21 February 2019
EMA/COMP/32255/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 22-24 January 2019

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

22 January 2019, 08:30-19:30, room 02-A

23 January 2019, 08:30-19:30, room 02-A

24 January 2019, 08:30-15:00, room 02-A

Disclaimers

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

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions. Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared. Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 22-24 January 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 4-6 December 2018 were tabled and will be further discussed next month.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. autologous adult live cultured osteoblasts - EMA/OD/0000001655

Clinical Network Services (UK) Limited; Treatment of non-traumatic osteonecrosis

COMP rapporteur: Elena KaisisAs 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 was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor should justify the assumed duration of the condition in the context of the chronicity of the osteonecrosis which may also be active in multiple sites. The sponsor was requested to perform a sensitivity analysis of the reported calculations. The final conclusion should include all potential sites of osteonecrosis.

In the written response, the sponsor retains the assumed incidence of non-traumatic osteonecrosis of 1.12 per 10,000 based on the study by Arbab and Koenig (Dtsch Arztebl Int 2016; 113: 31–8, by further assuming that 76% of cases pertain to the femoral head). This was considered acceptable by the COMP.

With regards to the duration, the applicant clarified that the duration in the initial application was calculated to be 3 years based on data for osteonecrosis of the femoral head, thereby not taking into account the duration at other sites. However, publications referring to sites other than the femur were cited, which reported comparable durations, with surgery within approximately 2 years after diagnosis. Moreover, to provide a sensitivity analysis, the sponsor noted that even if the duration was considered to be 4 years, the estimated figure still lie below the orphan threshold. The COMP considered that a duration of up to 3 years may be considered for the purpose of this application (Rajpura A *et al*, T Hip Int. 2011;21(4):385).

By assuming a 1.12 per 10,000 yearly incidence data and a duration of approximately 3 years, the estimated number of affected patients in the EU was concluded to be approximately 3.4 in 10.000 at the time of designation.

The Committee agreed that the condition, non-traumatic osteonecrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous adult live cultured osteoblasts was considered justified based on preliminary clinical observations in affected patients, who responded to treatment with improved function and symptoms, as assessed by established clinical scores.

The condition is chronically debilitating due to pain and reduced range of motion.

The condition was estimated to be affecting approximately 3.4 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for autologous adult live cultured osteoblasts, for treatment of non-traumatic osteonecrosis, was adopted by consensus.

2.1.2. - EMA/OD/0000001582

Treatment of acute myeloid leukaemia (AML)

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

To update the provided prevalence figure based on contemporaneous data sources (recently published IARC report (Ferlay 2018) or HMRN).

- Significant benefit

The sponsor was requested to provide data-driven arguments for significant benefit over all authorised products.

The sponsor was requested to provide further detail about the methodology of the non-clinical *in vivo* study that compared the proposed product to midostaurin. The sponsor was asked to explain the choice of dose and how this experimental setting (monotherapy and model) could translate to the clinical setting.

In the written response, and during an oral explanation before the Committee on 22 January 2019, the sponsor provided an updated prevalence calculation, which contained the newest data published. The COMP accepted the provided data sources for estimating the prevalence; however the conclusive conservative estimate was considered to be too high. The prevalence estimate was based on the formula P=I*D. The duration of condition was established in a very conservative way (life-expectancy of the population - median age at diagnosis of AML = 8.9 years for males and 14.9 years for females). This resulted in a quite high prevalence estimate of 3.2 in 10,000 (for males) and 3.4 in 10,000 (for males), respectively. In light of other published observational data showing lower partial prevalence rates (e.g. HMRN York), the COMP considered that a lower prevalence estimate of around 1.4 per 10,000 would be more accurate and in line with previous designations.

Regarding significant benefit, the sponsor elaborated on the available non-clinical evidence that has been generated with the proposed product. The proposed product has been tested in comparison to cytarabine/daunorubicin, azacitidine, and midostaurin. The efficacy of the product in terms of tumour volume reduction was considered inconsistent across studies. Also the dosing of the authorised counterparts in the non-clinical models was not sufficiently clear in order to determine if the proposed product had a better efficacy in the models. Therefore, the COMP could not conclude if there was a significant benefit over the authorised counterparts.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 January 2019, prior to final opinion.

2.1.3. - EMA/OD/0000001854

Treatment of myasthenia gravis

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 were based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor proposed indirect comparisons from several non-clinical models of the condition to support significant benefit where the product was used in prevention setting. Such data would not support the use of the product in the treatment setting.

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

The sponsor was requested to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients. Alternatively, details of planned clinical studies would further inform the discussion of significant benefit.

In the absence of comparative data with the product to the current standard of care significant benefit cannot be assessed.

In the written response, and during an oral explanation before the Committee on 22 January 2019, the sponsor provided details of all non-clinical studies presented to support the medical plausibility. The sponsor discussed in detail the limitations of the presented models of myasthenia gravis, claiming that the acute nature of the condition does not exactly recapitulate the human chronic myasthenia gravis. According to the sponsor, the neuromuscular junctions are damaged already long before the clinical score decline in rodents, therefore what was interpreted by the COMP as preventive setting, could in fact be 'treatment'. The committee considered that in absence of direct measurement of NMJ (neuromuscular junction) degeneration such conclusion is difficult to make. In addition, evident efficacy on functional endpoints in treatment setting would be expected to support medical plausibility. The COMP criticised small cohorts in experiments and the study design, in which randomisation should take place once the disease is established in the model.

The prevalence was discussed again taking into account only more recent literature (since 2009) and the final estimate of around 1.8 in 10,000 was accepted.

The significant benefit, as directly linked to medical plausibility was discussed as an assumption of improved efficacy. Comparative data versus methylprednisolone was generated in preventive setting, therefore the COMP had similar criticism as to all other experiments supporting medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 January 2019, prior to final opinion.

2.1.4. lurbinectedin - EMA/OD/0000001317

Pharma Mar S.A.; Treatment of small cell lung cancer

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 requested to provide more detail on trial design and methodology of the basket trial including more detail on patient population baseline characteristics and previous treatments.

The sponsor was requested to provide a data-driven discussion versus all authorised products in the envisaged patient population. For the demonstration of significant benefit based on indirect comparisons, the sponsor was requested to clarify similarities and differences of the compared patient populations and potentially provide additional historical control data.

In the written response, the sponsor has provided additional information on the SCLC (small cell lung cancer) cohort of a currently ongoing phase II basket trial. At this point in time, 88 second-line SCLC patients were evaluable. For the demonstration of significant benefit, the sponsor has provided a literature overview of studies in the second line and compared it to preliminary clinical data from the proposed product. The outcomes on overall response rate, progression free survival and overall survival were reported and compared. The presented indirect comparisons against topotecan, CAV (Cyclophosphamide, doxorubicin (Adriamycin) and Vincristine) and first-line platinum re-challenge suggest that the proposed product has

led to better outcomes. The COMP considered that sufficient evidence was presented to support the assumption of a significant benefit on improved efficacy in the second line of SCLC.

The oral explanation was cancelled.

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

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

The condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a 5-year overall survival of 5-10%.

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 lurbinectedin will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients respond to treatment. Indirect comparisons suggest that patients that were treated with the proposed products had better outcomes compared to published historical data of patients that have been treated with the best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lurbinectedin, for treatment of small cell lung cancer, was adopted by consensus.

2.1.5. - EMA/OD/0000001606

Treatment of pancreatic 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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of pancreatic cancer, the sponsor should further elaborate on the methodology of the non-clinical study in combination with a PD-L1 (Programmed death-ligand 1) inhibitor, and in particular:

- the type of mouse model used in the study (e.g. which type of mice, which tumour xenograft/cells);

- the doses of the proposed product and PD-L1 inhibitor used in the study and how they relate to the intended clinical dose of the two products;

- the design of the study, where each arm was separately compared to the control arm, and the interpretation of the results taking this into account.

Regarding the data on systemic immune inflammation in patients with late stage pancreatic cancer, the sponsor is invited to further elaborate on:

- the definition of 'systemic immune inflammation', i.e. which parameters/biomarkers are measured in order to determine the presence and levels of systemic immune inflammation;

- the validity of 'systemic immune inflammation' as endpoint in oncology, in particular in pancreatic cancer.

The sponsor is also invited to present any available clinical endpoints and any information about concomitant treatments in the study.

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor was invited to present any available data showing a potential clinical advantage of the proposed product *vis a vis* the currently authorised products for the condition.

The sponsor was reminded that in absence of data the significant benefit of the product cannot be assessed.

In the written response, and during an oral explanation before the Committee on 22 January 2019, the sponsor further elaborated on the non-clinical and on the available clinical data.

From the non-clinical perspective, there was still no comparative figure presented of the survival data between single arm treatments and the combination treatment including the proposed product. The applicant stated that all arms were tested at the same time but as no comparative figures are available, the COMP could not draw a clear conclusion on the potential benefit of the product.

The COMP then discussed with the sponsor the available data on systemic immune inflammation. The sponsor clarified that the systemic immune inflammation index (SIII) is calculated based on neutrophil, lymphocytes and platelets counts. It was objected that the components of the index are not specific for cancer and could be altered by different etiologies, and such index is not considered a valid pharmacodynamic measure in oncology. The discussion moved then to the survival data presented by the sponsor in patients with metastatic or locally advanced pancreatic cancer treated with the proposed product. While the results would appear encouraging, the patients started the new treatment just after treatment with the folfrinox regimen. It was therefore argued that it would not be possible to attribute the survival results to treatment with the proposed product, as they may be due to the effects of the folfrinox regimen. The COMP therefore was of the opinion that the intention to treat and the significant benefit of the proposed product were not sufficiently justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 January 2019, prior to final opinion.

2.1.6. - EMA/OD/0000001829

Treatment of ulcerative proctitis

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

Ulcerative proctitis should be further justified as a distinct medical entity or a valid subset. Based on a large body of literature the COMP considers that this is a subset of ulcerative colitis. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Number of people affected

The sponsor appears to have calculated the prevalence of a subgroup of ulcerative colitis. The sponsor should recalculate the prevalence for the broader condition of ulcerative colitis.

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

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

- Significant benefit

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

The sponsor should detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients including TNFα (Tumor necrosis factor α) inhibitors.

In the written response, and during an oral explanation before the Committee on 23 January 2019, the sponsor explained in their response that it was their belief that ulcerative proctitis was a distinct medical entity which qualified as an orphan condition. The COMP requested that the sponsor further elaborate on why ulcerative proctitis was cited within the Montreal classification of ulcerative colitis. The sponsor indicated that ulcerative proctitis was anatomically limited to the rectum and thus making it a different condition. The COMP while acknowledging that it was limited in its anatomical form the underlying pathophysiology and the grouping of the condition with other forms of ulcerative colitis meant that it was difficult to disentangle it from the broader term.

The COMP therefore was of the opinion that the sponsor had not established ulcerative proctitis as an orphan condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 24 January 2019, prior to final opinion.

2.1.7. - EMA/OD/0000001604

Treatment of Tuberous Sclerosis Complex

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 04 January 2019, prior to responding to the list of issues.

2.1.8. - EMA/OD/0000001791

Treatment of follicular lymphoma

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 14 December 2018, prior to responding to the list of issues.

2.1.9. - EMA/OD/0000001881

Treatment of pancreatic cancer

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 22 January 2019, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. humanised IGg1 monoclonal antibody targeting human transferrin receptor conjugated to human iduronate-2-sulfatase - EMA/OD/0000001793

Artemida Pharma Europe Limited; Treatment of mucopolysaccharidosis II (Hunter syndrome)

COMP coordinator: Annie LorenceThe Committee agreed that the condition, mucopolysaccharidosis II (Hunter's syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised IGg1 (immunoglobulin g1) monoclonal antibody targeting human transferrin receptor conjugated to human iduronate-2-sulfatase was considered justified based on non-clinical and on preliminary clinical data showing reduction of glycosaminoglycan deposition in different tissues and organs with the proposed product.

The condition is life-threatening and chronically debilitating due to progressive neurological impairment, and to cardiovascular and pulmonary complications. Survival after diagnosis is 10 to 15 years in the severe forms.

The condition was estimated to be affecting approximately 0.02 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 humanised IGg1 monoclonal antibody targeting human transferrin receptor conjugated to human iduronate-2-sulfatase will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical and preliminary clinical data that demonstrate that the proposed product reduces the accumulation of glycosaminoglycan components in the brain and cerebral fluids, while the authorised product for this condition does not reach the brain tissue. The Committee considered that this constitutes a clinically relevant advantage because it may lead to treatment of the neurological manifestations of the condition.

A positive opinion for humanised IGg1 monoclonal antibody targeting human transferrin receptor conjugated to human iduronate-2-sulfatase, for treatment of mucopolysaccharidosis II (Hunter's syndrome), was adopted by consensus.

2.2.2. risdiplam - EMA/OD/0000001899

Roche Registration GmbH; Treatment of spinal muscular atrophy

COMP coordinator: Elisabeth PenningaThe 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 risdiplam was considered justified based on preliminary clinical observations in affected patients that support improved survival and motor function.

The condition is chronically debilitating and life-threatening 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 risdiplam will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in treated patients that compare favourably to the described effects of the authorised counterpart in motor function and survival. Moreover, the oral formulation of the product could find applicability in a broader patient population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for risdiplam, for treatment of spinal muscular atrophy, was adopted by consensus.

2.2.3. - EMA/OD/0000001901

Treatment of Duchenne muscular dystrophy

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 February meeting.

2.2.4. - EMA/OD/0000001908

Treatment of polycythemia vera

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

2.2.5. - EMA/OD/0000002181

Treatment of endophthalmitis

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 February meeting.

2.2.6. - EMA/OD/0000002264

Treatment of Huntington's disease

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

2.2.7. 9-cis, 12-cis-11,11-D2-linoleic acid ethyl ester - EMA/OD/0000002279

FGK Representative Service GmbH; Treatment of infantile neuroaxonal dystrophy

COMP coordinator: Michel HoffmannThe Committee agreed that the condition, infantile neuroaxonal dystrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 9-cis, 12-cis-11,11-D2-linoleic acid ethyl ester was considered justified based on non-clinical data in an *in vivo* model of the condition and preliminary clinical observations in affected patients, supporting improvements in motor performance.

The condition is chronically debilitating and life threatening, in particular due to infantile onset of motor and cognitive regression, spasticity, muscle atrophy, hypotonia, cerebellar ataxia, dystonia, optic atrophy and distal sensory loss, and with a survival of less than 10 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 9-cis, 12-cis-11,11-D2-linoleic acid ethyl ester, for treatment of infantile neuroaxonal dystrophy, was adopted by consensus.

2.2.8. lentiviral vector encoding human coagulation factor IX - EMA/OD/0000002293

Fondazione Telethon; Treatment of haemophilia B

COMP coordinator: Fernando Mendez HermidaThe Committee agreed that the condition, haemophilia B, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat haemophilia B with the medicinal product containing lentiviral vector encoding human coagulation factor IX was considered justified based on non-clinical *in vivo* data in a model of the condition showing a relevant improvement in factor IX serum levels.

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

The condition was estimated to be affecting approximately 0.16 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 lentiviral vector encoding human coagulation factor IX will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate a sustained increase in factor IX which was long term. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lentiviral vector encoding human coagulation factor IX, for treatment of haemophilia B, was adopted by consensus.

2.2.9. - EMA/OD/0000002333

Treatment of cystic fibrosis

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

2.2.10. losartan - EMA/OD/0000002383

3R Pharma Consulting GmbH; Treatment of epidermolysis bullosa

COMP coordinator: Frauke Naumann-WinterThe Committee agreed that the condition, epidermolysis bullosa, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing losartan was considered justified based on non-clinical data in a model of the condition demonstrating reduction of fibrosis in sites of blistering and a delay in development of pseudosyndactyly.

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 approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for losartan, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.11. anti-Epstein Barr virus cytotoxic lymphocytes - EMA/OD/0000002426

Common Services Agency (National Health Services - Scotland); Treatment of post-transplant lymphoproliferative disorder

COMP coordinator: Frauke Naumann-WinterThe Committee agreed that the condition, post-transplant lymphoproliferative disorder, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing anti-Epstein Barr virus cytotoxic lymphocytes was considered justified based on clinical data demonstrating complete responses and improved survival.

The condition is life-threatening due to fulminant and lethal course of the disease and chronically debilitating due to transplant-specific organ dysfunction, malaise, lethargy, weight loss and fever.

The condition was estimated to be affecting approximately 0.8 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing anti-Epstein Barr virus cytotoxic lymphocytes will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who were left with no more treatment options achieved complete responses and improved survival upon treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for anti-Epstein Barr virus cytotoxic lymphocytes, for treatment of post-transplant lymphoproliferative disorder, was adopted by consensus.

2.2.12. poly(n-acetyl, n-arginyl)glucosamine - EMA/OD/0000002552

Accelsiors CRO And Consultancy Services Ltd.; Treatment of cystic fibrosis

COMP coordinator: Eva MalikovaThe 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 poly(N-acetyl, N-arginyl)glucosamine was considered justified based on non-clinical data in which an activity on bacterial biofilm formation as well as the clearance of obstructed airways in models of cystic fibrosis were observed.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing poly(N-acetyl, N-arginyl)glucosamine will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in the model of the condition that demonstrate that the activity of the product on disruption of bacterial biofilms (in addition to its mucolytic properties) was better than that of currently authorised mucolytic products. In another model of the condition the product was also shown to potentiate the activity of antibiotics used in the standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for poly(N-acetyl, N-arginyl)glucosamine, for treatment of cystic fibrosis, was adopted by consensus.

2.2.13. allogeneic cultured postnatal thymus-derived tissue - EMA/OD/0000002975

Enzyvant Therapeutics Ireland Limited; Treatment of DiGeorge syndrome

COMP coordinator: Dinah DuarteThe Committee agreed that the condition, DiGeorge syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic cultured postnatal thymus-derived tissue was considered justified based on preliminary clinical data

suggesting that the proposed treatment improved overall survival of patients affected by the condition.

The condition is life-threatening and chronically debilitating due to congenital heart disease, hypocalcaemia, respiratory failure, immunodeficiency due to partial or full athymia, and infections resulting from T cell deficiency.

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

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 allogeneic cultured postnatal thymus-derived tissue, for treatment of DiGeorge syndrome, was adopted by consensus.

2.2.14. allogeneic cultured postnatal thymus-derived tissue - EMA/OD/0000002977

Enzyvant Therapeutics Ireland Limited; Treatment of CHARGE syndrome

COMP coordinator: Dinah DuarteThe Committee agreed that the condition, CHARGE syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic cultured postnatal thymus-derived tissue was considered justified based on preliminary clinical data suggesting that the proposed treatment improved overall survival of patients affected by the condition.

The condition is life-threatening and chronically debilitating due to delays in development, heart defects, choanal atresia, growth deficiency, brain anomalies, ear anomalies and deafness, immunodeficiency due to partial or full athymia, and infections resulting from T cell deficiency.

The condition was estimated to be affecting approximately 0.9 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 allogeneic cultured postnatal thymus-derived tissue, for treatment of CHARGE syndrome, was adopted by consensus.

2.2.15. allogeneic cultured postnatal thymus-derived tissue - EMA/OD/0000002979

Enzyvant Therapeutics Ireland Limited; Treatment of FOXN1 deficiency

COMP coordinator: Dinah DuarteFollowing review of the application by the Committee, it was agreed to rename the orphan condition to severe combined immunodeficiency due to FOXN1 deficiency.

The Committee agreed that the condition, severe combined immunodeficiency due to FOXN1 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 cultured postnatal thymus-derived tissue was considered justified based on preliminary clinical data

suggesting that the proposed treatment improved overall survival of patients affected by the condition.

The condition is life-threatening and chronically debilitating due to congenital total alopecia, dysplastic nails, and immunodeficiency leading to severe, recurrent, and life-threatening infections.

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

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

A positive opinion for allogeneic cultured postnatal thymus-derived tissue, for treatment of severe combined immunodeficiency due to FOXN1 deficiency, was adopted by consensus.

2.2.16. - EMA/OD/0000002429

Treatment of essential thrombocythemia

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 February 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

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. - -

Treatment of multiple myeloma

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 diffuse large B-cell lymphoma

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 diffuse large B-cell lymphoma

The status of the procedure was noted.

3.2. Finalised letters

3.2.1. -

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

The finalised letter was circulated for information.

3.2.2. -

Treatment of neurofibromatosis type 1

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of ATTR amyloidosis

The new request was noted.

3.3.2. -

Treatment of congenital adrenal hyperplasia

The new request was noted.

3.3.3. -

Treatment of gastric carcinoid

The new request was noted.

3.3.4. - -

Treatment of beta-thalassaemia intermedia and major

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. – cannabidiol - EMEA/H/C/004675

GW Research Ltd;

a) Treatment of Dravet syndrome EMA/OD/083/14, EU/3/14/1339

b) Treatment of Lennox-Gastaut syndrome EMA/OD/275/16, EU/3/17/1855

The status of the procedure at CHMP was noted.

4.2.2. - 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.

4.3. Appeal

None

4.4. On-going procedures

None

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. Adcetris - Brentuximab vedotin – Type II variation – EMEA/H/C/002455/II/0055, EMEA/OD/073/08, EU/3/08/596

Takeda Pharma A/S; Treatment of Hodgkin lymphoma

CHMP rapporteur: Paula Boudewina van Hennik; CHMP co-rapporteur: Jan Mueller-Berghaus;

A list of issues was adopted on 13 September 2018.

An oral explanation was held on 22 January 2019.

An opinion recommending not to remove Adcetris 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. 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 status of the procedure at CHMP was noted.

5.2.2. 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 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

None

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

None

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 22 January 2019.

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 December 2018

7.2.2.

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)

Draft EMA PCWP Mandate and composition, draft EMA HCPWP Mandate and composition and draft EMA PCWP and HCPWP Rules of procedure were adopted.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

Action: For information

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 2019

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

None

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 22-24 January 2019 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	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Elizabeth Rook	Member	Netherlands	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:	3.1.3.
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
	Expert - in person*	MEB-NL	No interests declared	
	Expert - in person*	MEB-NL	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/