6 December 2018
EMA/COMP/712920/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 06-08 November 2018

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

06 November 2018, 08:30-19:30, room 02-F

07 November 2018, 08:30-19:30, room 02-F

08 November 2018, 08:30-17:00, room 02-F

Disclaimers

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

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members 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

The agenda for COMP 06-08 November 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 09-11 October 2018 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. Ivacaftor, N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide, tezacaftor - EMA/OD/139/18, EMA/OD/0000001208

Vertex Pharmaceuticals (Europe) Limited; Treatment of cystic fibrosis

COMP rapporteur: Eva Malikova

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

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor was invited to present and discuss any available data with the proposed product in relation to the current treatment regimen tezacaftor/ivacaftor plus ivacaftor (Symkevi plus Kalydeco as studied in

the clinical trials) in patients with homozygous F508del cystic fibrosis. The sponsor was also invited to clarify whether the proposed regimen using the triple combination plus ivacaftor has been administered in the clinical trials presented in this application.

In relation to the minimal function mutations, the sponsor was invited to clarify how minimal function is defined, including the calculation of the threshold of CFTR (cystic fibrosis transmembrane conductance regulator protein) response, and which genetic mutations are included in this definition and in the studies presented.

The sponsor was also invited to discuss the lack of forced expiratory volume in 1 second (FEV1) improvement in the TEZ/IVA arm in the clinical studies presented.

In the written response, and during an oral explanation before the Committee on 6 November 2018, the sponsor clarified the points raised by the COMP list of questions. The sponsor presented the design of the phase II trial comparing tezacaftor/ivacaftor (TEZ/IVA) to the tripe combination TEZ/IVA/ N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide in F508del (CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein) homozygous patients. The trial included a run-in period during which all patients were treated with TEZ/IVA, followed by 4 weeks during which patients were divided into a placebo arm (in which treatment with TEZ/IVA is continued) and an arm treated with the triple combination. Thus the effects seen in the triple combination are on a background of TEZ/IVA, and this explains the lack of improvement in the TEZ/IVA arm in the phase II study. The COMP was of the opinion that even with the limitation of the short observation period of the phase II study (4 weeks with the triple combination vs. TEZ/IVA) the improvement of ppFEV1 (percent predicted forced expiratory volume in 1 second) of more than 10% supports the assumption of significant benefit based on clinically relevant advantage versus TEZ/IVA at the current stage of development.

Regarding patients heterozygous for minimal function mutations/F508del, the sponsor clarified the threshold of CFTR activity and (lack of) response that qualifies them *in vitro*, and provided a list of the mutations that fall under this definition. It was also stated that these mutations are rather clinically homogeneous and have a severe phenotype. Asked about the mechanism of action of the triple combination and whether the active substance added to TEZ/IVA in this combination has a specific activity to this type of mutations, the sponsor clarified that the correcting and potentiating effect of the triple combination targets the F508del component rather than the minimal function one, as the latter offers minimum room for correction or potentiation of CFTR. Thus there is the potential to use the triple combination also in other kind of heterozygous mutations, including residual function mutations, for which TEZ/IVA is currently authorised.

The COMP concluded with a positive opinion. There is no specific CFTR modulator currently authorised for those mutations classified by the sponsor under minimal function/F508del, and the phase II study on top of standard of care showed a change of ppFEV1 that can be considered clinically relevant, albeit with the limitation of the short observation period. The similar ppFEV1 results in the homozygous F508del population, in the light of the clarifications provided by the sponsor, can support an assumption of clinically relevant advantage versus TEZ/IVA at the present stage. As recently the COMP considered that TEZ/IVA has comparable efficacy to Orkambi (TEZ/IVA orphan maintenance report), also

authorised for F508del homozygous patients, the assumption of significant benefit of the triple combination can be extrapolated also versus Orkambi.

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

The intention to treat the condition with the medicinal product containing ivacaftor, N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide, tezacaftor was considered justified based on preliminary clinical data showing improvement of lung function with the proposed product in patients homozygous for the F508del mutation and in patients heterozygous for F508del and a minimal function mutation.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ivacaftor, N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide, tezacaftor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that in the homozygous F508del patient population the proposed product has better effect on lung function than the combination of tezacaftor and ivacaftor, the CFTR modulators currently authorised for this patient population. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for ivacaftor, N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide, tezacaftor, for treatment of cystic fibrosis, was adopted by consensus.

2.1.2. Ivacaftor, potassium(benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl) cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide, tezacaftor - EMA/OD/137/18, EMA/OD/0000001207

Vertex Pharmaceuticals (Europe) Limited; Treatment of cystic fibrosis

COMP rapporteur: Eva Malikova

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

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor was invited to present and discuss any available data with the proposed product in relation to the current treatment regimen tezacaftor/ivacaftor plus ivacaftor (Symkevi plus Kalydeco as studied in the clinical trials) in patients with homozygous F508del cystic fibrosis. The sponsor is also

invited to clarify whether the proposed regimen using the triple combination plus ivacaftor has been administered in the clinical trials presented in this application.

In relation to the minimal function mutations, the sponsor was invited to clarify how minimal function is defined, including the calculation of the threshold of CFTR (cystic fibrosis transmembrane conductance regulator protein) response, and which genetic mutations are included in this definition and in the studies presented.

The sponsor was also invited to discuss the lack of forced expiratory volume in 1 second (FEV1) improvement in the TEZ/IVA arm in the clinical studies presented.

In the written response, and during an oral explanation before the Committee on 6 November 2018, the sponsor clarified the points raised by the COMP list of questions. The sponsor presented the design of the phase II trial comparing tezacaftor/ivacaftor (TEZ/IVA) to the tripe combination TEZ/IVA/ potassiumbenzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl) cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide in F508del (CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein) homozygous patients. The trial included a run-in period during which all patients were treated with TEZ/IVA, followed by 4 weeks during which patients were divided into a placebo arm (in which treatment with TEZ/IVA is continued) and an arm treated with the triple combination. Thus the effects seen in the triple combination are on a background of TEZ/IVA, and this explains the lack of improvement in the TEZ/IVA arm in the phase II study. The COMP was of the opinion that even with the limitation of the short observation period of the phase II study (4 weeks with the triple combination vs. TEZ/IVA) the improvement of ppFEV1 (percent predicted forced expiratory volume in 1 second) of more than 10% supports the assumption of significant benefit based on clinically relevant advantage versus TEZ/IVA at the current stage of development.

Regarding patients heterozygous for minimal function mutations/F508del, the sponsor clarified the threshold of CFTR activity and (lack of) response that qualifies them *in vitro*, and provided a list of the mutations that fall under this definition. It was also stated that these mutations are rather clinically homogeneous and have a severe phenotype. Asked about the mechanism of action of the triple combination and whether the active substance added to TEZ/IVA in this combination has a specific activity to this type of mutations, the sponsor clarified that the correcting and potentiating effect of the triple combination targets the F508del component rather than the minimal function one, as the latter offers minimum room for correction or potentiation of CFTR. Thus there is the potential to use the triple combination also in other kind of heterozygous mutations, including residual function mutations, for which TEZ/IVA is currently authorised.

The COMP concluded with a positive opinion. There is no specific CFTR modulator currently authorised for those mutations classified by the sponsor under minimal function/F508del, and the phase II study on top of standard of care showed a change of ppFEV1 that can be considered clinically relevant, albeit with the limitation of the short observation period. The similar ppFEV1 results in the homozygous F508del population, in the light of the clarifications provided by the sponsor, can support an assumption of clinically relevant advantage versus TEZ/IVA at the present stage. As recently the COMP considered that TEZ/IVA has comparable efficacy to Orkambi (TEZ/IVA orphan maintenance report), also authorised for F508del homozygous patients, the assumption of significant benefit of the triple combination can be extrapolated also versus Orkambi.

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

The intention to treat the condition with the medicinal product containing ivacaftor, potassium(benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl) cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide, tezacaftor was considered justified based on preliminary clinical data showing improvement of lung function with the proposed product in patients homozygous for the F508del mutation and in patients heterozygous for F508del and a minimal function mutation.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ivacaftor, potassium(benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl) cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide, tezacaftor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that in the homozygous F508del patient population the proposed product has better effect on lung function than the combination of tezacaftor and ivacaftor, the CFTR modulators currently authorised for this patient population. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for ivacaftor, potassium(benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl) cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide, tezacaftor, for treatment of cystic fibrosis, was adopted by consensus.

2.1.3. Adeno-associated viral vector expressing human 21-hydroxylase - EMA/OD/140/18, EMA/OD/0000001233

Pharma Gateway AB; Treatment of congenital adrenal hyperplasia

COMP rapporteur: Geraldine O'Dea

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 congenital adrenal hyperplasia, the sponsor should further elaborate on:

1. For the non-clinical proof of concept study, the sponsor should further elaborate on the methodology including gender.

2. The sponsor should justify why urine measurements of hormones were used, and if any hormones other than progesterone were measured. The sponsor should confirm whether androgen levels were measured and whether normalisation of adrenal androgen secretion was observed after treatment.

3. The sponsor should provide further information on the steroid sparing effects of the proposed therapy (reduction of the administered dose of glucocorticoids).

In the written response, and during an oral explanation before the Committee on 6 November 2018, the sponsor clarified the points raised by the COMP list of questions. The applicant explained that for the non-clinical testing both sexes were used. Regarding the lack of measurement of blood levels of progesterone (or deoxycorticosterone, corticosterone, dehydroepiandrosterone, androstenedione or aldosterone), the COMP acknowledged that repeated blood draws would not be feasible. However, blood levels could have been measured at least once at sacrifice and compared across the experimental groups, meaning that adrenal androgens could have been measured and compared across arms. Overall, the difficulties of the applicant and the available model were acknowledged by the COMP and the limited evidence obtained on restoration of glucocorticoid and mineralocorticoid functions were considered sufficient for the demonstration of medical plausibility for the purpose of orphan designation.

The observed marked reduction in progesterone (a major cyp21 substrate) was further discussed. These results in combination with the significant changes observed in the mineralocorticoid pathway predict a major impact on the hypothalamic-pituitary-adrenal (HPA) axis in the clinic. It is anticipated that this impact on the HPA axis would translate directly into a reduction in androgen production in patients, resulting in less exogenous glucocorticoids being required to achieve the same level of androgen suppression, i.e. "glucocorticoid sparing".

The Committee agreed that the condition, congenital adrenal hyperplasia, 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 expressing human 21-hydroxylase was considered justified based on non-clinical *in vivo* data which showed a reduction in urinary progesterone levels thus demonstrating correction of 21-hydroxylase deficiency, as well as weight gain.

The condition is life-threatening and chronically debilitating due to the development of adrenal insufficiency, virilisation in females, hyponatremia, hyperkalaemia, dehydration and hypotension.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector expressing human 21-hydroxylase will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate a marked reduction in renin mRNA content in the kidneys, which indicates a major correction of the mineralocorticoid function, without the administration of exogenous corticosteroids, the currently approved treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector expressing human 21-hydroxylase, for treatment of congenital adrenal hyperplasia, was adopted by consensus.

2.1.4. Human anti-promyostatin monoclonal antibody - EMA/OD/136/18, EMA/OD/0000001225

Yes Pharmaceutical Development Services GmbH; Treatment of spinal muscular atrophy

COMP rapporteur: Elizabeth Penninga

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

- Significant benefit

The sponsor was invited to provide further information on the clinical positioning of the product and the future clinical development.

The sponsor was invited to further elaborate on the expected clinical efficacy and safety, and how this is expected to compare to nusinersen.

In the written response, and during an oral explanation before the Committee on 6 November 2018, the sponsor explained that two patient populations were envisaged to benefit from the proposed product: monotherapy for patients who do not benefit from or cannot be treated with nusinersen, or alternatively adjunctive treatment on top of nusinersen. The sponsor acknowledged that there were no data yet to support the assumption of an add-on treatment effect on top of nusinersen therapy. Nevertheless, the sponsor outlined that for patients with less severe survival motor neuron (SMN) deficiency (e.g. ambulatory type 3 SMA), who have a considerably slower progression of disease, motor function-building therapies like the proposed product could have the potential to be effective as monotherapy. Spinal muscular atrophy (SMA) progresses slowly in type 3 patients, and there is minimal benefit expected from disease-stabilising therapies like the authorised nusinersen. The sponsor explained that they have tested the proposed product in the valid non-clinical SMNΔ7model of the condition, which was additionally modified to mimic different SMA types. The COMP acknowledged that the sponsor has demonstrated efficacy as monotherapy in a non-clinical model that could reflect those patients, who are not expected to benefit from and are not treated with the currently authorised product. The COMP considered that there was sufficient evidence to support the assumption of significant benefit for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing human anti-promyostatin monoclonal antibody was considered justified based on non-clinical data demonstrating that the product can enhance muscle mass and muscle strength.

The condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human anti-promyostatin monoclonal antibody will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating that the product can enhance muscle mass and muscle strength in a

model of the condition that has been modified to reflect patients, who are not treated with the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human anti-promyostatin monoclonal antibody, for treatment of spinal muscular atrophy, was adopted by consensus.

2.1.5. Venglustat - EMA/OD/148/18, EMA/OD/0000001060

Genzyme Europe BV; Treatment of autosomal dominant polycystic kidney disease (ADPKD)

COMP rapporteur: 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:

- Significant benefit

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

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

In the written response, the sponsor provided further preliminary clinical data to support the basis of significant benefit.

The clinical data show good clinical tolerance associated with efficacy. Of particular interest was that venglustat has not shown any impact on body water balance in non-clinical toxicology assessment and clinical phase 1 and phase 2 studies. Polyuria and dehydration is an issue with tolvaptan as is concentration of the urine in the patients in general. This is a major concern for tolvaptan where it causes intolerance in 40% of the patients treated. Venglustat can be used in patients who are intolerant to tolvaptan and does not cause polyuria. The COMP acknowledged the clinically relevant advantage of venglustat in the treatment of patients with the condition where currently there is only one authorised product which can only be used in 60% of these patients. The oral explanation was cancelled. The COMP recommended granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing venglustat was considered justified based on non-clinical *in vivo* data using a mouse model of the condition showing a relevant reduction in the number of renal and liver cysts.

The condition is chronically debilitating and life-threatening in particular due to the development of kidney failure, cardiovascular abnormalities and diverticulitis.

The condition was estimated to be affecting approximately 4.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing venglustat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the

product could be used in patients intolerant to tolvaptan. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for venglustat, for treatment of autosomal dominant polycystic kidney disease, was adopted by consensus.

2.1.6. Diacerein - EMA/OD/131/18, EMA/OD/0000001223

Therapicon Srl; Treatment of epidermolysis bullosa

COMP rapporteur: 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of epidermolysis bullosa, the sponsor should further elaborate on the particulars of the specific topical formulation under development. Any data generated by the sponsor with the proposed product in any setting (*in vitro* or *in vivo*) should be submitted to the COMP.

This is essential to understand if the results of the cited studies can be extrapolated to draw conclusions for the proposed niosomal formulation subject of the specific application for orphan medicinal product designation.

The sponsor provided written responses to the raised issues but declined to participate in the oral explanation with the COMP. In the written responses, the applicant discussed that a niosomal gel formulation is being developed in collaboration with a group of researchers of El Say and co-workers. This research group has published a paper entitled "Diacerein niosomal gel for topical delivery: development, in vitro and in vivo assessment" in J Liposome Res, 2016; 26(1): 57–68. The publication discusses different niosomal formulations, and makes reference to *in vitro* release as well as pharmacodynamic activity testing in the carrageenan-induced hind paw oedema method in the rat compared with a diacerein commercial gel. Out of the several formulations discussed the authors conclude that both 3% HPMC and 3% MC gel formulations were found to be the most appropriate gel formulations for topical application of diacerein.

The COMP discussed the scientific grounds of the proposal, noting that the bridging exercise from the cited literature studies cannot be performed in the absence of a specified proposal. The Committee was sceptical with regards to whether a product is under development, and no data were presented to clarify the issue. It was considered that the sponsor had not sufficiently addressed all the identified issues in writing and that the sponsor was not available to further discuss. Medical plausibility could therefore not be established. The application was not considered acceptable at this point in time, in the absence of further data, extrapolation from the cited published data to the particular development of the product subject of this application.

The intention to treat the condition with the medicinal product containing diacerein was not considered justified. The sponsor cited literature studies with another formulation reporting reduction in the number of blisters in affected patients, however data to justify the extrapolation of those effects to the specific product proposed for designation was not

provided. The COMP considered that in the absence of a justification of the extrapolation from the cited studies, medical plausibility could not be established.

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

The condition was estimated to be affecting less than 0.9 in 10,000 persons in the European Union, at the time the application was made.

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

A negative opinion for diacerein, for treatment of epidermolysis bullosa, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.1.7. Afatinib - EMA/OD/141/18, EMA/OD/0000001594

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of Fanconi anaemia

COMP rapporteur: Lyubina Racheva Todorova

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

- Significant benefit

The sponsor was invited to submit a significant benefit argumentation versus all products that are authorised for the treatment of head and neck squamous cell carcinoma (HNSCC), which do not exclude Fanconi anaemia (FA) patients in the therapeutic indication.

Should the significant benefit argumentation be based on an improved safety, the sponsor is requested to provide safety data of afitinib compared to the currently authorised products, which would demonstrate that FA patients could be systemically treated.

In the written response, the sponsor stresses the poor tolerability of radiation and chemotherapy in FA patients, with a focus on haemotoxicity. This is known in the literature and acknowledged by the COMP. New data in a murine non-clinical model of the condition were included in the response in FANCA-deficient mice. In that model, treatment with afatinib (20mg/K/day for 14 days) is reported to have mild or no effects in red and white blood cells, haemoglobin, haematocrit and body weight. Moreover, it was argued that (i) afatinib is not hemotoxic in the general population with locally advanced or metastatic non-small cell lung cancer (NSCLC) and that (ii) based on its mechanism of action afatinib does not target DNA and is therefore assumed to be non-genotoxic.

Taking this data into consideration, the Committee considered that the product may be a tolerable option to treat HNSCC in Fanconi anaemia patients. This compares favourably to the used treatments which are not tolerated in patients affected by the proposed condition. The COMP considered that this constitutes a clinically relevant advantage.

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

The intention to treat the condition with the medicinal product containing afatinib was considered justified. The COMP considered that head and neck squamous cell carcinoma is a

major manifestation of Fanconi anaemia. The justification for medical plausibility was based on data from valid non-clinical models demonstrating that the proposed product can reduce tumour volume in head and neck squamous cell carcinoma occurring in Fanconi anaemia.

The condition is life-threatening and chronically debilitating in particular due to bone marrow failure and the susceptibility to haematologic cancers, solid tumours, particularly squamous cell cancers of the head and neck and cervical/gynaecological cancers.

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 head and neck squamous cell carcinoma in the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing afatinib will be of significant benefit to those affected by the condition. The currently authorised treatments for the treatment of head and neck squamous cell carcinoma are not tolerated by Fanconi anaemia patients. The sponsor has provided non-clinical and preliminary clinical data that suggest that the proposed treatment of head and neck squamous cell carcinoma can be tolerated by Fanconi anaemia patients. The Committee considered that this constitutes a clinically relevant advantage. The oral explanation was cancelled.

A positive opinion for afatinib, for treatment of Fanconi anaemia, was adopted by consensus.

2.1.8. Acetylcysteine - EMA/OD/150/18, EMA/OD/0000001291

MUCPharm Pty Ltd; Treatment of pseudomyxoma peritonei

COMP rapporteur: 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:

- Significant benefit

The COMP considered that surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) are satisfactory methods for the treatment of patients with pseudomyxoma peritonei (PMP). Please provide arguments for significant benefit on the grounds of clinically relevant advantage or major contribution to patient care.

In the written response, the sponsor agreed with the COMP that surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) can be considered to be satisfactory methods in the treatment of the condition for about 40% of patients affected by the condition. Nevertheless, it was outlined that around 60% of patients will exhaust these options along the treatment journey. The sponsor argued that the combination therapy of bromelain and acetylcysteine treatment should only be considered as a second line therapy after patients have been assessed and determined to be unsuitable for surgery. Indeed, the currently ongoing pilot clinical trial has enrolled patients with recurrent pseudomyxoma peritonei, where a multidisciplinary team assessment of their case has found there is no role for further CRS/HIPEC or no other surgical procedure to be of benefit, or the patient is unfit for surgery. This study has now treated 11 patients and partial responses have been observed in 8 patients (72.2%). The COMP considered that the sponsor had provided sufficient evidence to support significant benefit in a patient population that currently has no

satisfactory methods of treatment. The Committee considered that this constitutes a clinically relevant advantage and cancelled the oral explanation.

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

The intention to treat the condition with the medicinal product containing acetylcysteine was considered justified based on non-clinical and preliminary clinical data demonstrating that treatment of acetylcysteine in combination with bromelain can dissolve mucin and lead to tumour volume reduction.

The condition is life-threatening and chronically debilitating due to pain, organ pressure symptoms, gastric and intestinal obstruction, malnutrition, internal bleeding due to erosion of gut, sepsis due to erosion of bowel or urinary system, and marked abdominal distension.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing acetylcysteine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that treatment of acetylcysteine in combination with bromelain can dissolve mucin and lead to tumour volume reduction in patients failing or not suitable for satisfactory methods including surgery and hyperthermic intraperitoneal chemotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for acetylcysteine, for treatment of pseudomyxoma peritonei, was adopted by consensus.

2.1.9. Bromelain - EMA/OD/144/18, EMA/OD/0000001290

MUCPharm Pty Ltd; Treatment of pseudomyxoma peritonei

COMP rapporteur: 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:

- Significant benefit

The COMP considered that surgery and surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) are satisfactory methods for the treatment of patients with PMP. Please provide arguments for significant benefit on the grounds of clinically relevant advantage or major contribution to patient care.

In the written response, the sponsor agreed with the COMP that surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) can be considered to be satisfactory methods in the treatment of the condition for about 40% of patients affected by the condition. Nevertheless, it was outlined that around 60% of patients will exhaust these options along the treatment journey. The sponsor argued that the combination therapy of bromelain and acetylcysteine treatment should only be considered as a second line therapy after patients have been assessed and determined to be unsuitable for surgery. Indeed, the currently ongoing pilot clinical trial has enrolled patients with recurrent pseudomyxoma peritonei, where a multidisciplinary team assessment of their case has found there is no role for

further CRS/HIPEC or no other surgical procedure to be of benefit, or the patient is unfit for surgery. This study has now treated 11 patients and partial responses have been observed in 8 patients (72.2%). The COMP considered that the sponsor had provided sufficient evidence to support significant benefit in a patient population that currently has no satisfactory methods of treatment. The Committee considered that this constitutes a clinically relevant advantage and cancelled the oral explanation.

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

The intention to treat the condition with the medicinal product containing bromelain was considered justified based on non-clinical and preliminary clinical data demonstrating that treatment of acetylcysteine in combination with bromelain can dissolve mucin and lead to tumour volume reduction.

The condition is life-threatening and chronically debilitating due to pain, organ pressure symptoms, gastric and intestinal obstruction, malnutrition, internal bleeding due to erosion of gut, sepsis due to erosion of bowel or urinary system, and marked abdominal distension.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing bromelain will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that treatment of acetylcysteine in combination with bromelain can dissolve mucin and lead to tumour volume reduction in patients failing or not suitable for satisfactory methods including surgery and hyperthermic intraperitoneal chemotherapy. The Committee considered that this constitutes a clinically relevant.

A positive opinion for bromelain, for treatment of pseudomyxoma peritonei, was adopted by consensus.

2.1.10. Sodium 2-hydroxylinoleate - EMA/OD/142/18, EMA/OD/0000001254

Ability Pharmaceuticals SL; Treatment of biliary tract cancer

COMP rapporteur: 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:

- Prevalence

The sponsor was invited to provide a revised prevalence calculation taking into consideration all scientific literature reporting on a higher incidence.

In the written response, the sponsor provided more literature on incidence and prevalence of all biliary tract cancers including gallbladder cancer and all three subtypes of cholangiocarcinoma. It was stressed that when considering these cancers, incidence rates in Europe do not exceed 0.71/10,000 cases (Italy) and 0.74 (Croatia) except for the specific countries that show incidences of 0.92 (Czech Republic), 1.12 (Slovakia) and 0.87 (Slovenia).The rest of the European countries are in the range of 0.18 – 0.53. The COMP considered that the prevalence of biliary tract cancer can be estimated to be approximately

1.5 per 10,000 when taking into consideration the more conservative incidence limit of 0.7 per 10,000 with a disease duration of around 2 years.

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

The intention to treat the condition with the medicinal product containing sodium 2-hydroxylinoleate was considered justified based on non-clinical and preliminary clinical data showing anti-tumour effects.

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

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for sodium 2-hydroxylinoleate, for treatment of biliary tract cancer, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. (2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro- 1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid - EMA/OD/165/18, EMA/OD/0000001616

Albireo AB; Treatment of biliary atresia

COMP rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing (2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid was considered justified based on preliminary clinical observations in patients affected by cholestatic liver diseases including biliary atresia, who responded to treatment with the product.

The condition is life-threatening and chronically debilitating due to development of portal hypertension, cholangitis, portal fibrosis and liver cirrhosis, and the need for liver transplantation.

The condition was estimated to be affecting approximately 0.15 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for (2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid, for treatment of biliary atresia, was adopted by consensus.

2.2.2. (4-{(2S,4S)-4-Ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) - EMA/OD/157/18, EMA/OD/0000001564

Novartis Europharm Limited; Treatment of C3 glomerulopathy

COMP rapporteur: Martin Možina

The Committee agreed that the condition, C3 glomerulopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) was considered justified based on non-clinical *in vivo* data showing an improvement in reduction of proteinuria and kidney damage.

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

The condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)), for treatment of C3 glomerulopathy, was adopted by consensus.

2.2.3. - EMA/OD/158/18, EMA/OD/0000001574

Treatment of primary IgA Nephropathy

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

2.2.4. - EMA/OD/172/18, EMA/OD/0000001633

Treatment of Burkitt lymphoma

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

2.2.5. 6,8-Bis(benzylthio)octanoic acid - EMA/OD/167/18, EMA/OD/0000001621

IQVIA RDS Ireland Limited; Treatment of pancreatic cancer

COMP rapporteur: Brigitte Bloechl-Daum

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

The intention to treat the condition with the medicinal product containing 6,8-bis(benzylthio)octanoic acid was considered justified based on clinical data in patients showing complete responses and improvement in overall survival.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression, and life-threatening with a median survival less than 1 year.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 6,8-bis(benzylthio)octanoic acid will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with metastatic disease and good performance status achieve complete responses and longer overall survival when the product is used in combination with the standard of care. This compares favourably to historical data with authorised treatment options for this patient population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6,8-bis(benzylthio)octanoic acid, for treatment of pancreatic cancer, was adopted by consensus.

2.2.6. 6,8-Bis(benzylthio)octanoic acid - EMA/OD/169/18, EMA/OD/0000001627

IQVIA RDS Ireland Limited; Treatment of acute myeloid leukaemia

COMP rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing 6,8-bis(benzylthio)octanoic acid was considered justified based on clinical data in patients showing improved overall survival.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation and the risk of severe infections. The condition progresses rapidly and is fatal if left untreated.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 6,8-bis(benzylthio)octanoic acid will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that older patients (>60 years of age) with relapsed/refractory acute myeloid leukaemia achieved better overall survival when the product was combined with existing treatment options. This compared favourably to survival times reported in combination treatments used in the standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6,8-bis(benzylthio)octanoic acid, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.7. 6-Fluoro-9-methyl-9H-pyrido[3,4-b]-indole - EMA/OD/170/18, EMA/OD/0000001998

AudioCure Pharma GmbH; Treatment of sudden sensorineural hearing loss

COMP rapporteur: Lyubina Racheva Todorova

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 6-fluoro-9-methyl-9H-pyrido[3,4-b]-indole was considered justified based on non-clinical data in a model of the condition demonstrating improved hearing recovery and protection of cochlear hair cells.

The condition is chronically debilitating due to sudden and often irreversible loss of hearing in one or 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 6-fluoro-9-methyl-9H-pyrido[3,4-b]-indole will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a model of the condition demonstrating improved hearing recovery and protection of cochlear hair cells. This compares favourably to the authorised products, which are used to alleviate the symptoms accompanying hearing loss or indicated for vascular disorders of the ear. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6-fluoro-9-methyl-9H-pyrido[3,4-b]-indole, for treatment of sudden sensorineural hearing loss, was adopted by consensus.

2.2.8. - EMA/OD/152/18, EMA/OD/0000001741

Treatment of Ataxia Telangiectasia

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

2.2.9. Adeno-associated virus serotype HSC15 expressing human phenylalanine hydroxylase - EMA/OD/153/18, EMA/OD/0000001685

Yes Pharmaceutical Development Services GmbH; Treatment of phenylanaline hydroxylase deficiency

COMP rapporteur: Robert Nistico

Following review of the application by the Committee, it was agreed to rename the indication to treatment of phenylanaline hydroxylase deficiency.

The Committee agreed that the condition, phenylanaline hydroxylase deficiency, 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 virus serotype HSC15 expressing human phenylalanine hydroxylase was considered justified based on non-clinical data demonstrating that the proposed product can normalise elevated blood phenylalanine levels in a valid model of the condition.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype HSC15 expressing human phenylalanine hydroxylase will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating that one single injection can lead to long-term normalisation of blood phenylalanine levels. This treatment could reduce the need to use the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype HSC15 expressing human phenylalanine hydroxylase, for treatment of phenylanaline hydroxylase deficiency, was adopted by consensus.

2.2.10. - EMA/OD/156/18, EMA/OD/0000001558

Treatment of haemophilia A

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

2.2.11. Allogeneic ABCB5-positive limbal stem cells - EMA/OD/155/18, EMA/OD/0000001302

Rheacell GmbH & Co. KG; Treatment of limbal stem cell deficiency

COMP rapporteur: Eva Malikova

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

The intention to treat the condition with the medicinal product containing allogeneic ABCB5-positive limbal stem cells was considered justified based on non-clinical *in vivo* data in a model of the condition showing good engraftment of the product and significant improvement in corneal healing.

The condition is chronically debilitating due to visual impairment.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic ABCB5-positive limbal stem cells will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that suggest the product can be used for engraftment in a broader patient population than the currently available cell-based therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic ABCB5-positive limbal stem cells, for treatment of limbal stem cell deficiency, was adopted by consensus.

2.2.12. - EMA/OD/151/18, EMA/OD/0000001719

Treatment of sickle cell disease

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

2.2.13. Bifunctional fusion protein composed of two extracellular domains of transforming growth factor beta receptor II fused with a human immunoglobulin G1 monoclonal antibody against programmed death ligand 1 - EMA/OD/154/18, EMA/OD/0000001641

Merck Europe B.V.; Treatment of biliary tract cancer

COMP rapporteur: Ingrid Wang

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

The intention to treat the condition with the medicinal product containing bifunctional fusion protein composed of two extracellular domains of transforming growth factor beta receptor II fused with a human immunoglobulin G1 monoclonal antibody against programmed death ligand 1 was considered justified based on preliminary clinical data demonstrating that patients affected by the condition respond to treatment.

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

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for bifunctional fusion protein composed of two extracellular domains of transforming growth factor beta receptor II fused with a human immunoglobulin G1 monoclonal antibody against programmed death ligand 1, for treatment of biliary tract cancer, was adopted by consensus.

2.2.14. C1 esterase inhibitor (human) - EMA/OD/173/18, EMA/OD/0000001430

Shire Pharmaceuticals Ireland Limited; Treatment in solid organ transplantation

COMP rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing C1 esterase inhibitor (human) was considered justified based on preliminary clinical data in patients with antibody-mediated kidney rejection suggesting that the product is able to improve kidney function.

The condition is chronically debilitating and life-threatening due to complications such as ischaemia-reperfusion injury, delayed graft function, and graft rejection.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing C1 esterase inhibitor (human) will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting that the product is able to improve kidney function when given as an add-on to standard of care for the treatment of antibody-mediated rejection, which may translate into improved transplantation outcomes. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for C1 esterase inhibitor (human), for treatment of solid organ transplantation, was adopted by consensus.

2.2.15. - EMA/OD/132/18, EMA/OD/0000001206

Treatment of small cell lung cancer

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

2.2.16. - EMA/OD/107/18, EMA/OD/0000001052

Treatment of eosinophilic esophagitis

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

2.2.17. - EMA/OD/162/18, EMA/OD/0000001592

Treatment of short bowel syndrome

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

2.2.18. Lonafarnib - EMA/OD/159/18, EMA/OD/0000001643

Eiger Biopharmaceuticals Europe Limited; Treatment of Hutchinson-Gilford progeria syndrome

COMP rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing lonafarnib was considered justified based on clinical observations supporting a lower mortality rate after treatment with the product compared to no treatment.

The condition is life-threatening and chronically debilitating in particular due to atherosclerotic cardiovascular disease and strokes, with death occurring at an average age of 14.6 years.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for lonafarnib, for treatment of Hutchinson-Gilford progeria syndrome, was adopted by consensus.

2.2.19. Marizomib - EMA/OD/161/18, EMA/OD/0000001585

Celgene Europe B.V.; Treatment of glioma

COMP rapporteur: Katerina Kopečková

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

The intention to treat the condition with the medicinal product containing marizomib was considered justified based on clinical data in patients who achieved partial response or stabilisation of the disease.

The condition is chronically debilitating due to symptoms caused by compression of the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing marizomib will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with advanced glioblastoma multiforme whose disease progressed despite prior treatment with authorised methods, temozolomide and radiation, responded to the treatment with the product and achieved either partial response or stable disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for marizomib, for treatment of glioma, was adopted by consensus.

2.2.20. - EMA/OD/076/18, EMA/OD/0000002033

Treatment of acetaminophen (paracetamol) poisoning

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

2.2.21. - EMA/OD/160/18, EMA/OD/0000002050

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

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

2.2.22. - EMA/OD/105/18, EMA/OD/0000001039

Diagnosis of medullary thyroid carcinoma

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

2.2.23. Pevonedistat - EMA/OD/164/18, EMA/OD/0000001749

Takeda Pharma A/S; Treatment of myelodysplastic syndromes

COMP rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing pevonedistat was considered justified based on preliminary clinical data showing favourable results in patients with the condition, including high risk subtypes.

The condition is life-threatening and chronically debilitating in particular due to anaemia, thrombocytopenia, neutropenia, as well as transformation into acute myeloid leukaemia.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing pevonedistat will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data showing longer event-free survival when the proposed product was given in combination with azacitidine versus azacitidine single-agent in patients with high-risk myelodysplastic syndromes. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for pevonedistat, for treatment of myelodysplastic syndromes, was adopted by consensus.

2.2.24. - EMA/OD/166/18, EMA/OD/0000002029

Treatment of immune thrombocytopenia

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

2.2.25. - EMA/OD/120/18, EMA/OD/0000001096

Treatment of soft tissue sarcoma

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

2.2.26. - EMA/OD/168/18, EMA/OD/0000001368

Treatment of active thyroid eye disease

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

2.2.27. - EMA/OD/171/18, EMA/OD/0000001988

Treatment of soft tissue sarcoma

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

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for sixteen submitted applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome)

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

3.1.2. -

Treatment of spinal cord injury

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

3.1.3. -

Treatment of glioma

The status at the SAWP was noted.

3.1.4. -

Treatment of neurotrophic keratitis

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

3.2. Finalised letters

3.2.1. -

Treatment of ovarian cancer

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

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

The new request was noted.

3.3.2. -

Treatment of neurofibromatosis type 1

The new request was noted.

3.3.3. -

Treatment of Leber's hereditary optic neuropathy

The new request was noted.

3.3.4. -

Diagnosis of glioma

The new request was noted.

3.3.5. -

Treatment of multiple myeloma

The new request was noted.

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

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

4.1.1. Namuscla - mexiletine hcl – EMEA/H/C/004584, EMA/OD/074/14, EU/3/14/1353

LUPIN (EUROPE) LIMITED; Treatment of myotonic disorders

A list of issues was adopted on 13 September 2018.

No oral explanation was held.

The Committee confirmed that all issues previously identified in this application had been addressed.

An opinion recommending not to remove Namuscla from the EC Register of Orphan Medicinal Products was adopted by consensus.

The Orphan Maintenance Assessment Report will be publicly available on the EMA website.

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

4.2.1. - pacritinib - EMEA/H/C/004793

CTI Life Sciences Ltd - United Kingdom;

a) Treatment of post-essential thrombocythaemia myelofibrosis EMA/OD/058/10, EU/3/10/767

b) Treatment of primary myelofibrosis EMA/OD/019/10, EU/3/10/768

c) Treatment of post-polycythemia vera myelofibrosis EMA/OD/057/10, EU/3/10/769

The status of the procedure at CHMP was noted.

4.2.2. - ropeginterferon alfa-2b - EMA/OD/055/11, EU/3/11/932, EMEA/H/C/004128

AOP Orphan Pharmaceuticals AG; Treatment of polycythaemia vera

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

4.2.3. - volanesorsen – EMEA/H/C/004538, EMA/OD/180/13, EU/3/14/1249

Akcea Therapeutics UK Ltd; Treatment of familial chylomicronemia syndrome

Action: For information

The status of the procedure at CHMP was noted.

4.2.4. - treosulfan - EMEA/H/C/004751, EMEA/OD/075/03, EU/3/04/186

medac Gesellschaft fur klinische Spezialpraparate mbH; Conditioning treatment prior to haematopoietic progenitor cell transplantation

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

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for two applications.

4.5. Orphan Maintenance Reports

Documents were circulated in MMD.

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Imnovid – pomalidomide Type II variation – - EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G

Celgene Europe Limited; Treatment of multiple myeloma

CHMP rapporteur: Robert James Hemmings

The status of the procedure at CHMP was noted.

5.2.2. Translarna - Ataluren - Type II variation – EMEA/H/C/002720/II/0047, EMEA/OD/106/04, EU/3/05/278

PTC Therapeutics International Limited; Treatment of duchenne muscular dystrophy

CHMP rapporteur: Johann Lodewijk Hillege

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

5.2.3. Opsumit - Macitentan - Type II variation – EMEA/H/C/002697/II/0029, EMA/OD/023/11, EU/3/11/909

Actelion Registration Limited; Treatment of pulmonary arterial hypertension

CHMP rapporteur: Concepcion Prieto Yerro

The status of the procedure at CHMP was noted.

5.2.4. Sirturo - bedaquiline - Type II variation – EMEA/H/C/002614/II/0033, EMEA/OD/024/05, EU/3/05/314

Janssen-Cilag International NV; Treatment of tuberculosis

CHMP rapporteur: Filip Josephson

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for one application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings, 23-24 October 2018, Vienna, Austria

Documents tabled:
Presentations

Agenda_SRLM SAWP-COMP_Vienna 2018

7.1.2. Protocol Assistance Working Group (PAWG)

Proposed meeting time on 7 November 2018 at 13:00

Document tabled:
PAWG draft agenda for 7 November 2018 meeting

7.1.3. Revision of "Points to Consider on the calculation and reporting of the prevalence of a condition for orphan designation" (COMP/436/01)

Discussion postponed to December meeting.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

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

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

7.3.1. SAWP/COMP joint membership

Election of new SAWP delegate to replace the current UK member - call for nomination - Deadline 5 November 2018

Action: For adoption

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

Action: For information

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

Action: For information

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

Action: For information

Notes: Monthly teleconference

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

Action: For information

Notes: Ad hoc basis meeting

7.5.3. The Therapeutic Goods Administration (TGA), Australia

Action: For information

Notes: Ad hoc basis meeting

7.5.4. Health Canada

Action: For information

Notes: Ad hoc basis meeting

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

None

7.7. COMP Work Plan

The Committee adopted the Work Plan for 2019.

Document(s) tabled:
Draft COMP Work Plan 2019

7.8. Planning and reporting

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

Action: For information

7.8.2. Overview of orphan marketing authorisations/applications

Action: For information

8. Any other business

8.1. Concepts of significant benefit (follow-up to COMP Work Plan 2017)

Presentation was given and the Committee was invited for further comments.

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

The new software was presented and discussed with the Committee members.

Document tabled: Presentation

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 6-8 November 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Elena Kaisis	Member	Cyprus	No interests declared	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
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	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	2.2.16, 2.2.19, 5.2.1.
Vacant	Member	Expert recommended by EMA		
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Meeting run with support from relevant EMA staff				

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

9. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from

the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/