7 May 2018
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Inspections, Human Medicines Pharmacovigilance and Committees

# Committee for Orphan Medicinal Products (COMP)

## Minutes for the meeting on 13-15 February 2018

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

13 February 2018, 09:00-19:15, room 2F14 February 2018, 08:30-19:00, room 2F

15 February 2018, 08:30-11:00, 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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# 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 13-15 February 2018 was adopted with no amendments.

## 1.3. Adoption of the minutes

COMP minutes for 16-18 January 2018 were adopted with no amendments and will be published on the EMA website.

# 2. Applications for orphan medicinal product designation

## 2.1. For opinion

### 2.1.1. - EMA/OD/062/17

Treatment of Dravet syndrome

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

- Medical plausibility

The sponsor is invited to discuss the relevance of the non-clinical model used for the proposed condition and justify the absence of data in other relevant models of the condition. The sponsor is also invited to justify the relevance of the effects seen in the studied models to draw conclusions for the treatment of the proposed condition.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any non-clinical or clinical study, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. A comparative discussion based on data is expected.

In the written response, and during an oral explanation before the Committee on 13 February 2018, the sponsor highlighted the relevance of the non-clinical *in vivo* models used to support the medical plausibility which the COMP accepted. The sponsor however did not submit any data with the product in the condition to support the basis of significant benefit so the COMP could not establish if this criteria was met and concluded that it could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 February 2018, prior to final opinion.

### 2.1.2. - EMA/OD/204/17

Treatment of graft-versus-host disease

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of graft-versus-host disease, the sponsor should further elaborate on:

  - the relevance of the endpoint used in the presented clinical study for the treatment of ocular manifestations of graft-versus-host disease
  - the interpretation of the results obtained in the preliminary clinical study, with regards to their extent and
  - present any other available outcomes in either relevant non-clinical models or preliminary clinical settings.

- Significant benefit

The sponsor is requested to discuss the effects of the standard of care including authorised products in the condition, and compare these results with any effects of the proposed compound in that setting.

In the written response, and during an oral explanation before the Committee on 13 February 2018, the sponsor discussed the raised issues. The clinical studies were elaborated in further detail and a preclinical model of scopolamine administration was discussed. It was argued that ocular redness is an important outcome in a variety of ocular disorders such as dry eye and keratitis, and a sign of underlying inflammation. The sponsor expected anti-inflammatory and analgesic effects based on the mechanism of action of their product.

The COMP considered that red eye score may be relevant for the medical plasubility, but that the scopolamine model was not directly relevant as it does not recapitulate a GVHD situation.

As for the significant benefit question, the applicant discussed that corticosteroid administration, alone or in combination with calcineurin inhibitors are often used in the

condition, and notes the limitations of these treatments. No comparative discussion is put forward with regards to effects on oGVHD, and the discussion deviated towards acute and chronic GVHD in general. In the absence of comparisons in oGVHD justifying a clinically relevant advantage or major contribution to patient care, the COMP considered that significant benefit may not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 February 2018, prior to final opinion.

### 2.1.3. - EMA/OD/181/17

Treatment of non-traumatic subarachnoid haemorrhage

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

- Significant benefit

The sponsor is proposing that their product offers a major contribution to patient care.

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

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

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

In the written response, and during an oral explanation before the Committee on 13 February 2018, the sponsor presented published non-clinical data to support the basis of significant benefit. The sponsor proposed better safety based on reduced alcohol content as a clinically relevant advantage as well as a major contribution to patient care based on the lack of the need for a central venous line. The COMP noted that there was no data to support either claim versus current formulations they were comparing themselves to. The COMP was of the opinion that they could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 February 2018, prior to final opinion.

### 2.1.4. Dimethyl fumarate - EMA/OD/219/17

PharmaBio Consulting; Treatment of Friedreich's ataxia

COMP coordinator: Violeta Stoyanova

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

- Medical plausibility

The sponsor reports that in a model of the proposed condition, treatment with the product results in increased frataxin levels.

The sponsor is invited to elaborate on:

- the relevance of the outcomes studied in the said model,
- the absence of functional data supporting the medical plausibility and
- present any further data available with the proposed product in relevant *in vivo* models or preliminary clinical settings.

In the written response, and during an oral explanation before the Committee on 14 February 2018, the sponsor discussed that frataxin levels were an adequate surrogate measure of the therapeutic potential of a treatment in the condition where no therapeutic options were available. The COMP discussed the limitations of this surrogate endpoint and highlighted that the nature of the data was very preliminary however that it had been accepted in earlier designations.

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

The intention to treat the condition with the medicinal product containing dimethyl fumarate was considered justified based on an increase of frataxin levels in non-clinical models of the condition.

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

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

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

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

### 2.1.5. - EMA/OD/211/17

Treatment of pancreatic cancer

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

- Intention to diagnose, prevent or treat

Medical plausibility is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of pancreatic cancer, the sponsor should further elaborate on:

1) the very limited nature of the preliminary clinical data and how this can support the feasibility of the potential of using this product in this condition,
2) the Sponsor should provide a discussion with the relevant data in the condition only,
3) provide supportive evidence that the product does not have any clinically relevant activity outside of the neurotrophic tyrosine receptor kinase subset,

4) clarify if the activity of the product has been investigated in valid non-clinical xenograft models without neurotrophic tyrosine receptor kinase fusion.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

Significant benefit is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims.

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

The sponsor should detail the results of any additional clinical data 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 14 February 2018, the sponsor informed the COMP that there was no additional data in patients in their on-going clinical trial work in the condition. The COMP considered that the preliminary clinical data continued to be very limited making it difficult to establish significant benefit. The COMP was of the opinion that it could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2018, prior to final opinion.

### 2.1.6. Larotrectinib - EMA/OD/213/17

Loxo Oncology Limited; Treatment of salivary gland cancer

COMP coordinator: Bożenna Dembowska-Bagińska

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

- Intention to diagnose, prevent or treat

Medical plausibility is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of salivary gland cancer, the sponsor should further elaborate on:

1) the very limited nature of the preliminary clinical data and how this can support the feasibility of the potential of using this product in this condition,

2) the Sponsor should provide a discussion with the relevant data in the condition only,

3) provide supportive evidence that the product does not have any clinically relevant activity outside of the neurotrophic tyrosine receptor kinase subset,

4) clarify if the activity of the product has been investigated in valid non-clinical xenograft models without neurotrophic tyrosine receptor kinase fusion.

In the written response, and during an oral explanation before the Committee on 14 February 2018, the sponsor presented additional clinical data with the product in the condition supporting the preliminary findings in the initial submission.

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

The intention to treat the condition with the medicinal product containing larotrectinib was considered justified based on preliminary clinical data showing partial and complete response in patients with the condition.

The condition is life-threatening due to neoplasms with high-risk features which tend to have an aggressive clinical course and 5-year survival rates ranging from 30% to 40%.

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

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

A positive opinion for larotrectinib, for treatment of salivary gland cancer, was adopted by consensus.

### 2.1.7. - EMA/OD/209/17

Treatment of biliary tract cancer

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

- Intention to diagnose, prevent or treat

Medical plausibility is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of biliary tract cancer, the sponsor should further elaborate on:

1) the very limited nature of the preliminary clinical data and how this can support the feasibility of the potential of using this product in this condition,
2) the Sponsor should provide a discussion with the relevant data in the condition only,
3) provide supportive evidence that the product does not have any clinically relevant activity outside of the neurotrophic tyrosine receptor kinase subset,
4) clarify if the activity of the product has been investigated in valid non-clinical xenograft models without neurotrophic tyrosine receptor kinase fusion.

In the written response, and during an oral explanation before the Committee on 14 February 2018, the sponsor did not present any additional clinical data from their on-going clinical trial programme to support the basis of the medical plausibility. As the preliminary clinical data submitted was considered insufficient the COMP was therefore of the opinion that they could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2018, prior to final opinion.

## 2.1.8. - EMA/OD/212/17

Treatment of papillary thyroid cancer

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

- Intention to diagnose, prevent or treat

Medical plausibility is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of papillary thyroid cancer, the sponsor should further elaborate on:

1) the very limited nature of the preliminary clinical data and how this can support the feasibility of the potential of using this product in this condition,
2) the Sponsor should provide a discussion with the relevant data in the condition only,
3) provide supportive evidence that the product does not have any clinically relevant activity outside of the neurotrophic tyrosine receptor kinase subset,
4) clarify if the activity of the product has been investigated in a valid non-clinical xenograft models without neurotrophic tyrosine receptor kinase fusion.

- Number of people affected

The sponsor has based their prevalence calculation on a partial prevalence of 5yr survival data. As these patients survive well at 10 years the sponsor should consider a full point prevalence calculation.

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

Significant benefit is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims.

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

The sponsor should detail the results of any additional clinical data 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 14 February 2018, the sponsor presented a prevalence calculation which was considered to adequately represent the current situation in Europe. They however did not present any

additional clinical data from their on-going clinical trial programme to support the basis of the medical plausibility. The Committee continued to be of the opinion that the initial data submitted were considered too limited to establish either criteria.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2018, prior to final opinion.

### 2.1.9. - EMA/OD/210/17

Treatment of NTRK-fusion non-small-cell lung cancer

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

- Intention to diagnose, prevent or treat

NTRK-Fusion non-small cell lung cancer should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00). Subsets of common conditions are only accepted as an exception and when specific criteria are confirmed with relevant data. The sponsor should discuss the data to support valid subsetting:

1) discuss the stability of neurotrophic tyrosine receptor kinase fusion in the pathogenesis of non-small-cell lung cancer and the definition of a distinct subset,
2) clarify and discuss the identification and diagnostic criteria of neurotrophic tyrosine receptor kinase fusion events in non-small-cell lung cancer patients,
3) provide supportive evidence that the product does not have any clinically relevant activity outside of the neurotrophic tyrosine receptor kinase subset in lung cancer, including a discussion on the lung cancer patients who were classed as negative for neurotrophic tyrosine receptor kinase fusion,
4) clarify if the activity of the product has been investigated in a valid non-clinical xenograft lung model without neurotrophic tyrosine receptor kinase fusion.

Medical plausibility is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of NTRK-fusion non-small-cell lung cancer, the sponsor should further elaborate on:

1) the very limited nature of the preliminary clinical data and how this can support the feasibility of the potential of using this product in this condition,
2) the Sponsor should provide a discussion with the relevant data in the condition only.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

Significant benefit is based on limited data in the condition to be designated, with evidence from other tumour types used to substantiate claims.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the very preliminary clinical data submitted to justify

the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor should detail the results of any additional clinical data 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 14 February 2018, the sponsor discussed the distinct characteristics of the neurotrophic tyrosine receptor kinase fusion protein non-small-cell lung cancer. The COMP noted that the expression of this protein was variable and heterogeneous across many different solid tumours and that more data was needed to establish the uniqueness of the marker to this particular cancer. The COMP acknowledged the stability of the marker but noted also that resistance has been noted to develop over time to the marker. This coupled with the heterogeneity of its expression across different tumour types led the COMP to conclude that this was a subset of non-small-cell lung cancer and not a distinct medical entity. The COMP was of the opinion that it could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2018, prior to final opinion.

### 2.1.10. Patidegib - EMA/OD/206/17

Blue-Reg Europe; Treatment of naevoid basal cell carcinoma syndrome (Gorlin syndrome)

COMP coordinator: 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:

- 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 naevoid basal-cell carcinoma syndrome (Gorlin syndrome), the sponsor, with regard to the clinical study described in the application, should further:

  - Elaborate on the choice of the unit of analysis.
  - Explain the apparent response of tumours to vehicle control compared to oral placebo.

- Significant benefit

The sponsor argues significant benefit against photodynamic therapy, imiquimod, sonidegib and vismodegib on the basis of improved safety and as a major contribution to patient care. With regard to major contribution to patient care, no data driven discussion is provided. With regard to safety, it is well known that extrapolation from early clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data is required to justify safety arguments in most cases.

The sponsor should clearly position the product within current treatment algorithms of naevoid basal-cell carcinoma syndrome and identify a subgroup of patients where data driven significant benefit against currently authorised treatment modalities can be demonstrated.

In the written response, and during an oral explanation before the Committee on 13 February 2018, the sponsor highlighted the deficiencies with current treatments and how the topical application of the sponsor's product offers a clinically relevant advantage due to the better observed efficacy and safety versus authorised products. The COMP acknowledged that this could be understood to be a clinically relevant advantage which would support a basis of significant benefit.

The Committee agreed that the condition, naevoid basal-cell carcinoma syndrome (Gorlin syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing patidegib was considered justified based on preliminary clinical data which showed a regression of existing basal-cell carcinomas and reduction in the number of new tumours.

The condition is chronically debilitating due to the occurrence of multiple basal-cell carcinomas of the skin, potentially invading vital tissues and leading to different types of deformities.

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 for treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing patidegib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical evidence that demonstrate reduction in the number of new basal-cell carcinomas in patients with Gorlin syndrome. The product's topical administration may allow the treatment of Gorlin syndrome patients who require lifelong management of basal-cell carcinomas and cannot tolerate other authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for patidegib, for treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome), was adopted by consensus.

### 2.1.11. Tazemetostat - EMA/OD/222/17

Quintiles Ireland Limited; Treatment of follicular lymphoma

COMP coordinator: Brigitte Bloechl-Daum

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

- Significant benefit

The sponsor is requested to provide specific data on significant benefit versus obinutuzumab, pixantrone, idelalisib, and ibritumomab. This should be addressed by adequate indirect comparisons and more details on the patient population from the clinical trials regarding previous treatments and their treatment responses to tazemetostat.

In the written response, and during an oral explanation before the Committee on 14 February 2018, the sponsor presented evidence confirming that some patients relapsed after treatment with authorised products and that the outcomes compared favourably with data from authorised products. Hence, COMP concluded that the assumption of a clinically relevant advantage due to an improved efficacy was sufficiently supported for orphan designation.

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

The intention to treat the condition with the medicinal product containing tazemetostat was considered justified based on preliminary clinical data showing that patients respond to treatment.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma.

The condition was estimated to be affecting approximately 3.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tazemetostat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that patients responded to treatment and indirect comparisons were favourable to authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tazemetostat, for treatment of follicular lymphoma, was adopted by consensus.

## 2.1.12. - EMA/OD/216/17

Treatment of soft tissue sarcoma

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

- Significant benefit

The sponsor is requested to provide specific data on significant benefit versus all authorised products in the first line and refractory patient population. In the refractory patient population of specific interest are dacarzabine and olaratumab. This should be addressed by adequate indirect comparisons and more details on the patient population from the clinical trials regarding previous treatments and their treatment responses to the proposed product.

In the written response, and during an oral explanation before the Committee on 14 February 2018, the sponsor presented evidence confirmed that some patients relapsed after treatment with authorised products, but not all authorised products were used. Moreover, the preliminary outcomes did not compare favourably with data from authorised products. Hence, COMP concluded that the assumption of a clinically relevant advantage due to an improved efficacy was not sufficiently supported for orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2018, prior to final opinion.

## 2.1.13. Tazemetostat - EMA/OD/217/17

Quintiles Ireland Limited; Treatment of diffuse large B-cell lymphoma

COMP coordinator: Brigitte Bloechl-Daum

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

- Significant benefit

The sponsor is requested to provide specific data on significant benefit versus pixantrone. This should be addressed by adequate indirect comparisons and more details on the patient population from the clinical trials regarding previous treatments and their treatment responses to tazemetostat.

In the written response, and during an oral explanation before the Committee on 14 February 2018, the sponsor presented evidence which confirmed that some patients relapsed after treatment with authorised products and that the outcomes compared favourably with data from authorised products. Hence, COMP concluded that the assumption of a clinically relevant advantage due to an improved efficacy was sufficiently supported for orphan designation.

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

The intention to treat the condition with the medicinal product containing tazemetostat was considered justified based on preliminary clinical data showing that patients respond to treatment.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tazemetostat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that patients responded to treatment and indirect comparisons were favourable to authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tazemetostat, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

### 2.1.14. (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/208/17

FGK Representative Service GmbH; Treatment of C3 glomerulopathy

COMP coordinator: Martin Možina

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

- Number of people affected

The sponsor has based their prevalence calculation on a limited literature search which appears to have led to an under-estimate of the potential prevalence of the condition.

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

In the written response, the sponsor provided an updated prevalence calculation which the COMP was of the opinion more adequately reflected the current prevalence of the condition in Europe.

The Committee agreed that the condition, C3 glomerulopathy, 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 showing improvements in proteinuria.

The condition is life-threatening and chronically debilitating due to the development of nephrotic syndrome and end-stage kidney disease leading to renal failure.

The condition was estimated to be affecting approximately 1.1 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 (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 C3 glomerulopathy, was adopted by consensus.

### 2.1.15. Ivosidenib - EMA/OD/172/17

QRC Consultants Ltd; Treatment of biliary tract cancer

COMP coordinator: 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:

- Number of people affected

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

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

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

In the written response, the sponsor provided an updated prevalence calculation which the COMP felt was a more accurate reflection of the prevalence in Europe.

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

The intention to treat the condition with the medicinal product containing ivosidenib was considered justified based on preliminary clinical observations in relapsed/refractory patients, who responded to treatment with the product as a monotherapy.

The condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6 and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction.

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.

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 ivosidenib, for treatment of biliary tract cancer, was adopted by consensus.

## 2.2. For discussion / preparation for an opinion

### 2.2.1. - EMA/OD/246/17

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 March meeting.

### 2.2.2. - EMA/OD/081/17

Treatment of intestinal failure-associated liver 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 March meeting.

### 2.2.3. Docosahexaenoic acid ethyl ester - EMA/OD/235/17

TurnKey PharmaConsulting Ireland Limited; Treatment of sickle cell disease

COMP coordinator: Irena Rogovska

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

The intention to treat the condition with the medicinal product containing docosahexaenoic acid ethyl ester was considered justified based on preliminary clinical data showing a reduction in the rate of vaso-occlusive crises in patients treated with the product compared to placebo.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing docosahexaenoic acid ethyl ester will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data supporting the use of the product in combination with hydroxycarbamide which is authorised for the condition by further reducing the rate of vaso-occlusive crises. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for docosahexaenoic acid ethyl ester, for treatment of sickle cell disease, was adopted by consensus.

### 2.2.4. Efgartigimod alfa - EMA/OD/245/17

argenx BVBA; Treatment of myasthenia gravis

COMP coordinator: Robert Nistico

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

The intention to treat the condition with the medicinal product containing efgartigimod alfa was considered justified based on non-clinical and on preliminary clinical data showing improvement of relevant functional endpoints and symptoms scores.

The condition is life-threatening and chronically debilitating due to recurrent crisis characterised by muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing. Crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing efgartigimod alfa will be of significant benefit to those affected by the condition. The sponsor has provided clinical data showing improvement of clinical scores and quality of life on top of standard of care with the proposed product. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for efgartigimod alfa, for treatment of myasthenia gravis, was adopted by consensus.

### 2.2.5. - EMA/OD/233/17

Treatment of snakebite envenomation

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 March meeting.

### 2.2.6. Gemfibrozil - EMA/OD/218/17

Quintiles Ireland Limited; Treatment of neuronal ceroid lipofuscinosis

COMP coordinator: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing gemfibrozil was considered justified based on improved survival and locomotor activity in a valid non-clinical model.

The condition is life-threatening and chronically debilitating due to visual, cognitive, and motor skills decline, speech impediment, behavioural problems, seizures and cerebral atrophy which lead to early death.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing gemfibrozil will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate significant improvement in survival and locomotor performance in a valid mouse model of the disease. The favourable route of administration compared with authorised products for the condition may allow the treatment of patients who cannot tolerate other authorised products or for whom other authorised products are contraindicated. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for gemfibrozil, for treatment of neuronal ceroid lipofuscinosis, was adopted by consensus.

### 2.2.7. - EMA/OD/244/17

Treatment of Epidermolysis Bullosa

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

### 2.2.8. - EMA/OD/194/17

Treatment of adrenal insufficiency

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 March meeting.

### 2.2.9. - EMA/OD/214/17

Treatment of polycythemia vera

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 March meeting.

### 2.2.10. - EMA/OD/247/17

Treatment of Guillain-Barré 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 March meeting.

### 2.2.11. - EMA/OD/237/17

Treatment of anaplastic thyroid 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 March meeting.

### 2.2.12. - EMA/OD/238/17

Treatment of follicular thyroid 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 March meeting.

### 2.2.13. - EMA/OD/187/17

Treatment of ornithine transcarbamylase deficiency (OTC)

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 March meeting.

### 2.2.14. - EMA/OD/065/17

Treatment of Dravet 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 March meeting.

### 2.2.15. Melatonin - EMA/OD/227/17

Therapicon Srl; Treatment of neonatal encephalopathy

COMP coordinator: Giuseppe Capovilla

Following review of the application by the Committee, it was agreed to rename the indication to treatment of neonatal encephalopathy.

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

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on literature data in affected patients supporting improved survival in combination with therapeutic hypothermia.

The condition is life-threatening and chronically debilitating due to long lasting neurological and developmental sequelae.

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 melatonin, for treatment of neonatal encephalopathy, was adopted by consensus.

### 2.2.16. Miransertib - EMA/OD/226/17

QRC Consultants Ltd; Treatment of Proteus Syndrome

COMP coordinator: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing miransertib was considered justified based on non-clinical and preliminary clinical observations supporting improvements in the size of cutaneous lesions in treated patients affected by the condition.

The condition is life-threatening and chronically debilitating in particular due to orthopaedic deformities, restrictive lung disease associated with profound scoliosis, cardiac, renal, pulmonary, gastrointestinal, and other parenchymal manifestations which can be fatal.

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 in the European Union for patients affected by the condition.

A positive opinion for miransertib, for treatment of Proteus syndrome, was adopted by consensus.

### 2.2.17. - EMA/OD/231/17

Treatment of diffuse large B-cell lymphoma

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 March meeting.

### 2.2.18. Recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA - EMA/OD/232/17

uniQure biopharma B.V.; Treatment of haemophilia B

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, haemophilia B, 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 containing a codon-optimized Padua derivative of human coagulation factor IX cDNA was considered justified based on non-clinical data in valid models of the condition showing significant improvement of circulating FIX protein levels, and of FIX activity levels.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury.

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 recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA will be of significant benefit to those affected by the condition. The product has a mechanism of action that offers the potential to reduce or eliminate the use of exogenous factor IX products currently authorised for the condition, and the sponsor has provided non-clinical data that demonstrate significant improvement of circulating FIX protein and activity levels in valid models of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA, for treatment of haemophilia B, was adopted by consensus.

### 2.2.19. Recombinant human acid alpha-glucosidase - EMA/OD/230/17

Amicus Therapeutics UK Ltd; Treatment of glycogen storage disease type II (Pompe's disease)

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, glycogen storage disease type II (Pompe's disease), 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 acid alpha-glucosidase when used in combination with miglustat was considered justified based on non-clinical data in a valid *in-vivo* model of the condition showing improved muscle function as well as preliminary clinical data showing improvement of motor function in patients with the condition.

The condition is life-threatening and chronically debilitating due to accumulation of glycogen in muscle and nerve cells leading to progressive skeletal myopathy, cardiomyopathy, and respiratory insufficiency, leading to death within two years of birth in the infantile forms, and in the fourth decade of life in forms with later onset.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human acid alpha-glucosidase when used in

combination with miglustat will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid model of the condition showing better responses on muscle function compared to Myozyme, currently authorised for the condition. In addition to that, the sponsor has provided preliminary clinical data indicating improvement in motor function in patients treated with the product used in combination with miglustat after switching from the currently authorised enzyme replacement therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human acid alpha-glucosidase, for treatment of glycogen storage disease type II (Pompe's disease), was adopted by consensus.

### 2.2.20. Ribavirin - EMA/OD/224/17

Pharmadev Healthcare Ltd; Treatment of Crimean-Congo haemorrhagic fever

COMP coordinator: Olimpia Neagu

The Committee agreed that the condition, Crimean-Congo haemorrhagic fever, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing ribavirin was considered justified based on preliminary clinical data showing that treatment reduced mortality in patients affected by the condition.

The condition is life-threatening with a case fatality ratio average of 13%; and chronically debilitating due to high fever, muscle pain, dizziness, photophobia, abdominal pain, diarrhoea, vomiting and, in severe cases, haemorrhage.

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 in the European Union for patients affected by the condition.

A positive opinion for ribavirin, for treatment of Crimean-Congo haemorrhagic fever, was adopted by consensus.

### 2.2.21. Ribavirin - EMA/OD/225/17

Pharmadev Healthcare Ltd; Treatment of Lassa fever

COMP coordinator: Nikolaos Sypsas

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

The intention to treat the condition with the medicinal product containing ribavirin was considered justified based on preliminary clinical data showing that treatment reduced mortality in patients affected by the condition.

The condition is life-threatening with overall case-fatality rate of 1%-2% increasing up to 50%-60% during outbreaks. The condition is also chronically debilitating due to abnormal bleeding, persistent low systolic blood pressure, persistent vomiting, diarrhoea, oedema, pleural effusion, ascites, renal failure, and neurological signs such as confusion and seizures.

The condition was estimated to be affecting less than 0.001 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 ribavirin, for treatment of Lassa fever, was adopted by consensus.

### 2.2.22. Recombinant Modified Ricin Toxin A-chain Subunit - EMA/OD/242/17

Soligenix UK Ltd.; Prevention of ricin poisoning

COMP coordinator: Martin Možina

Following review of the application by the Committee, it was agreed to rename the active substance to Recombinant modified ricin toxin A-chain subunit.

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

The intention to prevent the condition with the medicinal product containing recombinant modified ricin toxin A-chain subunit was considered justified based on non-clinical data showing improved survival with the proposed product in valid models of the condition.

The condition is life-threatening and chronically debilitating due to rapid development of multi-organ failure and shock, usually leading to death in a few days.

The population of patients eligible for prevention of the condition was estimated to be approximately less than 0.001 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 prevention in the European Union for the population at risk of developing the condition.

A positive opinion for recombinant modified ricin toxin A-chain subunit, for prevention of ricin poisoning, was adopted by consensus.

### 2.2.23. - EMA/OD/228/17

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 March meeting.

### 2.2.24. Tazemetostat - EMA/OD/234/17

Quintiles Ireland Limited; Treatment of malignant mesothelioma

COMP coordinator: Ingrid Wang

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

The intention to treat the condition with the medicinal product containing tazemetostat was considered justified based on nonclinical data in valid models and preliminary clinical data

demonstrating that patients affected by the condition did not progress after treatment with the proposed product.

The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise ("incarceration" of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tazemetostat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that patients affected by the condition did not progress after treatment with the proposed product. Patients were relapsed or refractory after treatment with best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tazemetostat, for treatment of malignant mesothelioma, was adopted by consensus.

## 2.3. Revision of the COMP opinions

None

## 2.4. Amendment of existing orphan designations

None

## 2.5. Appeal

### 2.5.1. Melatonin - EMA/OD/127/17

Therapicon Srl; Treatment of subarachnoid haemorrhage

Oral explanation took place on 13 February 2018. Adoption of the opinion is expected at the March 2018 COMP meeting.

## 2.6. Nominations

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

COMP coordinators were appointed for 18 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 Niemann-Pick disease, type C

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 mucopolysaccharidosis type I

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 glioma

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

### 3.1.4. -

Treatment of paroxysmal nocturnal haemoglobinuria

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 primary biliary cholangitis

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 primary focal segmental glomerulosclerosis

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 adenosine deaminase-deficient-severe combined immunodeficiency

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

### 3.1.8. -

Treatment of acute hepatic porphyria

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

### 3.1.9. -

Treatment of adrenoleukodystrophy

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 acute myeloid leukaemia

The finalised letter was circulated for information.

### 3.2.2. -

TKI inhibitor for treatment of gastrointestinal stromal tumors

The finalised letter was circulated for information.

### 3.2.3. -

Treatment of cutaneous T-cell lymphoma

The finalised letter was circulated for information.

### 3.2.4. -

Treatment of diffuse large B-cell lymphoma

The finalised letter was circulated for information.

### 3.2.5. -

Treatment of multiple myeloma

The finalised letter was circulated for information.

### 3.2.6. -

Treatment of multiple myeloma

The finalised letter was circulated for information.

## 3.3. New requests

### 3.3.1. -

Treatment of eosinophilic oesophagitis

The new request was noted.

### 3.3.2. -

Treatment of gastrointestinal stromal tumours

The new request was noted.

### 3.3.3. -

Treatment of pulmonary arterial hypertension

The new request was noted.

### 3.3.4. -

Treatment of partial deep dermal and full thickness burns

The new request was noted.

### 3.3.5. -

Treatment of amyotrophic lateral sclerosis

The new request was noted.

### 3.3.6. -

Treatment of sickle cell disease

The new request was noted.

### 3.3.7. -

Treatment of soft tissue sarcoma

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. Mylotarg - gemtuzumab ozogamicin – EMEA/H/C/004204, EMEA/OD/022/00, EU/3/00/005

Pfizer Limited; Treatment of acute myeloid leukaemia (AML)

The Committee adopted an opinion not to remove Mylotarg from the EC Register of Orphan Medicinal Products 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 February meeting and upon adoption of CHMP opinion.*]

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

Clovis Oncology UK Ltd; Treatment of ovarian cancer

The status of the procedure at CHMP was noted.

[*Post-meeting note: The sponsor will be invited to an oral explanation before the Committee at the March 2018 meeting.*]

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

Ammtek; Treatment of neonatal diabetes

The Committee adopted an opinion not to remove Amglidia from the EC Register of Orphan Medicinal Products 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 February meeting and upon adoption of CHMP opinion.*]

## 4.3. Appeal

None

## 4.4. On-going procedures

**Action**: For information

Document(s) tabled:

Review of orphan designation for OMP for MA - On-going procedures

## 4.5. Orphan Maintenance Reports

**Action**: For information

Document(s) tabled:

# 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. Venclyxto – Venetoclax – Type II variation – EMEA/H/C/004106/II/0008, EMA/OD/124/12, EU/3/12/1080

AbbVie Limited; Treatment of chronic lymphocytic leukaemia

CHMP rapporteur: Filip Josephson

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

### 5.2.2. Lynparza - Olaparib – Type II variation – EMEA/H/C/003726/X/0016/G, EMEA/OD/063/07, EU/3/07/501

AstraZeneca AB; Treatment of ovarian cancer

CHMP rapporteur: Alexandre Moreau; CHMP co-rapporteur: Bart Van der Schueren;

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 March 2018 meeting.

### 5.2.3. 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 at the March 2018 meeting.

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

Document(s) tabled:
Invitation COMP Strategic Review and Learning Meeting 26-28 March 2018

### 7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 13 February 2018.

### 7.1.3. Non-Clinical Working Group

The meeting was postponed to March 2018.

### 7.1.4. Condition Working Group

The working group on Condition met on 14 February 2018.

### 7.1.5. Prevalence Working Group

The working group on Prevalence met on 14 February 2018.

## 7.2. Coordination with EMA Scientific Committees or CMDh-v

### 7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

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

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

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

None

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

None

## 7.4. Cooperation within the EU regulatory network

### 7.4.1. European Commission

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

None

## 7.8. Planning and reporting

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

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

### 7.8.2. Overview of orphan marketing authorisations/applications

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

## 8. Any other business

### 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)

**Action**: For information

## 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/

## List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 13-15 February 2018 meeting.

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Bruno Sepodes | Chair | Expert recommended by EMA | No interests declared | |
| Brigitte Blöchl-Daum | Member | Austria | No interests declared | |
| Tim Leest | Member | Belgium | No interests declared | |
| Lyubina Racheva Todorova | Member | Bulgaria | No interests declared | |
| Dinko Vitezic | Member | Croatia | No restrictions applicable to this meeting | |
| Ioannis Kkolos | Member | Cyprus | No interests declared | |
| Katerina Kopeckova | Member - via telephone* | Czech Republic | No restrictions applicable to this meeting | |
| Elisabeth Penninga | Member | Denmark | No interests declared | |
| Vallo Tillmann | Member | Estonia | No interests declared | |
| Karri Penttilä | Member | Finland | No interests declared | |
| 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 | |

| 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 | |
| Martin Mozina | Member | Slovenia | No interests declared | |
| Fernando Mendez Hermida | Member | Spain | No interests declared | |
| Darius Matusevicius | Member | Sweden | No restrictions applicable to this meeting | |
| Daniel O'Connor | Member | United Kingdom | No interests declared | |
| Pauline Evers | Member | Patients' Organisation Representative | No interests declared | |
| Mario Ricciardi | Member | Patients' Organisation Representative | No interests declared | |
| Kerstin Westermark | Member | Expert recommended by EMA | No restrictions applicable to this meeting | |
| Ingeborg Barisic | Member | Expert recommended by EMA | No restrictions applicable to this meeting | |
| Giuseppe Capovilla | Member | Expert recommended by EMA | No interests declared | |
| Virginie Hivert | Expert - in person* | | No restrictions applicable to this meeting | |
| Julian Isla | Expert - in person* | | No restrictions applicable to this meeting | |
| Gabe Sonke | Expert witness - via telephone* | | | 2.1.9. |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| A representative from the European Commission attended the meeting | | | | |
| Meeting run with support from relevant EMA staff | | | | |

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