeting.

4.2.2. - trientine tetrahydrochloride – EMEA/H/C/004005/000, EMA/OD/001/15, EU/3/15/1471

GMP-Orphan SA; Treatment of Wilson's disease

The status of the procedure at CHMP was noted and a list of issues previously adopted by COMP will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the May meeting.

4.2.3. - inotuzumab ozogamicin – EMEA/H/C/004119, EMA/OD/194/12, EU/3/13/1127

Pfizer Limited; Treatment of B-cell acute lymphoblastic 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 May meeting.

4.2.4. - masitinib – EMEA/OD/062/04, EMEA/H/C/004159, EU/3/04/242

AB Science; Treatment of Mastocytosis

The status of the procedure at CHMP was noted.

4.2.5. Brineura - cerliponase alfa - EMA/OD/177/12, EU/3/13/1118, EMEA/H/C/004065

BioMarin International Limited; Treatment of neuronal ceroid lipofuscinosis

COMP coordinator: Armando Magrelli / Giuseppe Capovilla

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

- Condition

The COMP considered that the condition neuronal ceroid lipofuscinosis type 2 (also known as Classic Late Infantile Neuronal Ceroid Lipofuscinosis) is part of group of conditions which come under the larger condition neuronal ceroid lipofuscinosis which the COMP now considers as the Orphan Condition. The COMP would like the sponsor to amend the orphan condition therefore to neuronal ceroid lipofuscinosis.

- Prevalence

The sponsor is invited to recalculate and submit a revised prevalence for the broader orphan condition of neuronal ceroid lipofuscinosis as the current submission for neuronal ceroid lipofuscinosis Type 2 is a condition which is part of this larger condition.

The COMP concluded that:

The proposed therapeutic indication, treatment of neuronal ceroid lipofuscinosis type 2 falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of neuronal ceroid lipofuscinosis.

The prevalence of neuronal ceroid lipofuscinosis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.3 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 vision impairment and blindness, mental retardation, loss of motor control, speech impediment, behavioural problems, seizures, cerebral atrophy, parkinsonism, cardiac issues, and dementia. It is life-threatening as it leads to premature death as early as the second decade of life.

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

An opinion not recommending the removal of Brineura, recombinant human tripeptidyl-peptidase 1, Cerliponase alfa (EU/3/13/1118) 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.

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

4.3. Appeal

None

4.4. On-going procedures

None

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

None

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

None

7. Organisational, regulatory and methodological matters Mandate and organisation of the COMP

7.1. Mandate and organisation of the COMP

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

The meeting documents were circulated in MMD.

7.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 11 April 2017.

7.1.3. Preclinical Models Working Group

The working group on Preclinical Models met on 11 April 2017.

7.1.4. Conditions Steering Group

Cancelled

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. PDCO/COMP Working Group

Cancelled

7.2.2. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

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

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

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

PCWP meeting with all eligible organisations – 30 November 2016

Documents were circulated in MMD for information.

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

PCWP/HCPWP workshop on personalised medicines: role of patients, consumers and healthcare professionals – 14 March 2017

PCWP/HCPWP joint meeting - 15 March 2017

Documents were circulated in MMD for information.

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

7.6.1. EMA framework of collaboration with academia

The framework of collaboration with academia adopted by the Management Board on the 16th of March 2017 was presented by EMA. The published document on the framework and the related action plan were circulated to the COMP members after the meeting.

7.7. COMP work plan

7.7.1. COMP Work Plan 2017

Documents were circulated in MMD.

Document(s) tabled:
COMP Work Plan 2017

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 10-11 April 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	
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	
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	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
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	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
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	
Kerstin Westermark	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this 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/