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Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 15-17 February 2022

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

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.

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the COMP plenary session to be held 15-17 February 2022. See February 2022 COMP minutes (to be published post March 2022 COMP meeting).

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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 that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

COMP agenda for 15-17 February 2022 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 18-20 January 2022 were adopted and will be published on the EMA website

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. tropatepine hydrochloride - EMA/OD/0000068622

Laboratoires Delbert; Treatment of narcolepsy

COMP Rapporteur: Robert Nistico

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 estimation and presentation of the prevalence estimate the sponsor was requested to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation". The sponsor was asked to justify the choice of the sources selected for the estimation of the prevalence of the condition. Secondary narcolepsy has not been considered in the estimation provided. The sponsor was requested to re-calculate the prevalence by including secondary narcolepsy.

- Significant benefit

The arguments on significant benefit were based on a more favourable tolerability profile (based on the mechanism of action) compared to approved medications and on its potential in reducing cataplexy episodes in drug-resistant patients. The small sample size analysed limits the interpretation of the results obtained in the context of significant benefit. Therefore, the sponsor was asked to further elaborate the significant benefit assumption and the place in therapy of tropatepine within the current treatment algorithm.

In the written response, the sponsor used an equation for the estimate as follows: the prevalence of narcolepsy in equal to: $P = I_{narcolepsy} \times D_{narcolepsy} + I_{secondary\ narcolepsy} \times D_{secondary\ narcolepsy} = 0.0623 \times 57.9 + 0.55 \times 1 = 4.157$. The incidence of narcolepsy is composed of the addition of its incidence reported on the overall period covered by the studies (2000-2017), plus the incidence of secondary narcolepsy reported by Heier on the specific period covered (2009-2011). The duration of the narcolepsy was estimated to be 57.9 years based on the mean age at narcolepsy onset = 23.4 years (Dauvilliers, 2001) an the mean life expectancy at birth in Europe = 81.3 years (Eurostat, accessed in July 2021).

For secondary narcolepsy, the duration taken into account is 1 year (Julia Stowe, 2020). The COMP agreed with the prevalence of 4.2 in 10,0000 persons.

For the demonstration of significant benefit, the sponsor argued that all patients described in the 4 cases presented ineffective and/or not tolerated treatments and drug-resistant cataplexy. The efficacy of tropatepine on the frequency and severity of both partial and complete cataplexy was reported by all patients. Tropatepine had also shown efficacy on other narcolepsy symptoms, including nightmares, disturbed nocturnal sleeps, behavioural disorders in REM sleep, and hypnopompic hallucinations. The sponsor clarified that tropatepine will be used as second line treatment in patients with narcolepsy type 1, for whom existing treatments are either not tolerated or show no efficacy on narcolepsy symptoms.

Based on these arguments, the COMP considered that the reduction in severity and frequency of cataplexy in refractory patients can justify the significant benefit for the orphan designation and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing tropatepine hydrochloride was considered justified based on reduction in severity and frequency of cataplexy observed in clinical cases.
The condition is chronically debilitating in particular due to excessive daytime sleepiness and cataplexy episodes, as well as life-threatening with a 1.5-fold excess mortality in narcolepsy patients relative to those without narcolepsy.

The condition was estimated to be affecting approximately 4.2 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 tropatepine hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate reduction in severity and frequency of cataplexy in patients refractory to current authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tropatepine hydrochloride, for treatment of narcolepsy, was adopted by consensus.

2.1.2. - EMA/OD/0000073716

Treatment of epidermolysis bullosa

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 03 February 2022, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000073624

Prevention of graft versus host disease (GvHD)

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 potential improved efficacy in the condition. The sponsor was requested to further discuss the arguments provided for significant benefit and to further elaborate on the possible beneficial effect of the product, especially in combination with standard of care in the prevention of graft versus host disease.

In the written response and during an oral explanation before the Committee on 16 February 2022, the sponsor provided published clinical data reporting six patients with the most severe form of acute GvHD who were unresponsive to systemic steroids and ruxolitinib. All patients received teduglutide, a GLP-2 analogue such as the proposed product, combined with standard GvHD prophylaxis. All patients treated with teduglutide achieved a marked partial GvHD response on day 10, as shown by a substantial reduction of daily diarrhoea, together with an increase in serum albumin (Norona 2021).

In addition, the sponsor presented non-clinical data which showed that teduglutide added to prednisolone treatment increased survival rates from 20% to 90% in the study subjects.

However, the COMP considered that this data could not justify the significant benefit since they refer to a different product, and not the one for designation. The presented published evidence to support the assumption of improved efficacy was not considered sufficient to support this argumentation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2022, prior to final opinion.

2.1.4. - EMA/OD/0000068912

Treatment of gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs)

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 (patients amenable to loco-regional treatment).

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the comparability of the non-clinical models e.g. the different characteristics of the strains used. In addition, the sponsor was asked to elaborate on the selection criteria for treatment and submit clinical data if available in order to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response and during an oral explanation before the Committee on 16 February 2022, the sponsor argued that the cell line used for the non-clinical models was identical and administered in the same amount (5-10 x 106) and into the same location in all three models. The control tumour growth rate was similar in all three models (500 mm3 in 12-16 days). Regarding the different strains, in the non-clinical models, the sponsor underlined that the important feature is not the genetic background, but the Foxn1nu mutation which causes a deteriorated thymus and thus, the absence of T-cells. The sponsor also argued that the proposed product has a more pronounced effect on tumour growth and survival prolongation (with additional supportive evidence from different vector in outbred strain) when specific xenografts were studied (derived from metastatic pancreatic NET, known to be highly sensitive to mTOR inhibitors and somatostatin analogues (see Maharjan et al. 2021).

In addition, the sponsor provided preliminary clinical data from 3 GEP-NET patients with liver metastases (ongoing Phase I/IIa study). The patients were pretreated with (at least) somatostatin analogues and Peptide Receptor Radionuclide Therapy (PPRT, Lutathera).

The median overall survival (OS) observed in these patients was 14, 24 and 5 months respectively. The patient with the worst prognosis (pancreatic NET, advanced progressive unresectable, progressed on everolimus and ^{177}Lu) had the longest median OS (24 months). The sponsor acknowledged that it is difficult to draw any conclusion, however highlighted the outcome of the pancreatic NET patient as promising. Finally, the outcome of one patient with a different condition (bronchial NET) from the same study was provided. The patient had multiple liver metastases, progressive disease and 5 prior therapies. The sponsor presents response data based on shrinkage of metastases (in CT). One metastasis shrinked from 64mm to 55mm diameter, the other one did not change the size. After treatment with the proposed product, the patient became eligible to a chemotherapy regimen, for which he was not eligible before.

The COMP agreed with the sponsor that it is difficult to conclude based on the outcome from the three patients. Furthermore, the fourth patient had a different condition for which an extrapolation couldn't be accepted. In conclusion, the COMP considered that based on the absence of comparative nonclinical data and the limited preliminary clinical data the justification for the significant benefit is not acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2022, prior to final opinion.

2.1.5. hymecromone - EMA/OD/0000064376

Ros Lynch; Treatment of spinal cord injury

COMP Rapporteur: Michel Hoffmann

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 has applied for incomplete spinal cord injury however the COMP has previously designated spinal cord injury, the sponsor therefore was invited to amend to this condition. 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 whether there exists a scientific rationale for the development of the proposed product for treatment of spinal cord injury the sponsor should further elaborate on the methodology, trial design, numbers used per group, measures made in the non-clinical in vivo study submitted as well as the results from this study and its relevance for the development of the product in the condition.

- Number of people affected

The sponsor provided a prevalence estimate for incomplete spinal cord injury. The proposed condition appeared to be a subset of the broader condition spinal cord injury. The sponsor was asked to change the condition to spinal cord injury and provide a revised estimate.

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

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved efficacy in the condition.
The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the bibliographical studies and their non-clinical in vivo data to justify the assumption of significant benefit over methyl prednisone for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 16 February 2022, the sponsor proposed treatment of traumatic spinal cord injury which during the oral explanation they accepted to change to treatment of spinal cord injury. The COMP acknowledged the difficulties in establishing the prevalence for the condition in general and accepted the submitted estimate of 4.3 in 10,000 for the proposed condition of treatment of spinal cord injury.

The sponsor argued in their written response that the use of methyl prednisolone (MP) in spinal cord injury is controversial and despite the traditional use of MP, the effect is limited to a potential anti-inflammatory effect the acute phase of the trauma. The COMP noted that

the indirect comparison based on the sponsor's non-clinical in vivo data and published data continues to be inconsistent in supporting the basis of a clinically relevant advantage versus MP in the acute setting. The COMP asked the sponsor during the oral explanation if they had additional data for the use of 4MU in the sub-chronic or chronic setting as the non-clinical in vivo data in the presentation appeared to indicate that there was further testing in the subacute setting. The sponsor acknowledged that they did have additional data that they had not submitted in the written response nor during the main presentation of the oral explanation. This additional data was then presented. The data has been generated in the same non-clinical in vivo model of the condition but in the chronic setting where currently there are no authorized medicines. Behavioural assessments involved coarse motor function evaluations using the Basso, Beattie and Bresnahan hindlimb locomotor open field test and fine motor functions using the horizontal rung ladder test. They also measured glycosaminoglycans after treatment.

The study involved the generation of a spinal injury with 200 kdyn contusion at the level of T9 at the site of the T8 dorsal laminectomy. Treatment was started at 8 weeks post spinal cord injury and continued for 8 weeks. Rehabilitation was 5 days per week until perfusion.

The results showed that significant improvement was noted in the Basso, Beattie and Bresnahan test after 3 weeks of treatment with 4MU (that is 11 weeks after injury). In the Horizontal rung ladder test the animals showed a significantly higher proportion to controls who showed good stepping following 5weeks of treatment (13 weeks) after injury versus controls. Regarding glycosaminoglycans, it was noted that although rehabilitation improved their level in the spinal cord and brain, 4MU had a significantly better effect at week 8 of treatment or 16weeks following injury. The COMP accepted that this data could support the potential benefit in the sub-acute and chronic setting of the condition.

The COMP considered that sufficient data had been submitted to support significant benefit and agreed to recommend granting the orphan designation.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of spinal cord injury.

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

The intention to treat the condition with the medicinal product containing hymecromone was considered justified based on non-clinical in vivo data in a model of the condition which showed a partial motor and functional recovery within the context of rehabilitation.

The condition is life-threatening and chronically debilitating due to sensory and motor loss of function in the limbs, with reduced life expectancy.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing hymecromone will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that there was partial motor and functional recovery when the product was given in the sub-acute and chronic spinal injury setting where currently there are no

authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for hymecromone, for treatment of spinal cord injury, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. dersimelagon - EMA/OD/0000065936

Mitsubishi Tanabe Pharma GmbH; Treatment of erythropoietic protoporphyria

COMP Rapporteur: Enrico Costa

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

The intention to treat the condition with the medicinal product containing dersimelagon was considered justified based on preliminary clinical data which showed an improvement in average daily duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms in the group of patients treated with the proposed product compared to the placebo group.

The condition is chronically debilitating due to skin photosensitivity, anaemia and liver complications and life-threatening as patients may die from liver failure.

The condition was estimated to be affecting not more than 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 dersimelagon will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the proposed product covers a broader population in comparison to the authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for dersimelagon, for treatment of erythropoietic protoporphyria, was adopted by consensus.

2.2.2. codergocrine mesilate, oxitriptan - EMA/OD/0000066660

Purposeful I.K.E.; Treatment of fragile X syndrome

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing codergocrine mesilate, oxitriptan was considered justified based on non-clinical in vivo data in a model of the condition showing a reversal of several phenotypic behavioural features to that observed in the wild type control group.

The condition is chronically debilitating due to developmental delay as well as a range of behavioural and cognitive deficits.

The condition was estimated to be affecting approximately 2.4 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 codergocrine mesilate, oxitriptan, for treatment of fragile X syndrome, was adopted by consensus.

2.2.3. treprostinil sodium - EMA/OD/0000070626

Unither Therapeutik GmbH; Treatment of idiopathic pulmonary fibrosis

COMP Rapporteur: Eva Malikova

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

The intention to treat the condition with the medicinal product containing treprostinil sodium was considered justified based on non-clinical data showing reduced fibrosis, maintained lung function and prevented bleomycin induced lung injury and fibrosis in addition to vascular remodelling. In addition, preliminary clinical data showed a significant improvement in 6-minute walk distance compared to placebo, and significant improvements in forced vital capacity with inhaled treprostinil compared to placebo in patients who were on background therapy with standard of care.

The condition is chronically debilitating due to progressive dyspnoea and loss of lung function, with limited exercise capability and decreased quality of life and life threatening with a median survival of less than five years, and death ultimately occurs due to respiratory failure.

The condition was estimated to be affecting approximately 3.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing treprostinil sodium will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improvements in forced vital capacity with inhaled treprostinil in patients treated with the currently authorised products for the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for treprostinil sodium, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.4. heterologous human adult liver-derived stem cells - EMA/OD/0000071526

Unicyte S.R.L.; Treatment of argininosuccinic aciduria

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived stem cells was considered justified based on preliminary clinical data showing that ammonia concentration could be stabilised within normal limits.

The condition is chronically debilitating due to consequences of metabolic decompensation leading to developmental delay, intellectual disability and other types of neurological symptoms, and life threatening due to organ failure.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing heterologous human adult liver-derived stem cells will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product could be given as a bridging therapy for patients awaiting orthotic liver transplantation, for which limited treatment options are available. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for heterologous human adult liver-derived stem cells, for treatment of argininosuccinic aciduria, was adopted by consensus.

2.2.5. - EMA/OD/0000072331

Treatment of X-linked protoporphyria (XLP)

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

2.2.6. - EMA/OD/0000072395

Treatment of primary biliary cholangitis

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

2.2.7. (S)-12-fluoro-4-(2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine - EMA/OD/0000072776

Pharma Gateway AB; Treatment of sickle cell disease

COMP Rapporteur: Enrico Costa

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 (S)-12-fluoro-4-(2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine was considered justified based on non-clinical data in a valid disease model which demonstrated the products ability to increase foetal haemoglobin levels which is expected to reduce the symptoms of the condition.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, stroke, chronic kidney disease, pulmonary hypertension, susceptibility to infections and skin ulcers and life-threatening with reduced life expectancy.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-12-fluoro-4-(2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid disease model which demonstrated the products ability to increase foetal haemoglobin levels in comparison to the levels achieved with currently authorized medicinal products in the first line setting. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (S)-12-fluoro-4-(2-methylpyridin-3-yl)-7a,8,13,14-tetrahydro-7H-[1,2,4]triazolo[4',3':1,6]pyrido[3,2-b]benzofuro[4,3-fg][1,4]oxazonine, for treatment of sickle cell disease, was adopted by consensus.

2.2.8. alisporivir - EMA/OD/0000073495

Fondazione Telethon; Treatment of collagen VI-related myopathies

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, collagen VI-related myopathies, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing alisporivir was considered justified based on non-clinical data in a valid disease model suggesting a reduction in muscle degeneration.

The condition is chronically debilitating and life threatening in particular due to progressive muscular hypotonia and weakness, respiratory impairment and reduction of the life expectancy.

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

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

A positive opinion for alisporivir, for treatment of collagen VI-related myopathies, was adopted by consensus.

2.2.9. emactuzumab - EMA/OD/0000075927

Synox Therapeutics Limited; Treatment of tenosynovial giant-cell tumour, local and diffuse type

COMP Rapporteur: Frauke Naumann-Winter

The Committee agreed that the condition, tenosynovial giant-cell tumour, local and diffuse type, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing emactuzumab was considered justified based on preliminary clinical data showing reduction in tumour volume providing a symptomatic improvement.

The condition is chronically debilitating due to loss of function of the affected joints, the development of secondary arthritis and the high recurrent nature of the condition.

The condition was estimated to be affecting approximately 2.8 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 emactuzumab, for treatment of tenosynovial giant-cell tumour, local and diffuse type, was adopted by consensus.

2.2.10. adeno-associated virus serotype HSC 15 expressing human iduronate 2-sulfatase - EMA/OD/0000075990

Diamond Pharma Services Ireland Limited; Treatment of mucopolysaccharidosis type II (Hunter syndrome)

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, mucopolysaccharidosis type II (Hunter syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype HSC 15 expressing human iduronate sulfatase was considered justified based on non-clinical data which showed increased human idorunate-2-sulfatase activity in serum and in brain and glycosaminoglycans-heparin sulfate reduction in brain, urine, and peripheral organs.
The condition is chronically debilitating due to neurological and intellectual decline, cardiovascular and pulmonary complications and life-threatening with a survival of 10-15 years.
The condition was estimated to be affecting less than 0.04 in 10,000 persons in the European Union, at the time the application was made.
In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype HSC 15 expressing human iduronate 2-sulfatase will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data which showed that in a relevant non-clinical disease model a single administration of this medicinal product increased the human idorunate-2-sulfatase activity in serum and in brain and resulted in glycosaminoglycans-heparin sulfate reduction in urine and peripheral organs and in particular in brain which is not achieved with the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype HSC 15 expressing human iduronate 2-sulfatase, for treatment of mucopolysaccharidosis type II (Hunter syndrome), was adopted by consensus.

2.2.11. - EMA/OD/0000075999

Treatment of epilepsy with myoclonic-atonic seizures

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

2.2.12. - EMA/OD/0000076085

Prevention of ischaemia-reperfusion injury in solid organ transplantation

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

2.2.13. adeno-associated virus serotype HSC 15, containing human homology arms, expressing human phenylalanine hydroxylase - EMA/OD/0000076117

Diamond Pharma Services Ireland Limited; Treatment of phenylalanine hydroxylase deficiency

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype HSC 15, containing human homology arms, expressing human phenylalanine hydroxylase was considered justified based on non-clinical data demonstrating that the proposed product can decrease serum phenylalanine levels.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype HSC 15 expressing human phenylalanine hydroxylase will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating that one single administration with the proposed product is able to decrease serum phenylalanine levels over 12 weeks follow-up period. The proposed therapy could therefore treat a wider patient population than treated with currently authorised products and reduce the need for regular treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype HSC 15, containing human homology arms, expressing human phenylalanine hydroxylase, for treatment of phenylalanine hydroxylase deficiency, 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 rapporteurs were appointed for 18 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 21 applications.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of primary IgA nephropathy

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

3.2. Finalised letters

3.2.1. -

Treatment of cystic fibrosis

The finalised letter was circulated for information

3.3. New requests

3.3.1. -

Treatment of mucopolysaccharidosis type I

The new request was noted.

3.3.2. -

Treatment of acute myeloid leukaemia

The new request was noted.

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

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

4.1.1. Breyanzi – lisocabtagene maraleucel - EMEA/H/C/004731/0000

Celgene Europe B.V.

COMP Rapporteurs: Frauke Naumann-Winter; Karri Penttila

a) Treatment of primary mediastinal large-B-cell lymphoma, EMA/OD/0000001127, EU/3/18/2099, EMA/OD/0000039978

b) Treatment of diffuse large B-cell lymphoma, EMA/OD/045/17, EU/3/17/1890, EMA/OD/0000039934

c) Treatment of follicular lymphoma, EMA/OD/260/17, EU/3/18/2018, EMA/OD/0000039979

A list of issues was adopted on 20 January 2022.

An oral explanation was held on 15 February 2022.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the EC register of orphan medicinal products, on 20 February 2022, prior to final opinion.

The orphan designation withdrawal assessment report will be publicly available on the EMA website.

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

4.2.1. Kimmtrak – tebentafusp - EMEA/H/C/004929/0000, EU/3/21/2397, EMA/OD/0000068646

Accelerated assessment

Immunocore Ireland Limited; Treatment of uveal melanoma

COMP Rapporteurs: Armando Magrelli; Pauline Evers

An opinion recommending not to remove Kimmtrak, tebentafusp, EU/3/21/2397 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.

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

4.2.2. Yescarta - autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor - EMEA/H/C/004480/II/0042, EU/3/15/1579, EMA/OD/0000068456

Kite Pharma EU B.V.; 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 April meeting.

4.3. Appeal

4.3.1. Uplizna – inebilizumab - EMEA/H/C/005818/0000, EMA/OD/267/16, EU/3/17/1856, EMA/OD/0000079956

Viela Bio B.V.; Treatment of neuromyelitis optica spectrum disorders

COMP appeal rapporteurs: Michel Hoffmann, Tim Leest

In the grounds for appeal, and during an oral explanation before the Committee on 16 February 2022, the sponsor aimed to address the main issues which led to the negative opinion.

The COMP upheld the negative view and an opinion recommending removing Uplizna (EU/3/17/1856) 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

4.4. On-going procedures

The COMP noted the review of orphan designation for OMP for MA - On-going procedures. COMP co-ordinators were appointed for 1 application.

4.5. Orphan Maintenance Reports

None

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Yescarta - autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor - EMEA/H/C/004480/II/0046, EU/3/14/1393, EMA/OD/0000076832

Kite Pharma EU B.V.; Treatment of diffuse large B cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor.

5.3. Appeal

None

5.4. On-going procedures

The COMP noted the review of orphan designation for OMP for MA extension - On-going procedures

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The COMP noted that Mr George Dimopoulos' mandate as COMP member representing Greece has ended.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

None

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely 14 February 2022.

7.1.5. Principal Decisions Database

The COMP acknowledged the importance of adding further topics to the database.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

7.2.2. COMP-CAT Working Group

The meeting was held virtually on 14 February 2022 at 17:30

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 tabled for information.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. 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 2022

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2022 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. EMA survey on Orphan Maintenance Assessment Report (OMAR)

The COMP noted the presentation and survey conducted, which was one of the topics in the COMP 2021 work plan. The use of OMARs was evaluated by the external stakeholders (industry, patients organisations, NCAs etc) in November 2021. Answers were received until end of 2021. There were 81 responders.

The results of the survey were that OMARs were accessed 47% by the industry, followed by 60% of responders knew how to find OMARs. 92% had used/reviewed OMARs before. 44% thought that OMARs were informative, however there were comments that OMARs should have better structure in the document and more details should be provided about prevalence, existing treatments. In addition, the responders commented that OMARs should be more visible and easier to access on the EMA website. It was considered that EMA templates should be updated. COMP rapporteurs should be involved earlier in the review of the full report. It was agreed to further discuss how to update OMARs in any upcoming meetings or during the plenary.

8.2. Study on spinal muscular atrophy (SMA) using registry data

The COMP noted the presentation about EMA funded registry-based study on SMA (spinal muscular atrophy). The main objective of the study is to investigate SMA patients' course of disease and standards of care delivery over time in at least 5 European countries including at least 4 Member States of the EEA. The 2 main objectives include a description of the disease (by SMA type) and its progression based on patients' characteristics at baseline and throughout its course; and a description of the patients' clinical management and its evolution over time considering all available treatment options including gene therapy.

Deliverables and draft timelines of the study are:

1. Study plan: D + 1 month (D: contract signature date)

2. Study protocol: D + 3 months

3. Study report: D + 8 months

4. Manuscript: D + 9 months

It was agreed that COMP will be regularly updated on the progress of the study. Comments raised included the need to involve the patients association SMA Europe in the review of the deliverables and the need to explore possibility to take into account HTA requirements in the data elements that will be collected.

[Post meeting note: SMA Europe was contacted and agreed to provide comments on the deliverables.]

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 15-17 February 2022 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 Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No restrictions applicable to this meeting	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Enrico Costa	Member	Italy	No restrictions applicable to this meeting	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
Elizabeth Rook	Member	Netherlands	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Armando Magrelli	Member (Vice Chair)	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	
Maria Cavaller Bellaubi	Expert - via WebEx*	Patients' Organisation Representative	No restrictions applicable to this meeting	
	Patient expert - via WebEx*	European Union - EMA	No interests declared	
Jeanette McCallion	Expert - via WebEx*	Ireland	No interests declared	
Meeting run with support from relevant EMA staff				

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

10. 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/