21 February 2019
EMA/COMP/792954/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 04-06 December 2018

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

04 December 2018, 08:30-20:00, room 02-F

05 December 2018, 08:30-19:30, room 02-F

06 December 2018, 08:30-15:00, 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. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 04 - 06 December 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 06 - 08 November 2018 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000001052

Treatment of Eosinophilic Esophagitis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 16 November 2018, prior to responding to the list of issues.

2.1.2. acetylleucine - EMA/OD/0000001741

Intrabio Limited; Treatment of ataxia telangiectasia

COMP rapporteur: Giuseppe CapovillaAs 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 condition should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

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

- the relevance of the nonclinical models used for the treatment of ataxia telangiectasia, and the interpretation of the results obtained in the experiments;
- the absence of data in the available animal models for ataxia telangiectasia;
- with regards to the presented compassionate use observations, the applicant is invited to present the available long-term outcomes for all patients and comment on the duration of treatment and extent of the observed effects, including cumulative results and statistical considerations thereof;
- the sponsor is also invited to detail the particulars of the published clinical observations included in the application and clarify if patients affected by the proposed condition as applied for designation have been studied.

In the written response, and during an oral explanation before the Committee on 04 December 2018, the sponsor addressed the raised issues. It was discussed that ATM (Ataxia Telangiectasia Mutated)-deficient models do not display neurodegeneration, and reference was also made to the 3R principle for *in vivo* regulatory work. It was further clarified that no additional clinical observations in patients affected by the proposed condition were so far available.

The Committee considered that more relevant *in vivo* models have been described in the literature and could have been used (Beraldi *et al*, Hum Mol Gen, 2017) and reflected on the available clinical observations. Some limitations were identified, and in particular the importance of ataxia for the patients in the long term. However, an anti-ataxic profile for the active substance in question was acknowledged. It was considered that given that ataxia is a salient feature of ataxia-telangiectasia, and that the preliminary clinical observations support improvements in treated patients in that manifestation, the intention to treat the condition can be considered justified for the scope of orphan designation.

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

The intention to treat the condition with the medicinal product containing acetylleucine was considered justified based on preliminary clinical observations supporting an improvement in ataxic symptoms in a small cohort of compassionate use cases.

The condition is chronically debilitating due to motor symptoms and life-threatening due to immune deficiency which can be associated with infections and an increased risk of leukaemia and lymphoma.

The condition was estimated to be affecting less than 0.25 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for acetylleucine, for treatment of ataxia telangiectasia was adopted by consensus.

2.1.3. - EMA/OD/0000001574

Treatment of primary IgA nephropathy

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 primary IgA nephropathy, the sponsor should further elaborate on:

- the relevance of the non-clinical models used for the treatment of primary IgA nephropathy, and the interpretation of the results obtained in the experiments.

In the written response, and during an oral explanation before the Committee on 04 December 2018, the sponsor elaborated on the *in vivo* models used in the context of the application. The COMP raised questions regarding the relevance of the said models within the context of the primary IgA nephropathy, highlighting that C3 renal deposition is present in but not specific for the applied condition, a position which was also acknowledged by the sponsor. On that basis the medical plausibility was not considered established.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 04 December 2018, prior to final opinion.

2.1.4. - EMA/OD/0000001633

Treatment of Burkitt lymphoma

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 *in vitro* data in Burkitt lymphoma cells and clinical data from one patient to support medical plausibility of the product. Data from one patient are considered anecdotal and may not suffice in the absence of strong non-clinical supportive data.

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

- the results obtained *in vitro* in cell lines and any *in vivo* data in a model of the condition that may have been generated to date,
- the relevance of the non-clinical model used for the treatment of Burkitt lymphoma, and the interpretation of the results obtained in the experiments,

- the update on the clinical development in the proposed condition, especially in the previously reported patient and if more patients with Burkitt lymphoma have been treated to date.

- Significant benefit

The sponsor should detail the results of any additional available non-clinical or clinical data 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 05 December 2018, the sponsor elaborated on the available data obtained *in vitro* and in one patient who had received the treatment. The COMP questioned the medical history and it was confirmed that the patient subsequently suffered a new relapse in a distant location and it was unclear if the relapse was also a Burkitt Lymphoma. The COMP also asked if any non-clinical data was planned in development and the sponsor confirmed that given resources they would pursue that path too. In addition, the sponsor described the planned clinical development steps.

The COMP considered the responses of the sponsor to be insufficient for the demonstration of medical plausibility of the product in the sought indication. Observations from one patient only are considered anecdotal and *in vitro* data are not sufficient in the context of this condition. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 05 December 2018, prior to final opinion.

2.1.5. - EMA/OD/0000002033

Treatment of acetaminophen (paracetamol) 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

Acetaminophen (paracetamol) poisoning should be justified as a distinct medical entity or a valid subset. The COMP considers this is an adverse effect of an authorised medicinal product. As such it is difficult to see how such a condition could be accepted for an orphan drug designation. Orphan drugs are supposed to treat rare diseases, not rare adverse reactions to drugs, which are authorised with well described safety margins and risks of overdosing and poisoning (see O'Connor *et al.* Nature Reviews Drug Discovery on 12 September 2018).

Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acetaminophen (paracetamol) poisoning, the sponsor was requested to further elaborate on:

- the relevance of the non-clinical model used for the treatment of acetaminophen (paracetamol) poisoning, and the interpretation of the results obtained in the experiments. It appears that the data presented targets the prevention of the development of acetaminophen (paracetamol) poisoning and not its treatment.

- Number of people affected

The sponsor proposes that acetaminophen (paracetamol) poisoning is a distinct medical condition. The sponsor should provide a more thorough prevalence calculation.

The sponsor was also asked to 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 the sponsor was 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 a potential clinical relevant advantage of the use of the product in the condition.

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

The sponsor was also requested to further elaborate on the results of any clinical data in the public domain to support the significant benefit assumption in the context of the current standardised protocols which use N'acetylcysteine in these patients.

In the written response, and during an oral explanation before the Committee on 04 December 2018, the sponsor elaborated on the raised issues. The discussion focused primarily on the proposed condition of acetaminophen (paracetamol) poisoning. The sponsor was requested to discuss the interchangeable terminology associated with poisoning and intoxication in the context of medicinal overdose and drug safety. The sponsor was not in a position to differentiate the interplay between these terms and their association with drug safety.

This led the COMP to endorse the conclusions of a previous submission namely that: "From regulatory perspective, paracetamol overdoes is not a disease or a toxicity of an environmental pollutant (e.g. mercury). It is an adverse effect of an authorised medicinal product. As such it is difficult to see how such condition could be accepted for an orphan drug designation. Orphan drugs are supposed to treat rare diseases, not rare adverse reactions to drugs, which are authorised with well described safety margins and risks of overdosing".

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 05 December 2018, prior to final opinion.

2.1.6. benserazide hydrochloride - EMA/OD/0000001719

Isabelle Ramirez; Treatment of sickle cell disease

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

- Number of people affected

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

The sponsor should describe and justify the methodology used for the prevalence calculation. In detail it should be clarified if incidence or prevalence figures have been used. A revised prevalence estimate should be provided based on literature reporting on prevalence.

In the written response, the sponsor clarified the methodology of the prevalence estimation. The estimate of approximately 1 per 10,000 was derived from various epidemiological sources including studies by Angastionitis in 2013 and Piel in 2013. A correction factor was introduced to adjust for higher degree of migration for certain countries. The sponsor used absolute patient figures and as a consequence disregarded countries without available data. The COMP considered that the epidemiological sources are valid, but that relative figures in countries could have been used for extrapolation to other EU countries without available data. When calculating relative prevalence for individual countries, the COMP noted substantial heterogeneity across the EU with up to 2.5 in 10,000 people (for example in the UK). This heterogeneity might be explained by the variability of data sources and the variable degree of migration across Europe. Overall, the COMP accepted the proposed figure of approximately 1 per 10,000, while noting the variability of geo-epidemiology across European regions.

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 benserazide hydrochloride was considered justified based on preliminary clinical data suggesting that the proposed product led to increased levels of foetal haemoglobin, which can be linked to better patient outcomes.

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 1 in 10,000 persons in the European Union, at the time the application was made. The COMP notes substantial heterogeneity in prevalence of this condition across the EU.

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 benserazide hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting that the proposed product led to increased levels of foetal haemoglobin, which can be linked to better patient outcomes. This effect was observed on top of best standard of care including the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for benserazide hydrochloride, for treatment of sickle cell disease, was adopted by consensus.

2.1.7. human glucagon-like peptide-2 analogue linked to a human immunoglobulin Fc fragment - EMA/OD/0000001592

Hanmi Europe Limited; Treatment of short bowel syndrome

COMP rapporteur: Eva MalikovaAs 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 should re-calculate the prevalence estimate of short bowel syndrome taking into account also those patients who are not under home parenteral nutrition.

- Significant benefit

It would appear that the doses of teduglutide used in this application are lower than the one used in the non-clinical studies supporting the teduglutide marketing authorisation. The sponsor is invited to discuss the relation between the dose of teduglutide used in the non-clinical studies, and how this dose and its effects relate to the clinically effective dose in humans.

In the written response, and during an oral explanation before the Committee on 04 December 2018, the sponsor addressed raised questions. Regarding the issue of prevalence, the sponsor revised the calculations taking into account also patients not requiring parenteral nutrition, concluding with a number of affected people of 0.2 in 10,000.

As for the issue of significant benefit, the sponsor clarified that the dose of teduglutide that was used in the comparative animal studies presented in this application was based on the primary pharmacology studies reported in the respective EPAR. The sponsor also further clarified that the significantly longer half-life of the proposed product versus teduglutide is likely to be at the base of the higher efficacy on intestinal growth shown in the non-clinical model of short bowel syndrome.

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

The intention to treat the condition with the medicinal product containing human glucagon-like peptide-2 analogue linked to a human immunoglobulin Fc fragment was considered justified based on non-clinical data showing increase in small intestine weight and improvement of a number of intestine morphology parameters, including mucosal area and villar height in the jejunum intestine.

The condition is chronically debilitating due to severe nutritional deficiency, metabolic and/or septic complications and life-threatening due to liver failure and end stage renal disease.

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 human glucagon-like peptide-2 analogue linked to a human

immunoglobulin Fc fragment will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the proposed product resulted in improvement of intestinal weight and other parameters relevant for the condition as compared to teduglutide, currently authorised for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for human glucagon-like peptide-2 analogue linked to a human immunoglobulin Fc fragment, for treatment of short bowel syndrome, was adopted by consensus.

2.1.8. miglustat - EMA/OD/0000002050

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

COMP rapporteur: Annie LorenceAs 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 in a non-clinical model of the condition in which the combination of miglustat and enzyme replacement therapy seems to exert a clinically relevant effect on one functional test in late time points.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of glycogen storage disease type II (Pompe's disease), the sponsor should further elaborate on:

- 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.

- Significant benefit

The sponsor presented data in a non-clinical model of the condition in which the added effect of miglustat was demonstrated in one test in late time points. In addition, clinical data was presented but is inconclusive with regards to the added effect of miglustat to the enzyme replacement products.

The arguments on significant benefit are based on the new 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 and clinical 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 05 December 2018, the sponsor elaborated on the non-clinical and clinical data obtained with either enzyme replacement therapy alone or in combination with miglustat. The Committee questioned the dose selection, statistical analysis and pharmacokinetics of the products *in vivo* in non-clinical settings. The sponsor explained the importance of dose selection to achieve a chaperoning effect rather than an inhibition of the acid alphaglucosidase. The grip strength and wire hanging tests were discussed as prone to statistical variation. The Committee inquired also about the clinical data and the future clinical development plan for

this combination treatment. Overall, the medical plausibility and the significant benefit of the combination over Myozyme was accepted based on non-clinical data, where the added effect of miglustat was best understood to date.

The Committee agreed that the condition, glycogen storage disease type II (Pompe's disease), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing miglustat was considered justified based on non-clinical data in a model of the condition showing improvements in muscle function when used in combination with human recombinant acid alpha-glucosidase.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing miglustat will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate that the use of a combination of recombinant human acid alpha-glucosidase and miglustat resulted in improved muscle function as compared to the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for miglustat, for treatment of glycogen storage disease type II (Pompe's disease), was adopted by consensus.

2.1.9. - EMA/OD/0000001558

Treatment of haemophilia A

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 19 November 2018, prior to responding to the list of issues.

2.1.10. - EMA/OD/0000001096

Treatment of soft tissue sarcoma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 19 November 2018, prior to responding to the list of issues.

2.1.11. - EMA/OD/0000001368

Treatment of active thyroid eye disease

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

- Intention to diagnose, prevent or treat

The COMP considered that the orphan condition proposed for designation constitutes a manifestation that can occur in the course of Graves' disease.

Active thyroid eye disease should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

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

- the restriction of condition to only the active stage of Graves' orbitopathy and

- the exclusion of effects of the product in thyroid and other extra-thyroid manifestations of Graves' disease;

- Number of people affected

The COMP considered that the orphan condition proposed for designation constitutes a manifestation that can occur in the course of Graves' disease, and the prevalence has to be accordingly recalculated to reflect the broader underlying condition of Graves' disease. Also note that the entire course of the proposed condition is to be taken into consideration, including complications and even if it extends beyond the period where an intervention is deemed plausible.

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

- Significant benefit

In case of an amendment of the indication, the need to justify significant benefit may be revisited, and a comparative discussion versus any authorised counterparts will be expected to justify a clinically relevant advantage or a major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 05 December 2018, the sponsor further addressed the issues raised. The sponsor did not amend the proposed indication or any of the considerations for prevalence and significant benefit.

The applicant firstly argued in favour of the validity based on references on professional societies and references such as EUGOGO, (European Group on Graves' Orbitopathy). It was asserted that the terminology used is evolving and that "Graves' disease" would be an imprecise and broadly used term. The COMP however considered that such references refer to clinical benefit-risk considerations which would not suffice for the delineation of a valid condition for orphan designation in the EU.

The sponsor also argued that the pathophysiology of active TED (thyroid eye disease) is different to other Graves' manifestations and objected to the presence of TSHR (thyroid stimulating hormone receptor) autoantibodies as a unifying element of different Graves' manifestations. Literature was cited to argue that "20 to 25% of patients with euthyroid

TED are TSI (thyroid stimulating immunoglobulin) or TSHR antibodies negative". The COMP considered that this argument would have to be interpreted with caution, because serum autoantibodies against the IFG-1R are present in one-fourth of GD (Graves' disease) patients, regardless of the presence of GO (Graves' orbitopathy) (Marino *et al*. J Endocrinol Invest. 2018 Aug 21). Therefore, the COMP concluded that the argument of the presence of autoantibodies other than TSHR would not suffice to delineate a separate entity.

The applicant also stated that active TED is clinically and histologically distinct from non-active TED, and that there is no evidence that pharmacotherapies may work in non-active disease. In that regard, one argument of distinctiveness was the (over)expression of IGF-1 receptors. In particular the sponsor reported experimental data showing an overexpression of IGF-1R on the surface of orbital fibroblasts. However, during the OE it was conceded by the applicant that samples from both active and non-active TED have been found to overexpress the receptor, and consequently the COMP questioned the specificity of this feature in delineating active TED.

The COMP also remained skeptical on the distinction of active/non-active TED, because in several publications, recurrences of active TED have been reported, supporting that the two phases are part of the same continuum (Patel *et al* Ophthalmic Plast Reconstr Surg. 2015 Nov-Dec;31(6):445-8., Selva *et al*. Clin Exp Ophthalmol. 2004 Feb;32(1):46-50., Bunting *et al*. Postgrad Med J. 2008 Jul;84(993):388-90, Baldeschi *et al*. Ophthalmology. 2007 Jul;114(7):1395-402, Kalmann *et al*. Am J Ophthalmol. 2002 May;133(5):727-9, Shadpouret al. Jpn J Ophthalmol. 2009 Jan;53(1):44-46). The COMP considered overall that the presence of relapses in approximately 15% of thyroid eye disease has been described in the literature, which is a fact that challenges the discerning assumption based on the biphasic course of TED.

It was therefore considered that for the purpose of orphan designation, the applicant has neither discerned TED from other manifestations of Graves', nor active from non-active TED. Moreover, based on the common elements of pathophysiology and the unclear mechanisms of IGF-1R and TSHR signalling coupling, pharmacodynamic effects in other Graves' manifestations could not be excluded either.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 05 December 2018, prior to final opinion.

2.1.12. - EMA/OD/0000001039

Diagnosis of medullary thyroid carcinoma

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

- Number of people affected

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

The sponsor should provide an epidemiological figure for the patients eligible for the diagnostic procedure on an annual basis. The currently provided incidence figure does not

adequately reflect this patient population, as it does not include patients that are eligible for the diagnostic test and will have a negative diagnosis.

- Significant benefit

The COMP considers that the calcium test is a satisfactory method in the context of this application. Therefore, the COMP requests a data-driven demonstration of significant benefit versus the calcium stimulation test.

The proposed product is currently used in clinical practice. The sponsor should clarify, where the active substance is currently sourced. Particularly, the sponsor should explain if the active substance is produced as officinal or magistral formulation and if it can be considered well known and/or safe. In that case, significant benefit would need to be established by providing a data-driven argumentation on improved efficacy, improved safety or major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 05 December 2018, the sponsor provided a figure for patients eligible for the diagnostic procedure on an annual basis. This was calculated on the basis of the prevalence of nodular goiters (struma nodoa), by further assuming that 0.4% of those patients would be diagnosed with MTC (medullary thyroid carcinoma). The conclusive figure was above the current threshold of 5 per 10,000. While it was acknowledged that the provided figure could be considered conservative, it was impossible to determine the correct exclusion and inclusion criteria for the particular patient population that is eligible for the diagnostic procedure as well as fulfils the prevalence criterion.

Regarding significant benefit, the sponsor acknowledged that the proposed diagnostic would not be of improved efficacy, but might be used in combination with the satisfactory method. Furthermore, it was argued that the proposed diagnostic procedure would be safer as compared to the satisfactory method. The presented published evidence to support these assumptions was not considered yet sufficient to support this argumentation. Furthermore, the sponsor could not substantiate that the active substance of the proposed product is not available as magistral/official preparation across the EU.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 05 December 2018, prior to final opinion.

2.1.13. vinorelbine tartrate - EMA/OD/0000001988

TLC Biopharmaceuticals B.V.; Treatment of soft tissue sarcoma

COMP rapporteur: Daniel O'ConnorAs 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 reminded that any safety claim to the purpose of significant benefit needs to be supported by a discussion on the safety issues of the currently authorised products for the condition, and by preliminary data showing that the proposed product has a more favorable safety profile.

The sponsor was also invited to present and discuss any available non-clinical and/or clinical data supporting a potential clinical advantage of the proposed product, *e.g.*

better efficacy or efficacy in combination, in relation to the currently authorised treatments for the condition in the EU.

In the written response the applicant further discussed the available non-clinical data and presented some published clinical studies on free vinorelbine in soft tissue sarcoma.

In an *in vivo* model of the proposed condition, liposomal vinorelbin was tested against doxorubicine and showed improved tumour growth inhibition after 15 days of treatment. In the studied settings, treatment with vinorelbine also resulted in 14% complete regression and 86% partial regression, while no tumour regression was observed in the doxorubicin group.

It was also considered that vinorlebine formulated as free active substance is not authorised in the European Union for soft tissue sarcoma but it is used in clinical practice, especially in paediatric patients. Recently a randomised study showed that adding 6-month maintenance vinorelbine in combination with low-dose oral cyclophosphamide improves survival of children with high-risk rhabdomyosarcoma (RMS) (Bisogno *et al*. 2018, Hawkins 2018). The improvement in overall survival was statistically significant as compared to no maintenance treatment.

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

The intention to treat the condition with the medicinal product containing vinorelbine tartrate was considered justified based on non-clinical data showing reduction of tumour size in valid models of the condition.

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

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing vinorelbine tartrate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid model of the condition, showing higher anti-tumour activity of vinorelbine compared to doxorubicin, currently authorised for the condition, and representing a standard of care treatment. In addition, the sponsor presented clinical data showing that vinorelbine in combination with cyclophosphamide resulted in a statistically-significant improvement in overall survival over no maintenance therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for vinorelbine tartrate, for treatment of soft tissue sarcoma, was adopted by consensus.

2.1.14. rozanolixizumab - EMA/OD/0000002029

UCB Pharma; Treatment of immune thrombocytopenia

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

- Significant benefit

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

The sponsor should detail the results of any clinical data to support significant benefit in the context of the current therapeutic management of these patients. The sponsor should further elaborate on the patient characteristics and if they are expected to receive the proposed product as a first or second line therapy.

In the written response, and during an oral explanation before the Committee on 06 December 2018, the sponsor submitted data from a Phase II study in a target patient population which was described as difficult to treat. These patients had several lines of therapy including corticosteroids, IVIG (Intravenous immunoglobulin), rituximab and immunomodulators yet continued to have a low platelet count. The COMP considered that the sponsor has provided enough data from their Phase II study (including 64 patients with a platelet count below 30,000/µl who no longer responded adequately to treatment) showing an increase in platelet count to 50,000/µl and over when treated with the sponsor's product.

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

The intention to treat the condition with the medicinal product containing rozanolixizumab was considered justified based on preliminary clinical data showing an improvement in platelet count in patients with the condition.

The condition is life-threatening and chronically debilitating due to an increased risk of fatal haemorrhage such as intracranial haemorrhage.

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 rozanolixizumab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a clinically relevant improvement in platelet count in difficult to treat patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for rozanolixizumab, for treatment of immune thrombocytopenia, was adopted by consensus.

2.1.15. - EMA/OD/0000001206

Treatment of small cell lung cancer

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

- Intention to diagnose, prevent or treat

Data with the proposed product in either relevant non-clinical models or in affected patients are generally expected to justify medical plausibility. The sponsor was invited to provide any such data available.

The sponsor should also further elaborate on the available clinical observations in treated patients affected by the condition. The previous and concomitant treatments should be clarified. The extent of effects and any further cases and follow up data should be presented and discussed.

- Significant benefit

The sponsor is invited to further elaborate on the issue of significant benefit, taking into consideration the available data with the proposed product as applied for designation, and in the sought indication.

A direct or indirect comparison based on non-clinical or clinical data is expected versus existing treatments, to justify a clinically relevant advantage or a major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 05 December 2018, the sponsor discussed some *in vitro* data in pancreatic cell lines, noting the binding affinity of the product for somatostatin receptors. The sponsor also described *in vivo* data in pancreatic tumor xenografts with the same cell lines, noting inhibition of tumor growth by the product. Given that this non-clinical data pertains to pancreatic and not SCLC (small cell lung cancer) settings, their use for the justification of the criteria was not considered acceptable.

The applicant also discussed the available phase I data in a mixed population of small and non-small cell lung cancers, noting stable diseases for 8 weeks in 5/8 patients treated with a similar active substance. Given the differences in the active substance used and the population studied compared to the proposed designation, medical plausibility was not considered justified.

Regarding the significant benefit, the applicant discussed again the three treated refractory patients, noting that they had previously received the standard of care, and that they responded to treatment with the product. The COMP noted that the argued responses were limited and considered that the data would not allow a comparative discussion versus the authorised counterparts. Therefore significant benefit was not considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 December 2018, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000001317

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 January meeting.

2.2.2. - EMA/OD/0000001582

Treatment of acute myeloid leukaemia (AML)

2.2.3. 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 January meeting - EMA/OD/0000001604

Treatment of Tuberous Sclerosis Complex

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 January meeting.

2.2.4. - EMA/OD/0000001606

Treatment of Pancreatic 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 January meeting.

2.2.5. - EMA/OD/0000001655

Treatment of Non-traumatic osteonecrosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee January meeting.

2.2.6. - EMA/OD/0000001791

Treatment of follicular 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 January meeting.

2.2.7. - EMA/OD/0000001829

Treatment of Ulcerative Proctitis

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 January meeting.

2.2.8. synthetic double-stranded siRNA oligonucleotide directed against *TMPRSS6* mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues - EMA/OD/0000001845

Silence Therapeutics AG; Treatment of beta-thalassaemia intermedia and major

COMP rapporteur: Ingeborg Barisic / Angelo Loris BrunettaThe Committee agreed that the condition, beta-thalassaemia intermedia and major, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against TMPRSS6 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on non-clinical *in vivo* data in a model of the condition showing a dose ranging improvement on haemoglobin and haematocrit levels.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against TMPRSS6 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate an improvement in haemoglobin and haematocrit associated with better iron serum levels. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against *TMPRSS6* mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

2.2.9. - EMA/OD/0000001854

Treatment of Myasthenia gravis

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 January meeting.

2.2.10. balipodect - EMA/OD/0000001861

Takeda Pharma A/S; Proposed condition: Treatment of Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

COMP rapporteur: Robert Nistico

The sponsor initially applied for the condition Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder, however, following review of the application by the Committee, it was agreed that the condition originally proposed by the sponsor should be renamed as Rett syndrome based on the well-established practise of grouping Rett and Rett-like syndromes (including Cyclin-dependent kinase-like 5 deficiency disorder) under this umbrella term.

It was considered that for the purpose of orphan medicinal product designation in the EU Rett syndrome would be the appropriate broad term encompassing classic and Rett-like variants caused by MeCP2, FOXG1 and CDKL5 among other genes. In particular with regards to the latter, it was acknowledged that Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder is caused by mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene. Clinical features identified to date include early-onset seizures (generally within the first 3 months of life), severe global developmental delay, abnormal muscle tone, hand stereotypies, gastrointestinal problems, and bruxism.

The intention to treat the condition with the medicinal product containing balipodect was considered justified based on data in a non-clinical model of Cyclin-dependent kinase-like 5 deficiency disorder demonstrating improvements in open field activity and hind limb

clasping, further supported by antiepileptic activity in non-clinical models of other conditions.

The condition is life-threatening and chronically debilitating due to severe locomotor disability, sleep disturbances, seizures, respiratory complications and development of arrhythmias resulting in decreased life-expectancy.

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

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

A positive opinion for balipodect, for treatment of Rett Syndrome, was adopted by consensus.

2.2.11. - EMA/OD/0000001881

Treatment of Pancreatic Cancer

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

2.2.12. melatonin - EMA/OD/0000001921

Therapicon S.r.l.; Treatment of perinatal asphyxia

COMP rapporteur: Giuseppe CapovillaThe Committee agreed that the condition, perinatal asphyxia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on publications reporting clinical data showing improved survival of patients treated with a combination of melatonin and hypothermia.

The condition is chronically debilitating due to the long lasting neurological and developmental sequelae. The condition is also life threatening, with high mortality associated in the most severe cases.

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

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

A positive opinion for melatonin, for treatment of perinatal asphyxia, was adopted by consensus.

2.2.13. ralinepag - EMA/OD/0000002037

Arena Pharmaceuticals Limited; Treatment of Pulmonary Arterial Hypertension (PAH)

COMP rapporteur: Eva MalikovaThe Committee agreed that the condition, pulmonary arterial hypertension, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing ralinepag was considered justified based on preliminary clinical data showing reduction of pulmonary vascular resistance in patients affected by the condition.

The condition is life-threatening due to progressive dyspnoea and right hearth failure, leading to death in an average period of 2.8 years after diagnosis.

The condition was estimated to be affecting less than 1.8 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 ralinepag will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing effect on pulmonary vascular resistances and other relevant endpoints on top of standard of care treatment with several of the medicinal products currently authorised for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for ralinepag, for treatment of pulmonary arterial hypertension, was adopted by consensus.

2.2.14. mercaptamine-pantetheine disulfide - EMA/OD/0000002209

Thiogenesis Therapeutics S.A.R.L; Treatment of Rett syndrome

COMP rapporteur: Ingeborg BarisicThe Committee agreed that the condition, Rett syndrome, is a distinct medical entity and meets the criteria for orphan designation. The intention to treat the condition with the medicinal product containing mercaptamine-pantetheine disulfide was considered justified based on non-clinical data in a model of the condition where treatment with cysteamine improves life-span and motor ability.

The condition is life-threatening and chronically debilitating due to severe locomotor disability, sleep disturbances, seizures, respiratory complications and development of arrhythmias resulting in decreased life-expectancy.

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

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

A positive opinion for mercaptamine-pantetheine disulfide, for treatment of Rett syndrome, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP coordinators were appointed for eleven submitted applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of glioma

The status of the procedure was noted.

3.1.2. -

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

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 neurofibromatosis type 1

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

3.1.4. -

Diagnosis of glioma

The status of the procedure was noted.

3.1.5. - -

Treatment of multiple myeloma

The status of the procedure was noted.

3.2. Finalised letters

3.2.1. -

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

The finalised letter was circulated for information.

3.2.2. -

Treatment of spinal cord injury

The finalised letter was circulated for information.

3.2.3. -

Treatment of neurotrophic keratitis

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of diffuse large B-cell lymphoma

The new request was noted.

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

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

None

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

4.2.1. Trecondi - 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

A list of issues was adopted on 08 November 2018.

An oral explanation was held on 04 December 2018.

An opinion recommending to remove Trecondi 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.

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

AOP Orphan Pharmaceuticals AG; Treatment of polycythaemia vera

A list of issues was adopted on 08 November 2018.

An oral explanation was held on 05 December 2018.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 December 2018, prior to final opinion.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for one application.

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

5.1.1. Blincyto (blinatumomab) - Type II variation – EMEA/OD/029/09, EU/3/09/650, EMEA/H/C/003731/II/0011

Amgen Europe BV - The Netherlands; Treatment of acute lymphoblastic leukaemia

CHMP rapporteur: Alexandre Moreau; CHMP co-rapporteur: Daniela Melchiorri

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

An opinion recommending not to remove Blincyto 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.

5.2. Prior to adoption of CHMP opinion

5.2.1. Rubraca - rucaparib - Type II variation – EMEA/H/C/004272/II/0001, EMA/OD/085/12, EU/3/12/1049

Clovis Oncology UK Limited; Treatment of ovarian cancer

CHMP rapporteur: Jorge Camarero Jiménez

The sponsor formally withdrew the application for orphan designation on 27 November 2018.

5.2.2. Imbruvica – ibrutinib - Type II variation – EMEA/H/C/003791/II/0046, EMA/OD/0000002783

Janssen-Cilag International NV;

a) Treatment of chronic lymphocytic leukaemia EMA/OD/156/11, EU/3/12/984

b) Treatment of mantle cell lymphoma EMA/OD/171/12, EU/3/13/1115

c) Treatment of lymphoplasmacytic lymphoma EMA/OD/185/13, EU/3/14/1264

CHMP rapporteur: Filip Josephson

The COMP rapporteurs were appointed.

5.2.3. Imbruvica – ibrutinib - Type II variation – EMEA/H/C/003791/II/0047, EMA/OD/0000002367

Janssen-Cilag International NV;

a) Treatment of chronic lymphocytic leukaemia EMA/OD/156/11, EU/3/12/984

b) Treatment of mantle cell lymphoma EMA/OD/171/12, EU/3/13/1115

c) Treatment of lymphoplasmacytic lymphoma EMA/OD/185/13, EU/3/14/1264

CHMP rapporteur: Filip Josephson

The COMP rapporteurs were appointed.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for two applications.

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

Document was circulated in MMD.

Documents tabled:

Presentations

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 04 December 2018.

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)

Action: For discussion

Proposal for revision was presented.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

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

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

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

Documents were circulated in MMD.

Document(s) tabled:
Meeting Summary PCWP Plenary Meeting 25 Sep 2018
Meeting Summary PCWP/HCPWP Joint Meeting 25 Sep 2018

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

COMP representative at HCPWG was endorsed: Dinah Duarte

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.4.2. The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

COMP representative at ENCePP was endorsed: Frauke Naumann-Winter

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. The Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

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

Action: For discussion

Discussion was postponed.

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

Presentation was given to the Committee.

8.3. EMA Business Pipeline activity and Horizon scanning

Document was circulated in MMD.

Document tabled:
Q4/2018 Update of the Business Pipeline report for the human scientific committees

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 04-06 December 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	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Katerina Kopeckova	Member	Czech Republic	No participation in final deliberations and voting on:	EMEA/H/C/003791/II/0046EMEA/H/C/003791/II/0047
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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:	EMA/OD/0000001052
Bruno Sepodes	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	
A representative from the European Commission attended the meeting				
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/