14 November 2016
EMA/COMP/653816/2016
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 04-06 October 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

04 October 2016, 09:00-19:20, room 2F

05 October 2016, 08:30-20:00, room 2F

06 October 2016, 08:30-15:00, room 2F

Disclaimers

Some of the information contained in these minutes are 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, these minutes are 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 these 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. 22 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 4-6 October 2016 was adopted with amendments.

1.3. Adoption of the minutes

COMP minutes for 6-8 September 2016 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/137/16

Treatment of opioid poisoning

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

Name of the condition should be justified as a distinct medical entity or a valid subset. It would appear that the proposed condition is a degree of toxicity associated with opioid use. It should also be noted that the Diagnostic and Statistical Manual of Mental Disorders DSM-V describes a medical condition which is called *Opioid Addition*. The sponsor should further elaborate on why they think their condition is different from this condition. The sponsor's

attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

The sponsor has provided a limited source of data for what appears to be a subset of the condition.

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".

As it seems that the sponsor has excluded part of the population affected by the condition.

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

- Significant benefit

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

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.

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 4 October 2016, the sponsor discussed the proposed condition in the context of DSM-V, and also referred to classifications and definitions used in other sources such as ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Network) and the American College of Preventive Medicine. The applicant compared and contrasted terms such as abuse, misuse (non-compliant use), addiction and poisoning. It was argued that the sought indication cannot be summarised under the term of 'opioid addiction' alone. The applicant also elaborated on the calculation of prevalence and provided a sensitivity analysis by varying the assumed number of opioid deaths and the ratio of fatal to non-fatal overdoses. Significant benefit was also further elaborated on the basis of limitations of the current formulations available for the treatment of the proposed condition, as well as pharmacokinetic comparisons.

The COMP considered that in the absence of a clear definition of the condition, the prevalence calculation is also uncertain, while the sponsor has not presented any data to justify a clinically relevant advantage or major contribution to patient care with their proposed product. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 October 2016, prior to final opinion.

2.1.2. Live attenuated non replicative Pseudomonas aeruginosa strain expressing large T antigen of Merkel cell polyomavirus - EMA/OD/160/16

APCure SAS; Treatment of Merkel cell carcinoma

COMP coordinator: Daniel O'Connor

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to 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 Merkel cell carcinoma, the sponsor should further elaborate on:

– the relevance of the preclinical model used for the treatment of Merkel cell carcinoma, and the interpretation of the results obtained in the experiments;

– the availability of valid preclinical xenograft models with human MCC cell lines, and a justification why such models have not been used to test the product;

– the results of the preclinical study in the treatment setting, and if the results were statistically significant.

In the written response, the sponsor outlined that the direct target of the proposed product is the antigen presenting cell leading to the activation of the immune system against the LT oncogene. Therefore, in order to test the proposed product the preclinical model requires the presence of a functional immune system. Currently, xenograft models exist with human merkel cell carcinoma cell lines; however all models are established with an immunodeficient background. The COMP acknowledged that the current preclinical xenograft models could not have been used to test the proposed product. In the absence of adequate syngeneic models, the COMP accepted the validity of the preclinical model to test the proposed product.

The sponsor also presented the statistical methodology of the results obtained with the preclinical model and confirmed that the treatment-related decrease in tumour volume was statistically significant. In conclusion, the COMP was of the opinion that there was sufficient preclinical evidence to support the assumption of medical plausibility for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing live-attenuated non-replicative Pseudomonas aeruginosa strain expressing large T antigen of Merkel cell polyomavirus was considered justified based on preclinical data demonstrating that treatment can reduce tumour volume.

The condition is chronically debilitating and life-threatening with median survival of about a year reported in patients with advanced disease state.

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

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

A positive opinion for live-attenuated non-replicative *Pseudomonas aeruginosa* strain expressing large T antigen of Merkel cell polyomavirus, for treatment of Merkel cell carcinoma, was adopted by consensus.

2.1.3. Synthetic human hepcidin - EMA/OD/144/16

EMAS Pharma Limited; Treatment of sickle cell disease

COMP coordinator: Karri Penttila/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:

- 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 sickle cell disease, the sponsor should further elaborate on the clinical relevance of the surrogate endpoints as iron overload is often a secondary complication in this condition. Pain, acute chestpain syndrome and aseptic vascular crisis are more important and more common.

- 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 should further elaborate on additional details from results of the clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients. The sponsor is invited to further elaborate on additional characteristics of their product which could be disease modifying.

In the written response, and during an oral explanation before the Committee on 6 October 2016, the sponsor discussed the relevance of the endpoint used in the clinical studies. It was stressed that the product can potentially improve the major clinical consequences of sickle cell disease via its ability to lower transferrin saturation. The latter results in a reduced mean corpuscular haemoglobin concentration per red blood cell, eventually leading to smaller and longer-living cells, and reduced sickling. Thus fewer disease complications are expected such as acute chest syndrome, bone pain, and vaso-occlusive crisis pain.

As regards the significant benefit justification, the sponsor argued that the initial clinical observations were in iron-overloaded SCD patients who were no longer responding to or who can no longer tolerate their chelation therapy.

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 synthetic human hepcidin was considered justified based on preliminary clinical data which shows an improvement in iron surrogate end-points relevant to the condition.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic human hepcidin may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data supporting the potential use of the proposed product in reducing iron overload associated with currently the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by sickle cell disease.

A positive opinion for synthetic human hepcidin, for treatment of sickle cell disease, was adopted by consensus.

2.1.4. Allogeneic peripheral blood mononuclear cells (CD34+) incubated ex vivo with 16, 16-dimethyl prostaglandin E2 and dexamethasone - EMA/OD/149/16

Fate Therapeutics Ltd; Treatment in haematopoietic stem cell transplantation

COMP coordinator: Frauke Naumann-Winter

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

- Intention to diagnose, prevent or treat

The sponsor is invited to clarify whether the product contains sufficient CD34+ cells to allow multilineage reconstitution or whether is supposed to be used as donor cellular infusion.

According to the “guideline on the format and content”, data with the proposed product in the proposed condition are required.

It appears that only in vitro data are available with the proposed product and that in the other experiments, different stem cell sources or different protocols were used for programming the cells. Therefore the sponsor is invited to further justify the absence of in vivo data with the proposed product in the initially proposed condition.

- Significant benefit

In the proposed condition significant benefit needs to be demonstrated over authorised products.

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. However, no data are provided in relation to authorised products.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical or clinical studies to justify the assumption of significant benefit in relation to authorised medicinal products.

Furthermore, it would be useful to obtain more information on the planned clinical development for this product as this will help understand the target therapeutic indication the sponsor is working towards. This will help the COMP assess which orphan indication and significant benefit considerations best fit this product.

In the written response and during an oral explanation, the sponsor elaborated on the issues raised. The COMP was of the opinion that the sought condition should be amended to “haematopoietic stem cell transplantation”, based on the use of the proposed product as the graft for transplantation and its proposed mechanism of action. The sponsor agreed with this opinion.

Regarding the medical plausibility, the sponsor presented further detail on the in vivo preclinical data obtained from graft versus host disease models. The COMP recognised the validity of the models for the updated condition and acknowledged the treatment-related improvements in acute graft-versus-host disease scores, engraftment and survival. Regarding significant benefit, the COMP considered that the proposed type of graft could improve the outcome of patients undergoing transplantation while receiving the current best standard of care including authorised products. This assumption was supported by the provided preclinical data demonstrating that the treatment with the product can improve acute graft-versus-host disease scores, engraftment and survival in valid preclinical models of the condition.

The COMP also considered previous designations for this condition to estimate the prevalence for the amended condition. The estimate was based on yearly incidence as reported by the European Society for Blood and Marrow Transplantation.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment in haematopoietic stem cell transplantation and to broaden/rename the active substance to allogeneic peripheral blood mononuclear cells (CD34+) incubated ex vivo with 16, 16-dimethyl prostaglandin E2 and dexamethasone.

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

The intention to treat the condition with the medicinal product containing allogeneic peripheral blood mononuclear cells (CD34+) incubated ex vivo with 16, 16-dimethyl prostaglandin E2 and dexamethasone was considered justified based on data demonstrating improvements in acute graft-versus-host disease scores, engraftment and improved survival in valid preclinical models of the condition.

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

The condition was estimated to be occurring in approximately 1 in 10,000 persons per year 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 allogeneic peripheral blood mononuclear cells (CD34+) ex vivo incubated with 16, 16-dimethyl prostaglandin E2 and dexamethasone will be of significant benefit to those affected by the condition. The mechanism of action is in support of the assumption that the proposed type of graft could improve the outcome of patients undergoing transplantation while receiving the current best standard of care including authorised products. This is further supported by preclinical data demonstrating that the treatment with the proposed product can improve acute graft-versus-host disease scores, engraftment and survival in a valid preclinical model of the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic peripheral blood mononuclear cells (CD34+) incubated ex vivo with 16, 16-dimethyl prostaglandin E2 and dexamethasone, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.5. - EMA/OD/145/16

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:

- Intention to diagnose, prevent or treat

The sponsor presented data from preclinical studies demonstrating tumour growth reduction in a heterotopic model of glioma. No data in an orthotopic model of glioma was presented and no comparison to authorised products was done.

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

– the results obtained in preclinical studies using a heterotopic model of glioma;

– the relevance of the preclinical model used for the treatment of glioma, and the interpretation of the results obtained in the experiments;

– any future plans of preclinical studies using the proposed product.

- Number of people affected

The sponsor proposed a prevalence calculation based on single literature source from 2012. More recent sources are available and could impact on the over prevalence estimate.

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 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.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from preclinical study 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 data they have to support the significant benefit assumption in the context of the current therapeutic management of patients (in particular temolozomide).

In the written response, and during an oral explanation before the Committee on 5 October 2016, the sponsor provided additional arguments to support the assumption of significant

benefit of the product over temolozomide and carmustine. The sponsor provided published literature to indirectly conclude that the preclinical model used was temolozomide-resistant and that the product may have a synergistic effect when used in combination with temolozomide. The committee, however considered extrapolations from indirect data insufficient at this stage and proposed that the sponsor resubmits the application once more preclinical data, where the significant benefit will be built into the proof-of-concept experiments, is available.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 October 2016, prior to final opinion.

2.1.6. - EMA/OD/103/16

Treatment of ovarian 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 has not been demonstrated. The sponsor is reminded that the COMP cannot designate medical devices or other non-pharmacological therapeutic methods. The sponsor is invited to discuss the future development of the active substance(s) as defined in Article 2 of Directive 65/65/EEC, and justify that the product(s) for these applications are the medicinal products, and not the method and route of administration.

In addition, to establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of ovarian cancer, the sponsor should further elaborate on:

– the rationale to develop the proposed regimen;

– the patient population and their previous treatments, as well as the response to such treatments;

– the results of the clinical studies, by further contextualising the observed outcome with additional published data on the natural history/ study outcome of the patient population, similar to the trial population.

- Number of people affected

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

The sponsor should establish a full point prevalence of the condition without excluding patients that could survive longer than 10 years.

- Significant benefit

Significant benefit cannot be established without medical plausibility. Significant benefit will be assessed based on the responses to the above requests to establish medical plausibility.

Regarding the assumption of improved efficacy, the sponsor should contextualise the outcome data with further literature and provide significant benefit argumentation versus all

the authorised products for the intended target patient population including PLD-doxorubicin, and paclitaxel, topotecan, gemcitabine and bevacizumab.

Regarding the assumption of improved safety, it is noted that the argumentation is only based on the administration system and not the product/active substances. In this context, potential safety concerns associated with the proposed way of administration should be outlined and taken into consideration. It is well known that extrapolation from early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments in most cases.

Regarding the assumption of major contribution to patient care, the sponsor should provide some further information on the quality of life data that was collected during the presented trials and how it compares to the quality of life of patients that are currently treated with the best standard of care including authorised products.

In the written response, and during an oral explanation before the Committee on 5 October, the sponsor outlined that the study data was generated using intravenous formulations in the proposed administration system. The COMP considered that the currently proposed designations had a focus on the delivery system, while there was no data on an actual formulation that would ultimately be used.

The sponsor furthermore, contextualised the outcome data from its trials to the published literature, however it was unclear if the response rates were comparable or if an improvement could be determined. With regards to the significant benefit versus the authorised products, the sponsor clarified that there was insufficient bibliographical data to support a significant benefit on improved efficacy in later treatment lines, and that the proposed arguments on safety and major contribution to patient care were not attributable to the delivery system, but the compound(s) for designation. The COMP considered that at the moment there was only data with other formulations of the proposed active substance and the arguments for significant benefit were mostly attributable to the delivery system. In addition, the outcome would need to be compared more adequately to the published literature. The COMP therefore was not convinced that there was sufficient evidence to support 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 5 October 2016, prior to final opinion.

2.1.7. - EMA/OD/157/16

Treatment of ovarian 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 has not been demonstrated. The sponsor is reminded that the COMP cannot designate medical devices or other non-pharmacological therapeutic methods. The sponsor is invited to discuss the future development of both active substances as defined in Article 2 of Directive 65/65/EEC, and justify that the product(s) for these applications are the medicinal products, and not the way of administration.

In addition, to establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of ovarian cancer, the sponsor should further elaborate on:

- the rationale to develop the proposed sequential treatment regimen;
- the patient population and their previous treatments, as well as the response to such treatments;
- the results obtained in both trials, by further contextualising the observed outcome with additional published data on the natural history/ study outcome of the patient population, similar to the trial population.

- Number of people affected

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

The sponsor should establish a full point prevalence of the condition without excluding patients that could survive longer than 10 years.

- Significant benefit

Significant benefit cannot be established without medical plausibility. Significant benefit will be assessed based on the responses to the above requests to establish medical plausibility.

Regarding the assumption of improved efficacy, the sponsor should contextualise the outcome data with further literature and provide significant benefit argumentation versus all the authorised products for the intended target patient population including PLD-doxorubicin, and paclitaxel, topotecan, gemcitabine and bevacizumab.

Regarding the assumption of improved safety, it is noted that the argumentation is only based on the administration system and not the product/active substances. In this context, potential safety concerns associated with the proposed way of administration should be outlined and taken into consideration. It is well known that extrapolation from early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments in most cases.

Regarding the assumption of major contribution to patient care, the sponsor should provide some further information on the quality of life data that was collected during the presented trials and how it compares to the quality of life of patients that are currently treated with the best standard of care including authorised products.

In the written response, and during an oral explanation before the Committee on 5 October 2016, the sponsor outlined that the study data was generated using intravenous formulations in the proposed administration system. The COMP considered that the currently proposed designations had a focus on the delivery system, while there was no data on an actual formulation that would ultimately be used.

The sponsor furthermore, contextualised the outcome data from its trials to the published literature, however it was unclear if the response rates were comparable or if an improvement could be determined. With regards to the significant benefit versus the authorised products, the sponsor clarified that there was insufficient bibliographical data to support a significant benefit on improved efficacy in later treatment lines, and that the

proposed arguments on safety and major contribution to patient care were not attributable to the delivery system, but the compound(s) for designation. The COMP considered that at the moment there was only data with other formulations of the proposed active substance and the arguments for significant benefit were mostly attributable to the delivery system. In addition, the outcome would need to be compared more adequately to the published literature. The COMP therefore was not convinced that there was sufficient evidence to support 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 5 October 2016, prior to final opinion.

2.1.8. - EMA/OD/140/16

Treatment of spinal cord injury

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility for the purpose of designating a treatment for faecal incontinence under the indication “treatment of spinal cord injury” the sponsor is invited to further elaborate on the relevance of faecal incontinence among the plethora of clinical manifestations of spinal cord injury.

In relation to the clinical data presented by the sponsor, some aspects would need further clarification, including:

– the different effects of the product on anal pressure measured by rectal manometry and the implications of this difference in the clinical use of the proposed products in patients affected by spinal cord injury;

– the method of measurement of faecal incontinence episodes and the lack of effect on most items of the questionnaires on faecal incontinence;

– the clinical relevance of the effect only on gas-related bowel movements to the clinical use of the product in patients with spinal cord injury.

The sponsor is also invited to discuss the results of the clinical study in relation to the different patient populations in the study based on the anatomy and severity of the injury.

In the written response, and during an oral explanation before the Committee on 5 October 2016, the sponsor argued that current literature does not support the use of manometry as a predictive tool in the treatment of faecal incontinence, and that daily diary recording is superior to recall questionnaires which had not been validated for the specific studied population. It was also discussed that lack of flatulence is a significant contributor to the overall quality of life of patients, equal to that of faecal incontinence. The COMP considered that the clinical data did not support the argued effect on faecal incontinence, and that the outcome studied is a common symptom not strongly correlated with the proposed orphan condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 October 2016, prior to final opinion.

2.1.9. - EMA/OD/083/16

Prevention of short bowel syndrome

Action: For information

Documents tabled:
Withdrawal request of 19 September 2016

2.1.10. Vaccine consisting of 5 survivin peptides with different human leukocyte antigen restrictions - EMA/OD/159/16

Dr Ulrich Granzer; Treatment of ovarian cancer

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:

- 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 ovarian cancer, the sponsor should further elaborate on the patient outcome data from the preliminary clinical studies conducted by the sponsor.

- Number of people affected

The sponsor has only used one database to establish the prevalence. The sponsor should re-calculate the prevalence estimate based on additional relevant epidemiological studies and registers for the proposed orphan condition.

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".

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

In the written response, the sponsor further elaborated on the available clinical studies and discussed the previous treatment of the participating patients. The COMP thus understood that treatment with the product has shown responses in ovarian cancer patients who were relapsed or refractory to first and second line treatments.

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

The intention to treat the condition with the medicinal product containing vaccine consisting of 5 survivin peptides with different human leukocyte antigen restrictions was considered justified based on preliminary clinical data showing improved progression free survival in patients with the condition.

The condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

The condition was estimated to be affecting approximately 3.3 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 vaccine consisting of 5 survivin peptides with different human leukocyte antigen restrictions will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in progression free survival when used in second line in the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for vaccine consisting of 5 survivin peptides with different human leukocyte antigen restrictions, for treatment of ovarian cancer, was adopted by consensus.

2.1.11. R-azasetron besylate - EMA/OD/114/16

Sensorion; Treatment of sudden sensorineural hearing loss

COMP coordinator: Josep Torrent-Farnell

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

- Intention to diagnose, prevent or treat

The sponsor should justify the proposed subset, sudden sensorineural hearing loss, in the context of all types of hearing loss. The sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor presented data in a noise-induced model of the condition. The sponsor extrapolated the results from this model to sudden sensorineural hearing loss caused by other mechanisms but this extrapolation has not been substantiated by data.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of sudden sensorineural hearing loss, the sponsor should further elaborate on:

- mechanism of action of the proposed product in the context of the protection of hair cells,
- the relevance of the preclinical model used for the treatment of sudden sensorineural hearing loss, and the interpretation of the results obtained in the experiments,
- the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition,
- the pharmacological activity of the product outside of the proposed subset.

- Number of people affected

The sponsor based the estimate of prevalence on few, non-European epidemiological sources. No national registries or European literature was consulted.

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 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 of the proposed subset of hearing loss based on relevant epidemiological studies and registers for the proposed orphan condition, and given a 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, and during an oral explanation before the Committee on 4 October 2016, the sponsor provided details of the criteria for sudden sensorineural hearing loss based on a clinical practice guideline by Stachler et al (Head and Neck Surgery 2012 146: S1). The sponsor also added a description of the study design and results obtained in the preclinical model of the condition. Additional efficacy data were presented, demonstrating the preservation of hair cells in the cochlea.

With regards to the prevalence, the sponsor included an additional study to the list of available European epidemiological sources, and justified the exclusion of one study challenging the threshold on the basis of methodological limitations, such as broad inclusion criteria and potential duplication of entries.

The Committee agreed that the condition, sudden sensorineural hearing loss, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing R-azasetron besylate was considered justified based on preclinical data in a model of the condition demonstrating improved hearing recovery.

The condition is chronically debilitating due to sudden and often irreversible loss of hearing in one of both ears as well as symptoms associated with hearing loss such as tinnitus, vertigo and confusion.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing R-azasetron besylate will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product may have a disease modifying effect and improve hearing recovery. This compares favourably to the authorised products which are used to alleviate the symptoms accompanying hearing loss. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for R-azasetron besylate, for treatment of sudden sensorineural hearing loss, was adopted by consensus.

2.1.12. - EMA/OD/167/15

Treatment of acquired Factor Xa coagulopathy associated with severe, life threatening bleeding in a critical organ or compartment

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

- Intention to diagnose, prevent or treat

The proposed condition *acquired Factor Xa coagulopathy associated with severe, life-threatening bleeding in a critical organ or compartment* should be justified as a distinct medical entity or a valid subset. The proposed condition appears to be a subset of a broader condition *Acquired Factor X Deficiency*. The sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

The sponsor has submitted a prevalence calculation for acquired Factor Xa coagulopathy associated *with severe, life-threatening bleeding in a critical organ or compartment* which would appear to be a subset of the broader condition *Acquired Factor X Deficiency*. As it seems that the sponsor has excluded part of the population affected by condition; the sponsor should indicate on which population the prevalence calculation is based on.

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.

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".

- Significant benefit

The proposed condition appears to be a subset of the broader condition Acquired Factor X deficiency for which there appears to be authorised medicines.

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the two pre-clinical in vivo studies 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 5 October 2016, the sponsor elaborated on the differences between acquired FX deficiency and acquired FXa deficiency with respect to the underlying abnormalities and in particular the effects of FXa inhibitor coagulants, as well as with regards to the clinical management approach and target population. The sponsor thus did not revisit the proposed condition and further elaborated on the prevalence calculation using direct and indirect estimation methods. The COMP considered that the proposed indication is not a distinct medical entity valid for the purpose of orphan designation, because it can be viewed under the prism of complication of treatment of patients affected by other conditions, as well as under the prism of sub setting broader coagulation disorders involving factor X.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 October 2016, prior to final opinion.

2.1.13. N-(5-(6-chloro-2,2-difluorobenzo[d][1,3]dioxol-5-yl)pyrazin-2-yl)-2-fluoro-6-methylbenzamide - EMA/OD/138/16

EMAS Pharma Limited; Treatment of acute pancreatitis

COMP coordinator: Geraldine O'Dea/Olimpia Neagu

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

- Intention to diagnose, prevent or treat

The sponsor presented data from preclinical studies, in which 3 valid models of the condition were utilised. It is not clear, however, if the investigator allowed sufficient time for the development of the condition prior to initiating the treatment. It appears, that the setting in which the product was used may be regarded as prevention rather than treatment.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute pancreatitis, the sponsor should further elaborate on:

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

- Number of people affected

The sponsor presented incidence data instead of prevalence due to a short duration of the condition. It is not clear, however, whether the assumed annual increase of incidence was calculated for older sources and why certain sources were included in the estimation, while other were not.

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 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 incidence 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 incidence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, the sponsor provided details of preclinical models, particularly with regards to the dynamics of histopathology as compared to that of the human. The experimental design was therefore defended with literature resources clearly indicating that the disease process was under way at the time of treatment initiation. The committee accepted this response and discussed internally the relevance of histopathology scores and the absence of other functional endpoints such as clinical status or survival. The committee

acknowledged the endpoints measured in the preclinical setting as clinically relevant and the medical plausibility of the product was accepted.

With regards to the prevalence, the sponsor submitted a new calculation, which included a review from 2014 and an assumption of an annual increase of the incidence of the condition. The committee accepted the estimate provided but also discussed the uncertainty about the prevalence stemming from regional differences in reported incidence. The sponsor was urged to provide a solid calculation at the time of marketing authorisation due to the concern of the committee about this uncertainty.

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

The intention to treat the condition with the medicinal product containing N-(5-(6-chloro-2,2-difluorobenzo[d][1,3]dioxol-5-yl)pyrazin-2-yl)-2-fluoro-6-methylbenzamide was considered justified based on preclinical data demonstrating improved pancreatic histopathology scores.

The condition is life-threatening and chronically debilitating due to the need for hospitalisation associated with severe acute pancreatitis. Necrotising pancreatitis which is a consequence of the condition is often associated with a high morbidity and mortality.

The condition was estimated to be affecting approximately 4.1 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 n-(5-(6-chloro-2,2-difluorobenzo[d][1,3]dioxol-5-yl)pyrazin-2-yl)-2-fluoro-6-methylbenzamide, for treatment of acute pancreatitis, was adopted by consensus.

2.1.14. Budesonide - EMA/OD/139/16

Pharmalink AB; Treatment of IgA nephropathy

COMP coordinator: Josep Torrent-Farnell/Dinko Vitezic

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

- Intention to treat

The sponsor is invited to clarify if the sought after designation is intended for the primary forms of IgA nephropathy or if it would include the secondary forms as well. If the application is intended only for primary IgA nephropathy the sponsor is invited to justify its nature as distinct medical entity in relation to the broader umbrella condition of IgA nephropathy.

- Number of people affected

The sponsor is invited to present scenarios for both primary IgA nephropathy and the broader umbrella including also secondary forms. In addition, in consideration of the variability of prevalence values across the EU reported by the sponsor, including some outliers above 5 in 10,000, the sponsor is invited to perform a sensitivity analysis of the available data.

- Significant benefit

The sponsor states that there are no treatments specifically authorized in the EU for IgA nephropathy. However currently many anti-inflammatory and/or immunosuppressive agents have broad therapeutic indications that may cover this condition.

The sponsor is therefore invited to further elaborate on the available treatments for the condition and to discuss the significant benefit of the proposed product in relation to such treatments.

In the written response, and during an oral explanation before the Committee on 6 October 2016, the sponsor clarified that the application and clinical studies are primarily aimed at primary IgA nephropathy. The pathogenesis of primary IgA nephropathy is related to aberrantly glycosylated, galactose deficient IgA1 that originate from the Peyer patches in the gastrointestinal mucosa. It was argued that as such, the pathogenesis is different from that of secondary forms of IgA nephropathy where the origin of IgA is heterogeneous (e.g. in the context of an autoimmune response), and primary IgA nephropathy is considered to be primarily a disease of the mucosal system. Related to this, it was also asserted that the proposed product is expected to act locally on the Peyer patches in the intestinal mucosa, with low systemic absorption; therefore at the present state of knowledge its development in secondary forms of nephropathy would not be plausible.

Moreover, and in relation to prevalence estimation, the sponsor performed sensitivity analyses of the assumptions used. The applicant also clarified that there are no treatments authorized for primary IgA nephropathy.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of primary IgA nephropathy.

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

The intention to treat the condition with the medicinal product containing budesonide was considered justified based on clinical data showing improvement of kidney function in patients treated with the proposed product.

The condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to kidney failure requiring dialysis and transplantation.

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

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

A positive opinion for budesonide, for treatment of primary IgA nephropathy, was adopted by consensus.

2.1.15. 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride - EMA/OD/132/16

Minoryx Therapeutics S.L.; Treatment of X-linked adrenoleukodystrophy

COMP coordinator: Lesley Greene/Vallo Tillmann

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

- Number of people affected

The sponsor proposed a prevalence estimate based of secondary sources of epidemiological data.

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 epidemiological studies and registers for the proposed orphan condition.

In the written response, the sponsor provided a recalculation of prevalence based on acceptable sources and sensitivity analysis.

Following review of the application by the Committee, it was agreed to broaden/ the indication to treatment of adrenoleukodystrophy.

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

The intention to treat the condition with the medicinal product containing 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride was considered justified based on preclinical data demonstrating an improvement in motor control and a decrease in neuroinflammation.

The sponsor has established that the condition is chronically debilitating and life threatening. Two phenotypes of adrenoleukodystrophy result in different degrees of severity. Cerebral adrenoleukodystrophy is associated with behavioural abnormalities, seizures, spastic tetraplegia and dementia. Patients usually die within several years after the onset of symptoms. The second form of adrenoleukodystrophy, adrenomyeloneuropathy is associated with primary adrenocortical insufficiency as well as progressive stiffness and gait disturbance requiring the use of a cane or a wheelchair. Patients die within 20 years after the onset of symptoms.

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

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

A positive opinion for 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride, for treatment of adrenoleukodystrophy, was adopted by consensus.

2.1.16. Adeno-associated viral vector serotype 8 containing the human *UGT1A1 gene* - EMA/OD/133/16

Audentes Therapeutics UK Limited; Treatment of Crigler Najjar syndrome

COMP coordinator: Armando Magrelli

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

- Number of people affected

The sponsor submitted an estimate of prevalence of the condition including a combination of incidence and prevalence data as well as secondary source of epidemiological data, Orphanet. The methodology of this prevalence calculation has not been clearly presented. Disease duration has not been discussed.

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 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 a calculation of prevalence, which was based on limited resources and abridged methodology. The committee accepted the proposed prevalence of less than 0.1, acknowledging the scarcity of available data to base the calculation on.

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 containing the human UGT1A1 gene was considered justified based on preclinical data demonstrating a normalisation of bilirubin levels and improved survival.

The condition is long-term debilitating and life threatening due to the development of kernicterus.

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.

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 adeno-associated viral vector serotype 8 containing the human *UGT1A1* gene, for treatment of Crigler-Najjar syndrome, was adopted by consensus.

2.1.17. Allogeneic cytomegalovirus specific cytotoxic T lymphocytes - EMA/OD/151/16

Wainwright Associates Ltd; Treatment of cytomegalovirus infection in patients with impaired cell-mediated immunity

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:

- Number of people affected

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

As it seems that the sponsor has excluded part of the population affected by the condition. The sponsor should re-calculate the prevalence estimate to include all those patients in immunocompromised states that develop CMV disease.

In the written response, the sponsor updated the prevalence calculation to 1.65 per 10,000. This now also includes CMV infected patients with HIV/AIDS, haematologic malignancy (secondary to disease and/or chemotherapy), primary immunodeficiency and ulcerative colitis.

The Committee agreed that the condition, cytomegalovirus infection in patients with impaired cell-mediated immunity, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic cytomegalovirus-specific cytotoxic T lymphocytes was considered justified based on preliminary clinical data showing that treatment reduced infection, viraemia and improved survival in patients affected by the condition.

The condition is chronically debilitating and life-threatening in particular due to manifestations such as pneumonia, gastrointestinal infections, central nervous system infection, retinitis, and in transplant recipients graft failure, rejection, and graft-versus-host disease.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic cytomegalovirus-specific cytotoxic T lymphocytes will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients, who did not respond or were resistant to authorised treatments, responded to the proposed treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic cytomegalovirus-specific cytotoxic T lymphocytes, for treatment of cytomegalovirus infection in patients with impaired cell-mediated immunity, was adopted by consensus.

2.1.18. Valproic Acid - EMA/OD/162/16

Valcuria AB; Treatment of diffuse large B-Cell lymphoma

COMP coordinator: Jens Ersbøll

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

- Number of people affected

The sponsor presented an estimate of partial prevalence assuming the disease duration of 4.67 years. The sponsor is invited to provide point prevalence instead due to increasing survival times of patients suffering from this condition.

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 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.

In the written response, the sponsor further elaborated on the issue of prevalence by including also a 10-year prevalence estimate, which reaches 4.3 in 10,000 people in the EU. The sponsor maintained the position that this conservative values most likely included patients who have fully recovered from the disease and therefore overestimates the number of people affected by the condition. The committee was of the opinion that a potential of relapse still exists 10 years after the disease onset and that all persons with the diagnosis and alive should be considered in this area of oncology.

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 valproic acid was considered justified based on clinical data demonstrating improved survival in patients who received the product in addition to the standard of care.

The condition is chronically debilitating due to involvement of single or multiple nodal or extra nodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as 26% for the high risk patients.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing valproic acid will be of significant benefit to those affected by the condition. The sponsor has provided clinical data demonstrating that the product can be used in combination with the standard of care and offers a potential of improved survival. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.19. - EMA/OD/135/16

Treatment of acute myeloid leukaemia

Action: For information

Documents tabled:

Withdrawal request of 14 September 2016

2.1.20. - EMA/OD/136/16

Treatment of cutaneous T-cell lymphoma

Action: For information

Documents tabled:
Withdrawal request of 14 September 2016

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/181/16

Treatment of plasma cell myeloma

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 November meeting.

2.2.2. - EMA/OD/062/16

Treatment of poisoning by local anesthetics

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 November meeting.

2.2.3. 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde - EMA/OD/187/16

SynteractHCR Deutschland GmbH; Treatment of sickle cell disease

COMP coordinator: Karri Penttila

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 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde was considered justified based on clinical data demonstrating a reduction in haemolysis and sickling of red blood cells.

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 3.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a significant

reduction of haemolysis and sickling of red blood cells in patients with sickle cell disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde, for treatment of sickle cell disease, was adopted by consensus.

2.2.4. Adeno-associated viral vector serotype 8 containing the human glucose-6-phosphatase gene - EMA/OD/168/16

Pharma Gateway AB; Treatment of glycogen storage disease type Ia

COMP coordinator: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 containing the human glucose-6-phosphatase gene was considered justified based on a pre-clinical in vivo model of the condition showing improved survival and improved biochemical markers of the condition.

The condition is life-threatening due to the development of hepatocellular carcinoma and chronically debilitating due to development of liver and renal failure, anaemia, osteoporosis, fractures and renal glomerular dysfunction.

The condition was estimated to be affecting approximately 0.08 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 adeno-associated viral vector serotype 8 containing the human glucose-6-phosphatase gene, for treatment of glycogen storage disease type Ia, was adopted by consensus.

2.2.5. - EMA/OD/165/16

Treatment of retinitis pigmentosa

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

2.2.6. Alpha tocopherol - EMA/OD/175/16

Université de Montpellier; Treatment of facioscapulohumeral muscular dystrophy

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing alpha-tocopherol was considered justified based on preliminary clinical data demonstrating improvements in quadriceps muscle contraction and endurance upon treatment.

The condition is chronically debilitating due to progressive severe weakness of skeletal muscles, leading to impaired mobility, chronic fatigue and pain, visual loss and hearing impairment. Patients with infantile onset disease have a reduced life-expectancy, with death usually occurring in the 3rd decade of life.

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.

A positive opinion for alpha-tocopherol, for treatment of facioscapulohumeral muscular dystrophy, was adopted by consensus.

2.2.7. - EMA/OD/177/16

Treatment of recurrent *Clostridium difficile* infection

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 November meeting.

2.2.8. - EMA/OD/208/16

Treatment of graft versus host 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 November Committee meeting.

2.2.9. Ascorbic acid - EMA/OD/174/16

Université de Montpellier; Treatment of facioscapulohumeral muscular dystrophy

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing ascorbic acid was considered justified based on preliminary clinical data demonstrating improvements in quadriceps muscle contraction and endurance upon treatment.

The condition is chronically debilitating due to progressive severe weakness of skeletal muscles, leading to impaired mobility, chronic fatigue and pain, visual loss and hearing impairment. Patients with infantile onset disease have a reduced life-expectancy, with death usually occurring in the 3rd decade of life.

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 ascorbic acid, for treatment of facioscapulohumeral muscular dystrophy, was adopted by consensus.

2.2.10. - EMA/OD/170/16

Treatment of gastric 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 November meeting.

2.2.11. Brincidofovir - EMA/OD/180/16

Chimerix UK Ltd; Treatment of smallpox

COMP coordinator: Nikolaos Sypsas

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of smallpox.

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

The intention to treat the condition with the medicinal product containing brincidofovir was considered justified based on preclinical data showing significantly increased survival and improvement of symptoms with the proposed product in valid models of the condition.

The condition is chronically debilitating due to the development of disfiguring skin scarring, blindness, haemorrhagic complications and limb deformities. The condition is life threatening, with mortality estimated to be 30% or higher.

The condition was estimated to be affecting 0 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 brincidofovir, for treatment of smallpox, was adopted by consensus.

2.2.12. - EMA/OD/169/16

Treatment of tenosynovial giant cell tumour, localised and diffuse type

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 November meeting.

2.2.13. - EMA/OD/163/16

Treatment of congenital adrenal hyperplasia

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

2.2.14. Human monoclonal antibody against Activin A - EMA/OD/186/16

Regeneron Ireland; Treatment of fibrodysplasia ossificans progressiva

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing human monoclonal antibody against activin A was considered justified based on data showing that

the product is capable of significantly reducing heterotopic bone formation and skeletal deformities in relevant preclinical models of the condition.

The condition is chronically debilitating due to episodes of painful tumour-like soft-tissue swellings followed by the development of extra bone throughout the body and across joints causing progressive impairment of movement. The condition is life-threatening due to complications of thoracic insufficiency syndrome as a consequence of ankyloses in the thorax that lead to premature death around 50 years of age.

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 human monoclonal antibody against activin A, for treatment of fibrodysplasia ossificans progressiva, was adopted by consensus.

2.2.15. Ibrutinib - EMA/OD/178/16

Janssen-Cilag International N.V.; Treatment of graft-versus-host disease

COMP coordinator: Jens Ersbøll

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

The intention to treat the condition with the medicinal product containing ibrutinib was considered justified based on preclinical and on preliminary clinical data showing improvement of signs of graft-versus-host disease with the proposed product.

The condition is chronically debilitating and life-threatening in particular due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

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

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 ibrutinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses in patients that had not responded to previous treatments that are currently authorized for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for ibrutinib, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.16. L-Selenomethionine - EMA/OD/173/16

Université de Montpellier; Treatment of facioscapulohumeral muscular dystrophy

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing L-selenomethionine was considered justified based on preliminary clinical data demonstrating improvements in quadriceps muscle contraction and endurance upon treatment.

The condition is chronically debilitating due to progressive severe weakness of skeletal muscles, leading to impaired mobility, chronic fatigue and pain, visual loss and hearing impairment. Patients with infantile onset disease have a reduced life-expectancy, with death usually occurring in the 3rd decade of life.

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 L-selenomethionine, for treatment of facioscapulohumeral muscular dystrophy, was adopted by consensus.

2.2.17. Particles comprised of methacrylic acid based co-polymer, cross-linked with a bi-functional cross-linker, purified to bind L-phenylalanine and L-phenylalanine containing peptides - EMA/OD/061/16

MipSalus ApS – Denmark; Treatment of hyperphenylalaninemia

COMP coordinator: Irena Bradinova / Dinah Duarte

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

The intention to treat the condition with the medicinal product containing particles comprised of methacrylic acid based co-polymer, cross-linked with a bi-functional cross-linker, purified to bind L-phenylalanine and L-phenylalanine containing peptides was considered justified based on pre-clinical in vivo data using a model of the condition showing a net decrease in the uptake of phenylalanine.

The condition is chronically debilitating due to neurological impairment in patients who are untreated.

The condition was estimated to be affecting 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 particles comprised of methacrylic acid based co-polymer, cross-linked with a bi-functional cross-linker, purified to bind L-phenylalanine and L-phenylalanine containing peptides will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that demonstrate the potential to use the product in patients who cannot be treated with the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for particles comprised of methacrylic acid based co-polymer, cross-linked with a bi-functional cross-linker, purified to bind L-phenylalanine and L-phenylalanine containing peptides, for treatment of hyperphenylalaninaemia, was adopted by consensus.

2.2.18. - EMA/OD/166/16

Treatment of angiosarcoma

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 November meeting.

2.2.19. Recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein - EMA/OD/183/16

Voisin Consulting S.A.R.L.; Treatment of aromatic L-amino acid decarboxylase (AADC) deficiency

COMP coordinator: Dinah Duarte

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein.

The Committee agreed that the condition, aromatic L-amino acid decarboxylase deficiency, 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 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein was considered justified based on preliminary clinical data in patients with the condition which showed improvements in motor and cognitive function.

The condition is life-threatening due to death caused by multiple organ failure, sepsis, heart failure and pneumonia and chronically debilitating due to profound autonomic and hemodynamic regulatory dysfunction and potential implications regarding regulation of cerebrovascular blood flow. Gastroesophageal reflux is observed in the majority of patients and significantly contributes to feeding and swallowing difficulties.

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 adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein, for treatment of aromatic L-amino acid decarboxylase deficiency, was adopted by consensus.

2.2.20. Sodium benzoate - EMA/OD/184/16

Lucane Pharma SA; Treatment of argininosuccinic aciduria

COMP coordinator: Annie Lorence

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

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on published case reports demonstrating that the product could normalise serum ammonia.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium benzoate will be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in combination with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, for treatment of argininosuccinic aciduria, was adopted by consensus.

2.2.21. Sodium benzoate - EMA/OD/185/16

Lucane Pharma SA; Treatment of N-acetylglutamate synthase deficiency

COMP coordinator: Annie Lorence

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of N-acetylglutamate synthetase deficiency.

The Committee agreed that the condition, N-acetylglutamate synthetase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on published case reports demonstrating that the product could normalise serum ammonia.

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

The condition was estimated to be affecting less than 0.01 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 benzoate will be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in patients experiencing breakthrough hyperammonaemia during episodes of acute illness. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, for treatment of N-acetylglutamate synthetase deficiency, was adopted by consensus.

2.2.22. - EMA/OD/152/16

Treatment of Huntington's disease

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

2.2.23. - EMA/OD/134/16

Treatment of multiple myeloma

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 November meeting.

2.2.24. - EMA/OD/188/16

Treatment of pulmonary arterial 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 November meeting.

2.2.25. Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Gly-Gly-Asp-Leu-Leu-Pro-Arg-Gly-Ser - EMA/OD/172/16

Dr Ulrich Granzer; Treatment of Huntington's disease

COMP coordinator: Violeta Stoyanova

The Committee agreed that the condition, Huntington'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 Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Gly-Gly-Asp-Leu-Leu-Pro-Arg-Gly-Ser was considered justified based on an in vivo model of the condition where treatment resulted in improved motility, cognitive function and survival.

The condition is life-threatening and chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications; the condition is chronically debilitating due to progressive motor dysfunction, severe behavioural and cognitive disturbances, and life-threatening with a median survival time reported in the range of 15 to 18 years after onset.

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 Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Gly-Gly-Asp-Leu-Leu-Pro-Arg-Gly-Ser will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in an in vivo model of the condition where treatment with the active substance results in improved behaviour and survival, which are aspects of the condition not addressed by the authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Gly-Gly-Asp-Leu-Leu-Pro-Arg-Gly-Ser, for treatment of Huntington's disease, was adopted by consensus.

2.2.26. Zinc gluconate - EMA/OD/176/16

Université de Montpellier; Treatment of facioscapulohumeral muscular dystrophy

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing zinc gluconate was considered justified based on preliminary clinical data demonstrating improvements in quadriceps muscle contraction and endurance upon treatment.

The condition is chronically debilitating due to progressive severe weakness of skeletal muscles, leading to impaired mobility, chronic fatigue and pain, visual loss and hearing impairment. Patients with infantile onset disease have a reduced life-expectancy, with death usually occurring in the 3rd decade of life.

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 zinc gluconate, for treatment of facioscapulohumeral muscular dystrophy, was adopted by consensus.

2.3. Amendment of the COMP opinions

2.3.1. Recombinant human acid sphingomyelinase – EMEA/OD/004/01, EU/3/01/056

Genzyme Europe BV; Treatment of Niemann-Pick disease, type B; Amended indication: Treatment of Niemann-Pick disease

COMP coordinator: Pauline Evers

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of Niemann-Pick disease.

The intention to treat the amended condition with the medicinal product containing recombinant human acid sphingomyelinase was considered justified based on preliminary clinical data demonstrating that treatment improved spleen volume, liver volume and pulmonary function in patients affected by the condition.

The condition is chronically debilitating and life threatening due to severe early onset neurological symptoms, hepatosplenomegaly, thrombocytopenia, infiltrative lung disease, atherogenic lipid profile, osteoporosis, osteopenia, and cardiovascular disease leading to a significant reduction in life expectancy.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human acid sphingomyelinase will be of significant benefit to those affected by the condition. There is one product authorised for Niemann-Pick disease type C, and no authorised products for Niemann-Pick disease type A and B. The proposed product is an enzyme replacement therapy for the treatment of patients affected by patients that can be categorised as Niemann-Pick type A and B patients. This is supported by clinical data that demonstrate that the treatment improved spleen volume, liver volume and pulmonary function in Niemann-Pick disease type B patients. The Committee considered that this constitutes a clinically relevant advantage and meets the criteria for orphan designation.

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

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

2.4. COMP opinions adopted via written procedure following previous meeting

2.4.1. Carbamazepine - EMA/OD/148/16

University of Newcastle upon Tyne; Treatment of metaphyseal chondrodysplasia, Schmid type

COMP coordinator: Ingeborg Barisic

Action: For information

Document tabled:
Summary report

2.4.2. P-ethoxy growth factor receptor-bound protein 2 (Grb2) antisense oligonucleotide - EMA/OD/155/16

Clinical Network Services (UK) Ltd; Treatment of acute myeloid leukaemia

COMP coordinator: Frauke Naumann-Winter

Action: For information

Document tabled:
Summary report

2.4.3. Ubiquinol - EMA/OD/153/16

Centro de Investigación Biomédica en Red (CIBER); Treatment of coenzyme Q10 deficiency syndrome

COMP coordinator: Irena Bradinova/Pauline Evers

Action: For information

Document tabled:

2.5. Appeal

2.5.1. Naltrexone – EMA/OD/035/16

Able AB; Treatment of fibromyalgia

COMP coordinator: Michel Hoffmann; Expert: Dyfrig Hughes

In the grounds for appeal, and during an oral explanation before the Committee on 4 October 2016, the sponsor discussed the issues of medical plausibility, the seriousness of the condition, the significant benefit and the return of the investment.

The issue of medical plausibility was further supported in the grounds for re-examination by the following references:

- treatment popularity from a crowd sourcing project (curetogether.com) which supports the proposed active substance;
- use of the product in another setting, namely post-detoxification therapy in opioids patients arguing improvement in behaviour in these patients;
- a conference abstract (Metyas, and coworkers, 2013 ACR annual meeting) for a prospective, open label study carried out at a single centre. Twenty-five patients diagnosed with fibromyalgia were treated with naltrexone starting at a dose of 3 mg at night time and could be titrated up to a maximum of 4.5 mg at night time. Patients were permitted to continue pregabalin, milnacipran, or duloxetine. The primary outcome measure was the Revised Fibromyalgia Impact Questionnaire (FIQR) at month 3. Twenty-two patients completed the study. Seven (32%) patients were on naltrexone monotherapy throughout the study. There was a 19.5% overall improvement. Eleven (50%) had an average of a 41% improvement in the FIQR. The patients also reported decreases in anxiety, pain and sleeping habits from baseline;
- a citation of a presentation in the 32nd annual meeting of the American Academy of Pain Medicine whose particulars are not discussed;
- a citation of a paper by Malitt and coworkers (J Rheumatol 2011;38;2238-2246) discussing the associated morbidity, which is relevant for the seriousness of the condition but not the medical plausibility criterion.

The COMP reflected on the further justifications submitted, and in particular considered that the above mentioned conference abstract refers to an open and uncontrolled clinical study which also allowed other medications. Its findings are however in line with the two recently published studies that were initially presented in the sponsor's application which reported improvement in patients' symptomatology. It was considered that notwithstanding that fibromyalgia is a heterogeneous population and therefore it is not clear which patients may ultimately benefit from the treatment, published clinical observations support improvement of symptoms in patients affected by the condition. Therefore, the COMP revised its opinion with regards to the issue of medical plausibility.

As for the life-threatening, seriously debilitating or serious and chronic nature of the condition, the grounds of appeal contained narratives and expert opinions from TV shows and the webpages, but also cited three articles published in peer reviewed journals with

regards to the associated morbidity to the condition. These publications discuss increased suicidal rates in particular in female patients (Dryer et al, Arthritis and Rheumatology vol 62, issue 10, Oct. 2010, Irene Jimenez-Rodriguez et al, Neuropsychiatric Disease and treatment, vol 2014:10, April 2010) but overall the rate was reported as low and as such does not contribute to the seriousness of the disease. One publication (Walitt et an J Rheumatol 2011 (38) 2238-2246) discusses that about 25% of patients had at least moderate improvement in pain and global well-being over time. What is missing from the sponsor's position is the quantification of symptoms in the affected population. Of note, the sponsor cited a written statement from the European Parliament, which refers to the condition as 'debilitating condition resulting in chronic widespread pain' but the Committee considered that this was not a scientific statement nor was it supported by scientific references. The sponsor also discusses other co-morbidities that may be associated with the condition, including irritable bowel syndrome, psychiatric comorbidities and neuropathy. The COMP considered that the justification provided to support the 'seriously debilitating' or 'chronic and serious' nature of the condition was insufficient and therefore the sponsor has failed to establish that the condition is 'life-threatening, seriously debilitating or serious and chronic' as required by Art 3(1)a second paragraph of Regulation No (EC) 141/2000.

With regards to the significant benefit justification, the sponsor reiterates that there are no authorised products and referred to the updated European League Against Rheumatism (EULAR) recommendations (published on July 4, 2016). These recommendations discuss that the management of the condition should take the form of a graduated approach with the aim of improving health-related quality of life and that it should focus first on non-pharmacological modalities. Only exercise is strongly recommended by these revised recommendations. The COMP consequently revisited its initial position and accepted that no satisfactory methods existed at the time of application.

Finally, for the purpose of demonstrating insufficient return of investment the sponsor has further projected the scenario without orphan incentives up to 13 years, and also created a scenario should the product benefit from the incentives. The COMP, assisted by an independent expert in health economics, considered that the assumptions used with regard to the a) size of market b) market share, and c) discount rates used for the calculation of net present values, have not been adequately justified and a sensitivity analysis was not provided. In particular, it was considered that the projected penetration to the patients was not reliable and that by increasing the assumed market share, the product may be profitable from the first years after MA without any orphan incentives. In the absence of these justifications, the potential for return of investment cannot be assessed

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

The intention to treat the condition can be considered justified on the basis of preliminary clinical observations in published literature that support improvement of symptoms in patients affected by the condition.

The sponsor has failed to document with scientific references that the condition is life-threatening, seriously debilitating or a serious and chronic condition.

The sponsor has failed to establish that the expected revenues from marketing of the product in the European Union are unlikely to generate sufficient return to justify the necessary investment. In particular, justifications and sensitivity analyses of the

assumptions of market size and share, as well as the discount rates used to calculate net present values have not been provided.

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

A negative opinion for naltrexone, for treatment of fibromyalgia, was adopted by consensus.

2.6. Nominations

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

COMP coordinators were appointed for 34 applications submitted.

2.7. Evaluation on-going

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

Action: For information

Notes:
See 6.8.1. Table 6. Evaluation Ongoing.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of tuberculosis

The Committee was briefed on the significant benefit issues. The proposed answers on the significant benefit issues will be circulated after the meeting for adoption by written procedure.

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

3.1.2. -

Treatment in haematopoietic stem cell transplantation

The discussion was postponed.

3.2. Finalised letters

3.2.1. -

Treatment of soft tissue sarcoma

The finalised letter was circulated for information.

3.3. New requests

None

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. Zemfirza (previously known as Cediranib AstraZeneca AB) - cediranib - EMEA/H/C/004003, EU/3/14/1303, EMA/OD/059/14

AstraZeneca AB; Treatment of ovarian cancer

The discussion did not take place in COMP as the Marketing Authorisation Application was withdrawn on 19 September after the CHMP September meeting.

4.1.2. Ninlaro - ixazomib - EMEA/H/C/003844, EU/3/11/899, EMA/OD/048/11

Takeda Pharma A/S; Treatment of multiple myeloma

COMP coordinator: Karri Pentilla / Frauke Naumann-Winter; Patient's expert: Hans Scheurer

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

- Significant Benefit

The sponsor should further elaborate on the basis of their claim for significant benefit as there are many therapeutic options available in patients who are relapsed or refractory to first line treatment in Multiple Myeloma. The data that has been submitted by the sponsor does not conclusively support a clinically relevant advantage over other currently approved treatments used in the same therapeutic setting with respect to treatment effect size in the overall population or in subgroups. A discussion on the limitations on indirect comparisons to the recently authorised products is expected.

Further consideration with data generated by the sponsor should also be given regarding a major contribution to patient care of an oral formulation over currently authorised products which are IV. The sponsor is asked to compare efficacy of their oral product to intravenous products in order to rule out any loss of efficacy.

In its written response, and during an oral explanation before the Committee on 4 October 2016, the sponsor submitted a justification for the significant benefit based on a need in progressive, relapsing, refractory patients, on the basis of data from their pivotal trial for licencing. The sponsor positioned use of the product as a third line treatment following two prior lines of treatment and discussed that the treatment offers the first triple oral therapy in this setting and involves the use of ixazomib+lenalidomide+dexamethasone in combination. It was pointed out that to date all other triple combination treatments involve the use of an IV formulation of a proteasome inhibitor in this combination. The sponsor claims that the progression free survival in this line of treatment offers better outcomes with this triple combination when compared to the control group (lenalidomide +

dexamethasone). It was noted that this efficacy benefit was not accompanied by substantial additional toxicity, which allows for long-term treatment and disease control. Additionally, within the pivotal study patient reported outcomes illustrated that patients were able to maintain their quality of life, go about their usual activities, and not miss many days of work during their treatment period. The efficacy benefit with the favourable safety profile of ixazomib+LenDex combined with the convenience of an all dosing regimen offers patients the opportunity to work and live almost normally, while effectively controlling their disease. This provides an important contribution to the care of patients with MM according to the sponsor.

The sponsor asserted that current options for patients with relapsed refractory multiple myeloma have significant limitations due to toxicity issues (cardiovascular, renal, peripheral neuropathy, injection site reactions), lack of convenience impacting patients quality of life and resource utilisation and limited translations of effects into real life (duration of therapy is shorter than in clinical trials) potentially impacting efficacy. They proposed that ixazomib, the only oral proteasome inhibitor, would be of significant benefit to patients with relapsed refractory multiple myeloma and represents a major contribution to patient care as it provides efficacy that is consistent with other authorised regimens in clinical trials but with a superior safety profile. They noted its convenience – one capsule weekly at home – may be key in delivering results that are closer to those from clinical trials. The COMP first discussed the proposed better efficacy of the triple oral therapy vs the control group which used lenalidomide+dexamethasone in third line therapy. The proposed better progression free survival was not felt to support a clinically relevant advantage. The sponsor claimed that in the proposed indication of patients with at least 2 prior therapies, the clinical benefit of ixazomib (PFS HR=0.58) compares to other recently approved combinations: panobinostat HR=0.64, carfilzomib HR=0.69, and elotuzumab HR=0.65. However it was not more efficacious. The adverse events profile of carfilzomib notably the cardiotoxicity and renotoxicity were highlighted as major drawbacks to the use of this agent as well as problems with hydration. It was discussed that the better tolerability of ixazomib could support the claim of a clinically relevant advantage although there were limitations due to the small dataset that had been submitted. It was also noted that the CHMP established that the efficacy and safety data met the requirements for the basis of a conditional licence.

The COMP then discussed the merits of the data submitted for major contribution to patient care. This is the first oral proteasome inhibitor to be authorised in the treatment of relapsed refractory multiple myeloma. It is proposed to be used as a triple oral combination therapy with lenalidomide and dexamethasone in third line treatment of relapsed refractory multiple myeloma patients. Patient representatives present in the plenary indicated that this approach to therapy would offer a major contribution to patient care as it would reduce the need for hospital visits and the use of IV formulations which are associated with tolerability and toxicity issues. The option to reduce hospital visits which are needed for the IV administration of alternative proteasome inhibitors and the improved tolerability of the oral administration of ixazomib were deemed important by members of the COMP and of significant benefit in the treatment of these patients.

The COMP concluded that:

The proposed therapeutic indication, treatment of adult patients with multiple myeloma who have received at least one prior therapy falls entirely within the scope of the orphan indication of the designated orphan medicinal product, for treatment of multiple myeloma.

The prevalence of multiple myeloma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

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

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Ninlaro will be of significant benefit due to a major contribution to patient care has been demonstrated by the sponsor. The oral product allows an all-oral triple therapy with a major reduction in treatment burden compared to authorised intravenous products. Furthermore, the therapy with the proposed product could be regarded as well tolerated and safe. This constitutes a clinically relevant advantage.

An opinion not recommending the removal of Ninlaro, ixazomib (EU/3/11/899) from the EC Register of Orphan Medicinal Products was adopted by majority (27 positive votes out of 30 votes). The Icelandic member supported the majority.

The divergent position (Brigitte Blöchl-Daum, Daniel O’Connor and Violeta Stoyanova-Beninska) was appended to the opinion. The Norwegian member supported this divergent view.

The COMP was informed that a public summary of the COMP opinion will be prepared for publication on the EMA website.

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

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

COMP coordinator: Geraldine O’Dea/Ingeborg Barisic/Josep Torrent-Farnell

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

The sponsor is invited to provide a significant benefit argumentation versus the authorised product Kolbam. The discussion should present and discuss the clinical outcome from the retrospective studies in the context of data available from Kolbam to establish significant benefit on the grounds of clinically relevant advantage and/or major contribution to patient care.

Specifically, the sponsor is requested to discuss the observed effects on clinical manifestations compared to Kolbam (cholic acid), e.g. diarrhoea, xanthomas and cataracts, Rankin Scale, or EDSS. In this context, please discuss and contextualise the observed effect sizes.

In addition, the sponsor should provide further information on the patient population that received concomitant cholic acid. In its written response, and during an oral explanation before the Committee on 6 October 2016, the sponsor outlined disease characteristics and a high level overview of the clinical development .The sponsor presented the outcomes of the retrospective studies demonstrating improvements in biochemical manifestations associated with the condition (serum cholestenol), and non-statistically significant improvements and/or stabilisation in cognitive and neurological impairment and two disability scores

(expanded disability status scale and Rankin scale). In addition, the Kolbam EPAR was cited and more detailed results were presented on the effects of Chenodeoxycholic acid on the disability scale EDSS. The analysis of a natural history cohort showed that age and disability were correlated in patients affected by cerebrotendinous xanthomatosis. Furthermore, EDSS scores of patients after treatment were shown in correlation to the expected/predicted EDSS scores as per natural history cohort. Improvements were observed on the EDSS scale after chenodeoxycholic treatment.

During the oral explanation, the COMP discussed with the sponsor if a specific CTX patient sub-population could be identified for whom Chenodeoxycholic acid sigma-tau treatment could be of significant benefit, or if concomitant treatment with Kolbam (cholic acid) could be considered to be of significant benefit. The sponsor clarified that no CTX patients were concomitantly treated with Chenodeoxycholic acid and Kolbam (cholic acid) in the presented studies. Furthermore, the sponsor also outlined that there was no specific patient sub-population that could benefit from chenodeoxycholic acid due to any type of ineligibility for treatment with Kolbam. Therefore, the COMP considered that significant benefit would need to be demonstrated for the same CTX patient population that is currently indicated for Kolbam.

The sponsor contextualised the outcomes clinically and also presented the main efficacy findings from the clinical development of Kolbam as per its EPAR. The clinical development of Kolbam as per the EPAR measured different biochemical and clinical outcomes; an indirect comparison between the already existing pivotal trial data could not be made. In addition, the sponsor did not present any other indirect comparisons on any outcomes between Kolbam and Chenodeoxycholic acid sigma-tau that could support a significant benefit. The sponsor was of the opinion that further indirect comparisons with Kolbam were unnecessary and that a clinically relevant advantage could be established solely based on improvements on the outlined outcome measures after Chenodeoxycholic acid treatment.

The COMP recognised the rarity of the condition and acknowledged that only limited published data exists on patients treated with Kolbam, however the COMP was of the opinion that in order to confirm the assumption of significant benefit as proposed by the sponsor, evidence was required. In particular, evidence would need to be presented demonstrating that Chenodeoxycholic acid improves patient outcomes on parameters that would allow for direct or indirect comparison. The sponsor was not able to present additional data to compare the outcomes of Kolbam (cholic acid) versus Chenodeoxycholic acid on serum cholestenol and neurological disability.

The COMP concluded that:

The proposed therapeutic indication, treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of inborn errors of primary bile acid synthesis.

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

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

As satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Chenodeoxycholic acid sigma-tau may be of potential significant benefit to those affected by the orphan condition does not hold.

The treatment with Chenodeoxycholic acid sigma-tau was analysed in two retrospective single arm studies. Treatment led to improvements in biochemical manifestations associated with the condition (serum cholestenol), and non-statistically significant improvements and/or stabilisation in cognitive and neurological impairment and two disability scores (Expanded Disability Status Scale and Rankin Scale). There were no data to compare these outcomes on serum cholestenol and neurological disability to the authorised product Kolbam (cholic acid). Therefore, insufficient evidence was presented that could support a clinically relevant advantage of Chenodeoxycholic acid sigma-tau over Kolbam. Significant benefit on the grounds of clinically relevant advantage was not justified.

An opinion recommending the removal of Chenodeoxycholic acid sigma-tau, chenodeoxycholic acid (EU/3/14/1406) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.4. Lartruvo – olaratumab – EMA/OD/266/14, EU/3/15/1447, EMEA/H/C/004216

Eli Lilly Nederland B.V.; Treatment of soft tissue sarcoma

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 elaborate on the following issues:

The sponsor proposed a wide range of values as an estimate of the prevalence of soft tissue sarcoma. The sponsor should provide a final conclusion and a final prevalence figure instead of a range.

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 justify the 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 its written response, the sponsor submitted a renewed calculation of prevalence and performed a sensitivity analysis of the assumptions used. Due to a varied distribution of prevalence across Europe and the highest incidence reported in Nordic countries, the sponsor assumed a value lower than the most conservative end of the range. The sponsor proposed the prevalence to be around 2.68 in 10,000 persons in the EU. The committee considered this value to be questionable because of the uncertainty about the reporting of all cases in other countries. Therefore the committee decided to adopt the value of 3 in 10,000 which is in line with the number accepted at the time of orphan drug designation.

The COMP concluded that:

The proposed therapeutic indication, treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin, falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of soft tissue sarcoma.

The prevalence of soft tissue sarcoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Lartruvo will be of significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The treatment with Lartruvo improved overall survival and progression free survival in patients who received Lartruvo in combination with doxorubicin. This compared favourably to the outcomes in patients receiving doxorubicin alone.

An opinion not recommending the removal of Lartuvo, olaratumab (EU/3/15/1447) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

4.2.1. SomaKit-TOC - edotreotide – EMA/OD/219/14, EU/3/15/1450, EMEA/H/C/004140

Advanced Accelerator Applications; Diagnosis of gastro-entero-pancreatic neuroendocrine tumours

COMP coordinator: Brigitte Bloechl-Daum / Katerina Kopečková

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

- Significant benefit

The sponsor is asked to further elaborate on the clinically relevant advantage of their product over currently approved diagnostics used in this condition. Consideration should be given to the very recently approved product (gallium (68Ga) edotreotide) by the French National Competent Authority which is very similar to the sponsor's product.

Additional consideration and elaboration should be given to supply of this diagnostic in the different Member States so that the COMP can appreciate the availability of similar mode of action products in Europe.

In its written response, and during an oral explanation before the Committee on 4 October 2016, the sponsor used bibliographical data which reported in some instances head to head comparisons and in other instances indirect comparisons with the authorised products in

Europe namely, Indium (111In) pentetreotide, meta-iodo-(123I)-benzylguanidine, (99mTc) hynic-octreotide and technetium (99mTc) depreotide. The sponsor highlighted the better sensitivity of their product over the currently most used product in Europe which is Indium (111In) pentetreotide, and referred to recent review articles that highlight the proven impact on patient management. As for the clinically relevant advantage of their product with regards to the use 99mTc hynic-octreotide or 99mTc depreotide it was noted that the latter is no longer widely used. Concerning (99mTc) hynic-octreotide, it was noted that it had a similar sensitivity to Indium (111In) pentetreotide therefore the same arguments used with regards to this product would hold in this case.

The COMP reflected on the very recent approval (July 2016) of an identical product, Gallium (68Ga) edotreotide 20 MBq/mL solution for injection by the French National Competent Authority (ANSM) for another sponsor. It was recognised that the diagnostic characteristics and properties of this product and the sponsor's product were basically identical. The recently ANSM approved product is produced by automatic synthesis modules installed in the production of the MAH or sub-contracted to external parties. It was noted that there were a limited number of manufacturing sites currently approved for production, and addition of new sites is costly and time-consuming. This ultimately has an impact on the distribution and availability of the product which once manufactured has a shelf-life of 4 hours.

In contrast, the sponsor's product follows a different process and involves a kit for reconstitution with the eluate of 68Ge/68Ga generator directly in the hospital radiopharmacy, independently from synthesis modules. Minimum equipment needed to perform the reconstitution which can be performed in any radiopharmacy in the entire Community authorised to handle Gallium-68. Guidance provided by the manufacturer to introduce the new technology to the hospitals. This offers greater availability because of the manufacturing and distribution approach differs significantly from the French authorised product which needs to have certified manufacturing sites by the MAH. This would support better availability of the sponsor's product through-out the Member States in the European Union as there is no need to use a modular approach to manufacturing or the need to set-up certified manufacturing sites near the area proposed use.

The COMP considered that this addressed the concerns of lack of supply across Europe and the possibility of using a kit over the modular manufacturing of the diagnostic a major contribution to patient care.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated orphan medicinal product, diagnosis of gastro-entero-pancreatic neuroendocrine tumours.

The population of patients eligible for diagnosis of gastro-entero-pancreatic neuroendocrine tumours (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 3.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and life-threatening, in particular due to the debilitating symptoms and the poor prognosis in patients with localised advanced or metastatic disease.

Although satisfactory methods of diagnosis of the condition have been authorised in the European Union, SomaKit TOC will be of significant benefit to patients with the condition due to its improved sensitivity when compared to other products, which leads to improvement in patient management. This constitutes a major contribution to patient care.

An opinion not recommending the removal of SomaKit TOC (gallium (68Ga)-edotreotide, edotreotide) (EU/3/15/1450) 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 October meeting.]

4.2.2. Venclyxto - venetoclax – EMA/OD/124/12, EMEA/H/C/004106, EU/3/12/1080

AbbVie Ltd.; Treatment of chronic lymphocytic leukaemia

COMP coordinator: Martin Mozina / Frauke Naumann-Winter / Jens Ersbøll; Experts: Johannes W. W. Coebergh / Gabriele Nagel

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

- Prevalence

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

a) the appropriateness of the epidemiological index used, based on the characteristics of the disease;

b) the inclusion/choice of the sources selected for the estimation of the prevalence of the condition.

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

- Significant benefit

The sponsor should further elaborate the clinically relevant advantage of their product with regards to the current use of ibrutinib and idelalisib-rituximab in the target CLL/SLL patient population with the 17p deletion and/or TP53 mutation. Further elaboration of data generated by the sponsor as well as the indirect comparisons submitted should be presented to further establish what the clinically relevant advantage is.

In its written response, and during an oral explanation before the Committee on 4 October 2016, the sponsor further elaborated on the issues raised. As regards the prevalence issue, the sponsor presented additional 10 year (3.65 per 10,000), and 20 year (4.84 per 10,000) partial prevalence estimations for the year 2016. It was noted that the sponsor based a substantial part of their calculation on the German registry of haematological malignancies. Both experts (participating over the phone) highlighted the lack of reliability of this database due to the manner in which the data was collected. The experts and COMP highlighted the limited number of databases used by the sponsor indicating that in other Member States such as the Netherlands and the United Kingdom, more reliable registries

existed which had not been consulted for the revised prevalence calculation. The COMP discussed the impact of selection bias due to the data sources used for these estimates. The experts further raised concern about this particular aspect of the calculation, without however concluding that it would disqualify the sources and therefore invalidated the prevalence conclusion made by the sponsor.

The experts acknowledged the difficulty in establishing a final number and both noted that patients with CLL/SLL are undiagnosed and therefore do not appear in the registries of Member States. This is one of the reasons why it is difficult to establish with certainty a final number for the point prevalence of the condition in Europe. Both experts and the COMP noted that the use of 20 year survival estimates reflected more accurately the improved survival of these patients and therefore the current situation in Europe. The COMP noted that the closeness of the final prevalence number of 4.84 in 10,000 reflects current trends seen in more recent submissions and expressed concerns about whether the prevalence could be indeed above 5 in 10,000. The COMP will continue to remain vigilant regarding the prevalence estimate for this condition, in order to ensure that point prevalence (and not partial prevalence) observes the statutory limit.

With regards to the justification of significant benefit, the sponsor highlighted that the CHMP had reached consensus on the following indication for their product: “Venclyxto monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor” and “Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor”.

The COMP noted that the CHMP had included the target patient population of 17p deletion or TP53 mutation patients who were intolerant to or resistant/relapsed to ibrutinib and idelalisib (or agents which are inhibitors of kinases downstream of the B-cell receptor, such as ibrutinib and idelalisib (BCR signal inhibitors [BCRi])).

The sponsor highlighted that there was no standard of care for patients failing BCRi irrespective of mutation status and provided an estimate of the progression free survival at 12 months had the study continued past its cut off of 3 months. The proposed PFS was estimated to be 71.7% and it was further elaborated that it could be estimated to be 67.9% in prior BCRi refractory patients.

The sponsor further elaborated on the nature of the target patient population highlighting that these were primarily elderly patients with co-morbidities for whom there is an increased risks of treatment with a BCRi. It was noted that ibrutinib is not recommended for patients at risk of bleeding or atrial fibrillation patients requiring anticoagulants and that significant adverse events with idelalisib increases risk for patients with relevant co-morbidities.

The COMP considered these arguments, however, more weight was given to the CHMP consensus regarding the inclusion of patients who were unsuitable for or have failed a B-cell receptor pathway inhibitor both 17p deletion/TP53 mutation and non 17p deletion/TP53 mutation CLL/SLL patients. As this represented a revised target patient population which validated the findings of study M14-032 in relapsed/refractory prior treated BRCi 17-deletion/TP53 mutation patients, the COMP considered that sufficient evidence and argumentation now existed to support the clinically relevant advantage of using Venclyxto in

this context. It was concluded that significant benefit now was sufficiently supported to recommend the maintenance of the orphan designation.

The COMP concluded that:

The proposed therapeutic indication, treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of chronic lymphocytic leukaemia.

The prevalence of chronic lymphocytic leukaemia/small lymphocytic lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.84 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to development of pancytopaenia (anaemia, neutropaenia, thrombocytopaenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Venclyxto will be of significant benefit is supported by favourable clinical data in two patient populations with limited treatment options. Venclyxto has induced response which correlate with improvement in symptoms in 77.2 % patients in the presence of 17p deletion and/or TP53 mutations, who are either unsuitable for or have failed a B-cell receptor pathway inhibitor. Furthermore, Venclyxto induced response in more than 50% of patients without the 17p deletion and/or TP53 mutations who failed treatment both with chemoimmunotherapy and with a B-cell receptor pathway inhibitor. This constitutes a clinically relevant advantage.

An opinion not recommending the removal of Venclyxto, venetoclax (EU/3/12/1080) 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 October meeting.]

4.2.3. Ocaliva - obeticholic acid – EMEA/OD/073/09, EU/3/10/753, EMEA/H/C/004093

Intercept Italia s.r.l; Treatment of primary biliary cirrhosis

COMP coordinator: Ingeborg Barisic / Armando Magrelli

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

- Significant Benefit

The sponsor is invited to further elaborate on the effects of obeticholic acid (OCA) in the treatment of patients who are UDCA resistant. The data submitted does not separate the effects of the use of OCA in combination with UDCA and in patients who are UDCA resistant. 40% of these patients are resistant to UDCA representing a substantial population and

therefore important for the consideration of the clinically relevant advantage of the product as they evolve more quickly to liver failure.

In its written response, and during an oral explanation before the Committee on 4 October 2016, the sponsor clarified the characteristics of the patient population in the pivotal Phase III study which was used for the Market Authorisation Application. The study was specifically designed to assess the effect, in combination with UDCA, in patients who are "resistant" to UDCA. These patients constitute approximately 40% of PBC patients and comprise a spectrum of those patients who do not respond at all and those who do not respond "adequately" to UDCA treatment. Patients who were deemed to have adequately responded to UDCA (according to the established criteria described below) were not included in the trial. The small proportion of patients who did not receive UDCA were those who were considered "intolerant" to UDCA .

The COMP concluded that:

The proposed therapeutic indication, treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of primary biliary cirrhosis.

The prevalence of primary biliary cirrhosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 3.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to the eventual development of liver fibrosis and cirrhosis and a potential need for liver transplantation.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Ocaliva will be of significant benefit due to a clinically relevant advantage which shows that the product can improve hepatic function and parameters in patients with the condition who are resistant or intolerant to treatment with ursodeoxycholic acid.

An opinion not recommending the removal of Ocaliva, 6alpha-ethyl-chenodeoxycholic acid, obeticholic acid (EU/3/10/753) 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 October meeting.]

4.2.4. Cystadrops – mercaptamine - EMA/OD/036/08, EU/3/08/578, EMEA/H/C/003769

Orphan Europe S.A.R.L.; Treatment of cystinosis

The COMP discussed the applicant's report on the maintenance of designation criteria but couldn't adopt the opinion during the meeting.

[Post-meeting note: it was decided to continue the discussion at the November COMP meeting.]

4.3. On-going procedures

COMP co-ordinators were appointed for 3 applications.

4.4. Public Summary of Opinion

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

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

None

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. Strategic Review & Learning meetings

COMP Strategy Review & Learning meetings, 17-18 October 2016, Rome, Italy

The draft agenda was presented for information.

Document tabled:
Draft agenda

6.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 5 October 2016.

Document(s) tabled:
Draft agenda
Draft minutes from September meeting

6.1.3. COMP Drafting Group

Cancelled

6.1.4. Preclinical Models Working Group

None

6.1.5. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes September 2016

6.1.6. Process for communication of applications from the EMA and the company to COMP members

A COMP member raised concerns that sponsors for orphan designation application do not systematically send the documentation to the COMP coordinators and prompted the discussion how this could be remedied.

COMP concluded that the best option to make sure no procedure is overlooked would be for COMP coordinators to receive the summary reports directly from EMA coordinators.

EMA reminded COMP members that early information on applications under evaluation is made available every month in MMD at time of 2nd mailing (agenda point 6.8.1, see table 6 within the document). Closer to the 1st discussion, products appear in the agenda circulated with the post-mailing message of previous meeting (4 or 3 weeks before the discussion).

6.1.7. Significant Benefit Working Group

The working group on Significant Benefit met on 4 October 2016.

6.2. Coordination with EMA Scientific Committees or CMDh-v

6.2.1. PDCO/COMP Working Group

The PDCO/COMP working group took place on 5 October 2016 by teleconference.

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

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

None

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

None

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

None

6.5. Cooperation with International Regulators

6.5.1. Food and Drug Administration (FDA)

The draft agenda of the monthly teleconference with FDA held on 13 September 2016 is available in MMD for information.

Document tabled:
Draft agenda September 13 2016

6.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

6.5.3. The Therapeutic Goods Administration (TGA), Australia

None

6.5.4. Health Canada

None

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

None

6.7. COMP work plan

6.7.1. COMP Work Plan 2016

Documents were circulated in MMD.

Document(s) tabled:
COMP Work Plan 2016
COMP Work plan tracking tool 2016

6.7.2. COMP Work Plan 2017

Documents were circulated in MMD.

Document(s) tabled:
COMP draft Work Plan 2017

6.8. Planning and reporting

6.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016 were circulated.

6.8.2. Overview of orphan marketing authorisations/applications

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

7. 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 4-6 October 2016 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	
Irena Bradinova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No participation in final deliberations and voting on:	2.2.10
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	
Judit Eggenhofer	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 Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	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	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Hans Scheurer	Expert - in person*		No interests declared	4.1.3.
Dyfrig Hughes	Expert - via telephone*		No restrictions applicable to this meeting	2.5.1.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Johannes Coebergh	Expert - via telephone*		No interests declared	4.2.2.
Gabriele Nagel	Expert - via telephone*		No interests declared	4.2.2.
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/