EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 December 2012
EMA/COMP/648772/2012
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 6 - 7 November 2012 meeting

Note on access to documents

Documents under points 1.1 and 2 to 7 cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form 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 Adoption of the draft agenda EMA/COMP/645431/2912

The agenda was adopted with no amendments.

1.2 Adoption of the draft minutes of the COMP meeting held on 3 - 5 October 2012, EMA/COMP/589195/2012

The minutes were adopted with a minor correction.

1.3 Conflicts of Interest

The COMP secretariat was informed as follows:

- K. Kubacková declared a potential conflict of interest for agenda point 2.2.3;

- Eurordis receives funding from the sponsor who have submitted an application to be considered for orphan designation at the current meeting (2.2.3). Nevertheless, no direct conflicts of interest have been identified for L. Greene and B. Byskov Holm, who are the volunteer patient representatives for EURORDIS;

- EGAN received grants from the sponsor of the product under agenda point 5.2.2 (review of the OMP designation). Nevertheless, no direct conflicts of interest have been identified for P. Evers, who is representing EGAN in the COMP.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 For treatment of diffuse large B-cell lymphoma, EMA/OD/073/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor was requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

The sponsor was requested to further elaborate on the justification of significant benefit. In particular the sponsor was asked to discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor defended the choice of the preclinical model used in the application on the grounds that this presents with lymphadenopathy and that the product is expected to have a relevant effect on this. The sponsor discussed that no other models that target this feature of non-Hodgkin lymphomas had been identified and that lymphadenopathy was not reproduced in xenograft models.

With regards to the selectivity of the product's activity, the sponsor stated that the product seems to induce apoptosis in lower concentrations for B cells from CLL patients compared to B-cells from healthy controls or compared to T or NK cells from CLL patients.

The significant benefit was argued on the basis of a clinically relevant advantage supported by improved efficacy and safety. Improved efficacy is claimed on the basis of "targeting" lymph nodes as well as ex vivo data in CLL samples showing additive (or even synergistic) effects in lower concentrations on top of rituximab. The safety argument is based on the potential absence of myelotoxicity.

The Committee considered that the proposed mechanism of action remained assumptive and that other potential alternative mechanisms had also been discussed in the literature (e.g. mTOR inhibition). The Committee also inquired into the formulation of the product and sought clarification with regards to a potential liposomal formulation and its pharmacokinetic properties. With regards to the significant benefit the alternative mechanism of action would not suffice per se to translate into a potential for a major contribution to patient care and further data were considered necessary to justify the claim.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 November 2012, prior to final opinion.

2.1.2 For treatment of follicular lymphoma - EMA/OD/076/12

[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor was requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor was requested to further elaborate on the justification of significant benefit. In particular the sponsor was asked to discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor defended the choice of the preclinical model used in the application on the grounds of the feature of lymphadenopathy. The sponsor discussed that no other models that target this feature of non-Hodgkin lymphomas had been identified and that lymphadenopathy was not reproduced in xenograft models.

As per the requested clarification for the selectivity of the product, the sponsor stated that a mitochondrial mechanism of action would preferentially target more active cells such as neoplastic cells and discussed in vitro data showing that the pro-apoptotic profile of the product on CLL patient samples. In these studies, the product was appearing to induce apoptosis in lower concentrations for B cells from CLL patients compared to B-cells from healthy controls or compared to T or NK cells from CLL patients.

The proposed dose for humans was also discussed based on allometry and was proposed to be well below the maximum dose in humans referred in the SPC for the per os already marketed formulation.

The significant benefit was argued on the basis of improved efficacy and safety. Improved efficacy is argued on the basis of "targeting" lymph nodes as well as ex vivo data in CLL samples showing additive (or even synergistic) effects in lower concentrations on top of rituximab. The safety argument is based on the argued absence of myelotoxicity.

The Committee considered that the proposed mitochondrial mechanism of action remained assumptive and that other potential alternative mechanisms had also been discussed in the literature (e.g. mTOR inhibition). The Committee also inquired into the formulation of the product and sought clarification with regards to a potential liposomal formulation and its pharmacokinetic properties. With regards to the significant benefit the alternative mechanism of action would not suffice per se to translate into a potential for a major contribution to patient care and further data were considered necessary to justify the claim.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 November 2012, prior to final opinion.

2.1.3 For treatment of mantle cell lymphoma - EMA/OD/077/12

[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor was requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor was requested to further elaborate on the justification of significant benefit. In particular the sponsor was asked to discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor defended the choice of the preclinical model used in the application on the grounds of the feature of lymphadenopathy. The sponsor discussed that no other models that target this feature of non-Hodgkin lymphomas had been identified and that lymphadenopathy was not reproduced in xenograft models.

As per the requested clarification for the selectivity of the product, the sponsor stated that a mitochondrial mechanism of action would preferentially target more active cells such as neoplastic cells and discussed in vitro data showing that the pro-apoptotic profile of the product on CLL patient samples. In these studies, the product was appearing to induce apoptosis in lower concentrations for B cells from CLL patients compared to B-cells from healthy controls or compared to T or NK cells from CLL patients.

The proposed dose for humans was also discussed based on allometry and was proposed to be well below the maximum dose in humans referred in the SPC for the per os already marketed formulation.

The significant benefit was argued on the basis of improved efficacy and safety. Improved efficacy is argued on the basis of "targeting" lymph nodes as well as ex vivo data in CLL samples showing additive (or even synergistic) effects in lower concentrations on top of rituximab. The safety argument is based on the argued absence of myelotoxicity.

The Committee considered that the proposed mitochondrial mechanism of action remained assumptive and that other potential alternative mechanisms had also been discussed in the literature (e.g. mTOR inhibition). The Committee also inquired into the formulation of the product and sought clarification with regards to a potential liposomal formulation and its pharmacokinetic properties. With regards to the significant benefit the alternative mechanism of action would not suffice per se to translate into a potential for a major contribution to patient care and further data were considered necessary to justify the claim.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 November 2012, prior to final opinion.

2.1.4 For treatment of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma - EMA/OD/083/12

[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor was requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor was requested to further elaborate on the justification of significant benefit. In particular the sponsor was asked to discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor defended the choice of the preclinical model used in the application on the grounds of the feature of lymphadenopathy. The sponsor discussed that no other models that target this feature of non-Hodgkin lymphomas had been identified and that lymphadenopathy was not reproduced in xenograft models.

As per the requested clarification for the selectivity of the product, the sponsor stated that a mitochondrial mechanism of action would preferentially target more active cells such as neoplastic cells and discussed in vitro data showing that the pro-apoptotic profile of the product on CLL patient samples. In these studies, the product was appearing to induce apoptosis in lower concentrations for B cells from CLL patients compared to B-cells from healthy controls or compared to T or NK cells from CLL patients.

The proposed dose for humans was also discussed based on allometry and was proposed to be well below the maximum dose in humans referred in the SPC for the per os already marketed formulation.

The significant benefit was argued on the basis of improved efficacy and safety. Improved efficacy is argued on the basis of "targeting" lymph nodes as well as ex vivo data in CLL samples showing additive (or even synergistic) effects in lower concentrations on top of rituximab. The safety argument is based on the argued absence of myelotoxicity.

The Committee considered that the proposed mitochondrial mechanism of action remained assumptive and that other potential alternative mechanisms had also been discussed in the literature (e.g. mTOR inhibition). The Committee also inquired into the formulation of the product and sought clarification with regards to a potential liposomal formulation and its pharmacokinetic properties. With regards to the significant benefit the alternative mechanism of action would not suffice per se to translate into a potential for a major contribution to patient care and further data were considered necessary to justify the claim.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 November 2012, prior to final opinion.

2.1.5 For treatment of Extranodal Marginal Zone B-cell Lymphoma of the MALT type - EMA/OD/072/12

For treatment of B-cell prolymphocytic leukemia - EMA/OD/074/12

For treatment of Burkitt lymphoma - EMA/OD/075/12

For treatment of nodal marginal zone B-cell lymphoma ± monocytoid - EMA/OD/078/12

For treatment of splenic marginal zone B-cell lymphoma - EMA/OD/079/12

For treatment of mature B-cell lymphoma: plasma cell lymphoma/plastocytoma - EMA/OD/080/12

For treatment of lymphoplasmacytic lymphoma - EMA/OD/081/12

For treatment of hairy cell leukemia - EMA/OD/082/12

[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

The Committee noted the withdrawal of the applications prior to responding to the COMP list of questions.

2.1.6 Cyclo(-gamma-aminobutyryl-L-phenylalanyl-L-tryptophanyl-D-tryptophanyl-L-lysyl-L-threonyl-L phenylalanyl-N-3-carboxypropyl)-glycine amide, acetate salt for treatment of acromegaly, Dr Ulrich Granzer - EMA/OD/107/12

[Co-ordinators: K. Westermark / S. Tsigkos]

As agreed during the October meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the significant benefit jusitfication. The arguments on significant benefit are based on the potentially clinically relevant advantage supported by improved efficacy and safety in the condition, based on preclinical comparisons to octreotide. In the preclinical settings discussed, the sponsor was requested to further elaborate on the product's activity and GH response in adenoma cells tested.

The sponsor was also requested to elaborate on the clinical relevance of the proposed safety profile in the in vivo preclinical studies. The grounds on which the preclinical data presented are expected to be translated into a clinically relevant advantage should be discussed.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor elaborated on the argument of significant benefit on the grounds of clinically relevant advantage supported by both improved efficacy and safety compared to octreotide.

The improved efficacy was based on a novel pharmacodynamics profile versus octreotide, with the proposed active substance activating somatostatin receptor 4. To further justify the claims of improved efficacy the sponsor also discussed some unpublished observations: in vitro 48% (10/21) of adenomas from acromegaly patients responded to DG3173 compared to 24% (5/21) responding to octreotide treatment.

With regards to the argument of improved safety, the sponsor reported data from studies in healthy subjects and showed statistical significant differences with regards to gastric emptying and postprandial glucose profiles. The sponsor also reported preliminary clinical data of phase I from an on-going safety study comparing to octreotide in healthy volunteers.

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

The intention to treat the condition with the proposed product was considered justified based on preclinical studies, showing responses in human growth hormone secreting adenoma cells. The

condition was estimated to be affecting less than 1.2 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to the development of respiratory dysfunction and joint arthropathy and life-threatening due to increased risk for cardiovascular disease. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that cyclo(-gamma-aminobutyryl-L-phenylalanyl-L-tryptophanyl-D-tryptophanyl-L-lysyl-L-threonyl-L phenylalanyl-N-3-carboxypropyl)-glycine amide, acetate salt may be of significant benefit to those affected by the condition. This was considered justified on the basis of the clinically relevant advantage of improved efficacy, on the grounds of preclinical studies showing improved response in human adenoma cells in comparison to octreotide. A potentially improved safety profile was also supported by preclinical animal studies showing improved glucose tolerance and biliary tract function in comparison to octreotide.

A positive opinion for cyclo(-gamma-aminobutyryl-L-phenylalanyl-L-tryptophanyl-D-tryptophanyl-L-lysyl-L-threonyl-L phenylalanyl-N-3-carboxypropyl)-glycine amide, acetate salt, for treatment of acromegaly, was adopted by consensus.

2.1.7 Voclosporin for treatment of non-infectious uveitis, Granzer Regulatory Consulting & Services - EMA/OD/118/12
[Co-ordinators: V. Stoyanova / S. Tsigkos]

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

- Medical plausibility

In view of the results of the earlier presented pivotal studies, the sponsor was asked to elaborate on the medical plausibility, by providing any available preliminary data from the additional phase 3 study.

- Prevalence

The sponsor was asked to provide a comparative discussion on the prevalence of non-infectious uveitis versus the prevalence of chronic-non-infectious uveitis.

The sponsor was asked to explain the discrepancy between the calculations presented in the previous designation held by the sponsor which is understood as a subset of the current indication and consequently should have a lower prevalence estimate.

- Justification of significant benefit

The justification of significant benefit is argued on the basis of a clinically relevant advantage supported by the potential improved safety of the product versus cyclosporin, on a comparative trial in psoriasis. The sponsor was invited to further elaborate on this comparison and clearly justify how these data may be translated into a clinically relevant advantage or a major contribution to patient care.

In addition the sponsor was invited to position the proposed product in the current management of non-infectious uveitis patients, by providing a comparative discussion versus all authorised products.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor reported that no further clinical data were available, but counter argued that the results in the vitreal haze reduction already shown in the clinical setting would be enough to justify medical plausibility for the purposes of orphan designation. With regards to the apparent paradox of the prevalence when cross examined with the previous designation, the sponsor asserts that "chronic" is not actually a subset of the previous designation, but that it is a new amended wording following the

recommendations of the Uveitis Nomenclature Working group. Finally, the sponsor reiterated the significant benefit arguments of improved safety based on a psoriasis comparative trial, and also noted that the dose of ciclosporin used (3 mg/kg) is lower than the dose of ciclosporin (5-7 mg/kg) approved for treatment of uveitis.

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

The intention to treat the proposed condition with voclosporin is considered justified based on preclinical data in animal models and preliminary clinical data showing improved vitreal haze score compared to placebo. The condition was estimated to be affecting less than 4.8 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to visual loss. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that voclosporin may be of significant benefit to those affected by the condition. This is based on the clinically relevant advantage of improved safety, based on preliminary clinical data in other indications that show an improved safety profile over ciclosporin. The potential to reduce the dose of corticosteroid use was also considered justified on the grounds of preliminary clinical data.

A positive opinion for voclosporin, for treatment of non-infectious uveitis, was adopted by consensus.

2.1.8 For treatment of squamous cell carcinoma of the head and neck - EMA/OD/120/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor was requested to further elaborate on the proposed mechanism of action. In particular, the kinetics of the proposed product, including the selective uptake by the tumour cells, is to be further discussed.

- Prevalence

The sponsor was invited to re-calculate the prevalence based on a justified duration of the condition and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was asked to perform a sensitivity analysis of the reported calculations. 5-year prevalence data are also expected.

- Justification of significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit versus authorised products for the proposed condition as applied for.

The sponsor was asked to position the proposed treatment in the current management of head and neck patients and provide data to justify a clinically relevant advantage or a major contribution to patient care.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor proposed to change the indication to a subset of SCHNC, namely patients undergoing chemotherapy. The sponsor elaborated on the mechanism of action, and stressed that due to its amphiphilic properties the compound is expected to be localised initially on the outside membrane of

the cell but after endocytosis on the inside of the membranes of the endocytic vesicles. The kinetic properties of the product were not specifically discussed, nor the selectivity of the product. The sponsor only stated that "at least" some selectivity for the tumour exists, based on an experimental model that shows increased concentration in the tumour compared to adjacent muscle but not compared to normal skin.

With regards to the prevalence calculation, the sponsor acknowledged that 5-year prevalence exceeds the provisioned threshold for designation (5.9/10,000 if 90% of head and neck cancers are assumed to be squamous) and restricted the indication to only patients undergoing chemotherapy. The sponsor proposed that early stage patients are not to be taken into account and postulated a 25 to 40% of patients as the relevant fraction for the calculation of prevalence, based on NHS and US data. The upper limit with this calculation takes the calculation up to 4.65. Finally, for the significant benefit the sponsor focused on the alternative mechanism of action.

The Committee considered that the proposed subset cannot be considered acceptable, on the basis of guideline ENTR6283/00 Rev 03 that states that different degrees of severity or stages of a disease would not generally be considered as distinct conditions. The COMP discussed that even though early stage patients may not be treated with chemotherapy in clinical practice, there are no pharmacological grounds to support that the product might not work in early stage patients in combination with bleomycin as proposed. In addition, for the justification of significant benefit, the Committee requested the presentation of data in either preclinical or preliminary clinical settings in order to be able to justify translating the proposed new mechanism into a clinically relevant advantage or major contribution to patient care. The response from the sponsor in this regard was not satisfactory.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 November 2012, prior to final opinion.

2.1.9 For treatment of acquired aplastic anaemia - EMA/OD/100/12

[Co-ordinators: R. Elbers / S. Tsigkos]

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

- Description of the condition

Acquired aplastic anaemia should be justified as a distinct medical entity or the indication should be changed accordingly. In particular the company was asked to explain why the proposed product might not work in other forms of aplastic anaemia.

- Medical plausibility

To establish if a scientific rationale exists for the development of the product for treatment of aplastic anaemia, the sponsor was invited to further elaborate on:

- the proposed mechanism of "retro-differentiation",

- the absence of any preclinical models in the condition as applied for (acquired aplastic anaemia),

- the referenced clinical data, including a detailed account of the underlying conditions, previous treatments received and the uncontrolled nature of the observations.

- Life-threatening and debilitating nature of the condition

The sponsor was asked to further elaborate on the life threatening or chronically debilitating nature of the condition. From the data provided and the sponsor's arguments it is not well substantiated that the condition represents a life threatening or chronically debilitating condition.

- Prevalence

The sponsor was asked to justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

The sponsor was invited to re-calculate the prevalence based on relevant epidemiological studies and registries for the proposed orphan condition. Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was asked to perform a sensitivity analysis of the reported calculations.

- Existing methods of treatment

The sponsor was invited to perform a search through EU national formularies and central databases and confirm any existing authorised products for the proposed indication as applied for. If non-pharmacologic methods, as for example haematopoietic stem cell transplantation and agents to support these procedures, are considered satisfactory, adequate argumentation is to be provided in the application.

- Justification of significant benefit

In the absence of a justified medical plausibility the significant benefit cannot be considered. In case the sponsor submits further arguments for the medical plausibility section, the significant benefit should also be further elaborated versus the existing satisfactory methods of treatment and supported by any available scientific results.

A comparative discussion versus non-pharmacologic treatments, e.g. stem cell transplantation is also expected to be provided.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor acknowledged that the mechanism of action is not yet understood, but discussed that there have been clinical responses in aplastic anaemia patients treated with the proposed product that, according to the sponsor, would suffice to justify the intention to treat these patients with the proposed product. The sponsor also elaborated on the proposed condition, its chronically debilitating and life-threatening nature, its management and the calculation of prevalence.

The Committee considered that the proof of concept at this point in time rests mainly with four case reports as presented by the sponsor. These data are uncontrolled and of doubtful value due to the fact that some cases of the condition resolve spontaneously. In the absence of other medical plausibility justifications the justification of the intention to treat the condition cannot be accepted. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 November 2012, prior to final opinion.

2.1.10 For treatment of acanthamoeba keratitis - EMA/OD/090/12
[Co-ordinators: S. Thorsteinsson / S. Tsigkos]

The Committee noted the withdrawal of the application prior to responding to the COMP list of questions.

2.1.11 Alisertib sodium (alisertib) for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated), Takeda Global Research and Development Centre (Europe) Ltd - EMA/OD/104/12
[Co-ordinators: D. O'Connor / L. Fregonese]

As agreed during the October meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the prevalence. The sponsor calculated prevalence from incidence data and the estimated duration of the disease. The prevalence is considered by the sponsor to be 0.075 in 10,000 people, which is much lower than previous estimates for this condition, and the duration of the disease data are from the US and not from the EU. The sponsor was invited to re-calculate the prevalence using updated sources, and relevant European sources.

In its written response, the sponsor presented a recalculation of the prevalence in line with the request of the Committee. As per the sponsor's position, the highest prevalence estimates of PTCL in the EU-27 ranged from 0.18 per 10,000 people over 1 year to 0.71 per 10,000 people over a 5 year period.

The Committee agreed that the condition, peripheral T-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

Peripheral T-cell lymphoma was estimated to be affecting less than 1 in 10,000 people in the European Union when the application was made. The condition is chronically debilitating and life-threatening due to poor response to therapy and high rate of relapses. Five year overall survival is reported at average 25% to 40%, depending on sub-type, with most relapses occurring within 12 months. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive sub-types. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that alisertib may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on the alternative mechanism of action which has the potential to translate into clinical efficacy. This is suggested by early clinical results showing that the product resulted in complete and partial responses in some patients with aggressive relapsing or refractory peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated).

A positive opinion for alisertib, for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated), was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide for treatment of chronic lymphocytic leukaemia, AbbVie Ltd - EMA/OD/124/12
[Co-ordinators: D. O'Connor / S. Mariz]

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

The intention to treat the condition with the medicinal product was considered justified based on preliminary clinical data showing partial response in patients who have refractory chronic lymphocytic leukaemia. Chronic lymphocytic leukaemia was estimated to be affecting approximately 3 in 10,000 people in the European Union, at the time the application was made; the sponsor used several European registries to calculate the prevalence of the condition. The condition is life-threatening and

chronically debilitating due to development of cytopaenias (anaemia, neutropaenia, thrombocytopaenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide may be of significant benefit to those affected by the condition. This appears justified on the grounds of the clinically relevant advantage based on the alternative mode of action namely inhibition of the Bcl-2 protein which is an important regulator of the intrinsic apoptosis pathway which can translate into improved efficacy. This is supported by preliminary clinical data with the product in patients with refractory/ relapsed CLL showing partial response in these patients

A positive opinion for 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide, for treatment of chronic lymphocytic leukaemia, was adopted by consensus.

2.2.2 **Allopurinol sodium** for treatment of perinatal asphyxia, Pharmathen S.A. - EMA/OD/134/12

[Co-ordinators: A. Corrêa Nunes / S. Mariz]

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

Perinatal asphyxia was estimated to be affecting approximately 0.7 in 10,000 people in the European Union, at the time the application was made; this was established through an extensive literature search that the sponsor has conducted, which included many European countries. The condition is life-threatening and chronically debilitating due to deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain. Hypoxic damage can occur to most of the infant's organs (heart, lungs, liver, gut, kidneys), but brain damage is of most concern and perhaps the least likely to quickly or completely heal. In the more pronounced cases, an infant will survive, but with damage to the brain manifested as either mental, such as developmental delay or intellectual disability, or physical, such as spasticity and other muscular dysfunctions. Extreme degrees of asphyxia can cause cardiac arrest and death. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

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

2.2.3 **Maytansinoid-conjugated human monoclonal antibody against mesothelin** for treatment of malignant mesothelioma, Bayer Pharma AG - EMA/OD/063/12

[Co-ordinators: D. O'Connor / L. Fregonese]

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

Malignant mesothelioma was estimated to be affecting not more than 0.3 in 10,000 people in the European Union, at the time the application was made; the prevalence was estimated based on an analysis of the available literature, and on incidence data from international databases including reports from the WHO international mortality database and the EU-funded Rarecare project on rare cancers. The condition is life-threatening due to the invasion of the pleura leading to pleural effusions,

dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise ("incarceration" of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that maytansinoid-conjugated human monoclonal antibody against mesothelin may be of significant benefit to those affected by the condition. This appears justified by an alternative mechanism of action as compared to the currently authorized treatment for malignant mesothelioma. The proposed product enables the cytotoxic agent to enter mesothelioma cells by binding to mesothelin expressed on the tumour cells. Such mechanism of action is assumed to result in higher selectivity of the product for tumour cells. This has the potential to translate into a clinically relevant advantage in terms of an improved clinical efficacy when the product is used alone or in combination with other antineoplastic agents. Preliminary evidence of efficacy is supported by a xenograft model showing reduced tumour growth.

A positive opinion for maytansinoid-conjugated human monoclonal antibody against mesothelin, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.4 **Artesunate** for treatment of malaria, Dafra Pharma International nv - EMA/OD/123/12

[Co-ordinators: V. Stoyanova / L. Fregonese]

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

Malaria was estimated to be affecting not more than 0.3 in 10,000 people in the European Union, at the time the application was made. This value represents the annual incidence, which is to be considered a valid proxy for prevalence for conditions with duration of less than one year. The main sources used for estimating incidence of malaria in the EU were the literature and the Centralized Information System for Infectious Diseases database. The condition is life-threatening due to the possibility of severe systemic complications such as cerebral malaria with coma, cardiogenic shock, acute renal failure, coagulation disorders and pulmonary oedema. By the severe stage of the disease, the fatality rate in people receiving treatment is 10 to 20%. The overall mortality rate of imported Plasmodium falciparum malaria in Europe is 0.4%. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that artesunate may be of significant benefit to those affected by the condition. This appears justified by the superior clinical efficacy of artesunate administered intravenously as monotherapy in the treatment of severe malaria as compared to quinine, the only currently authorized product for intravenous use in the EU. This has been demonstrated in terms of significantly improved survival of patients with severe malaria treated with artesunate as compared to those treated with quinine (absolute reduction of mortality up to 34.7%) in large comparative clinical trials. Artesunate was also characterised by better tolerability than quinine. Based on these results intravenous artesunate is recommended by the World Health Organization as first choice in the treatment of severe malaria. The superior clinical efficacy of intravenous artesunate compared to intravenous quinine may represent a clinically relevant advantage for patients affected by severe malaria in the EU.

A positive opinion for artesunate, for treatment of malaria, was adopted by consensus.

2.2.5 For treatment of Familial Adenomatous Polyposis - EMA/OD/130/12
[Co-ordinators: D. O'Connor / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the productfor treatment of familial adenomatous polyposis, the sponsor is invited to further elaborate on:

- the availability of a specific product, as proposed for designation

- any proof of concept study in a relevant preclinical model or clinical setting with the specific product as proposed for designation, since orphan designation refers to a specific condition and one specific product.

- the relevance of the clinical studies presented with regards to any existing specific product for designation

- Development of Medicinal Product

The sponsor should clarify if the product applied for will be developed, and provide detailed information and update the Committee on the current stage of development of the product

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 its December meeting.

2.2.6 **Erdosteine** for treatment of lead toxicity, Rafifarm SRL - EMA/OD/131/12
[Co-ordinators: M. Možina / S. Mariz]

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

The intention to treat the condition was considered justified based on non-clinical data. Lead toxicity was estimated to be affecting approximately 0.23 in 10,000 people in the European Union, at the time the application was made; the sponsor has based their calculation on several European based registries and literature searches. The condition is life-threatening and chronically debilitating due to lead interfering with a variety of body processes. Lead is toxic to many organs and tissues including the heart, bones, intestines, kidneys, and reproductive and nervous systems. It interferes with the development of the nervous system and is therefore particularly toxic to children, causing among others potentially permanent learning and behavior disorders. Symptoms include abdominal pain, confusion, headache, anemia, irritability, and in severe cases seizures, coma, and death. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that erdosteine may be of significant benefit to those affected by the condition. This appears justified on the grounds of a clinically relevant advantage based on improved efficacy. This was based on non-clinical data showing improved survival over current therapies.

A positive opinion for erdosteine, for treatment of lead toxicity, was adopted by consensus.

2.2.7 For treatment of paracetamol toxicity - EMA/OD/132/12
[Co-ordinators: M. Možina / S. Mariz]

The Committee considered that the following issues require clarification by the sponsor:

- Prevalence

The sponsor is invited to re-calculate the prevalence based on all additional relevant epidemiological studies and registries for the proposed orphan condition.

- Justification of significant benefit

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

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

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 its December meeting.

2.2.8 Exon 52 specific phosphorothioate oligonucleotide for treatment of Duchenne muscular dystrophy, Prosensa Therapeutics B.V. - EMA/OD/121/12
[Co-ordinators: P. Evers / L. Fregonese]

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

The sponsor evaluated the prevalence of Duchenne muscular dystrophy based on an extensive literature search, including also a review article of more than 150 studies. Duchenne muscular dystrophy was estimated to be affecting approximately 0.52 in 10,000 people in the European Union, at the time the application was made; this is not more than 5 in 10,000 people as established in Article 3(1) (a) of Regulation (EC) No 141/2000. The condition is chronically debilitating and life-threatening due to progressive muscle weakness with loss of function of voluntary muscles. All voluntary muscles are affected, and most children affected by Duchenne muscular dystrophy will need a wheel chair before 12 years of age. Respiratory muscles deteriorate also resulting in progressive reduction of forced vital capacity of the lungs, requiring ventilation support. Without ventilation support, a median survival age of 19 years has been reported. Death occurs at median age of 25 years, usually due to respiratory or cardiac failure. There is, at present, no satisfactory treatment authorised in the European Union for patients affected by the condition.

A positive opinion for exon 52 specific phosphorothioate oligonucleotide, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.9 Exon 55 specific phosphorothioate oligonucleotide for treatment of Duchenne muscular dystrophy, Prosensa Therapeutics B.V. - EMA/OD/122/12
[Co-ordinators: P. Evers / L. Fregonese]

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

The sponsor evaluated the prevalence of Duchenne muscular dystrophy based on an extensive literature search, including also a review article of more than 150 studies. Duchenne muscular dystrophy was estimated to be affecting approximately 0.52 in 10,000 people in the European Union,

at the time the application was made; this is not more than 5 in 10,000 people as established in Article 3(1) (a) of Regulation (EC) No 141/2000. The condition is chronically debilitating and life-threatening due to progressive muscle weakness with loss of function of voluntary muscles. All voluntary muscles are affected, and most children affected by Duchenne muscular dystrophy will need a wheel chair before 12 years of age. Respiratory muscles deteriorate also resulting in progressive reduction of forced vital capacity of the lungs, requiring ventilation support. Without ventilation support, a median survival age of 19 years has been reported. Death occurs at median age of 25 years, usually due to respiratory or cardiac failure. There is, at present, no satisfactory treatment authorised in the European Union for patients affected by the condition.

A positive opinion for exon 55 specific phosphorothioate oligonucleotide, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.10 Humanized Single Chain Monoclonal Antibody to CD37 for treatment chronic lymphocytic leukemia, Emergent Product Development UK Limited - EMA/OD/128/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

Following review of the application by the Committee, it was agreed to rename active substance should be renamed as "humanised single chain monoclonal antibody against CD37".

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

The intention to treat the condition with the product was considered justified on the basis of preclinical data in preclinical models of lymphoma and leukaemia showing that treatment with the product reduces tumour volume and increases survival, as well as preliminary clinical data in CLL patients showing some responses when treated with the proposed product. The condition was estimated to be affecting approximately 3 in 10,000 people in the European Union, at the time the application was made. The condition is life-threatening and chronically debilitating due to development of cytopaenias (anaemia, neutropaenia, thrombocytopaenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that humanised single chain monoclonal antibody against CD37 may be of significant benefit to those affected by the condition. This appears justified on the grounds of a novel mechanism of action, which may result in the clinically relevant advantage of improved efficacy. This is supported by data in preclinical models of lymphoma showing an improved effect of the product if it is combined with rituximab and/or bendamustine, as well as clinical data in CLL patients showing responses in patients who have relapsed following previous treatment with other products.

A positive opinion for humanised single chain monoclonal antibody against CD37, for treatment of chronic lymphocytic leukaemia, was adopted by consensus.

2.2.11 For treatment of growth hormone deficiency - EMA/OD/133/12
[Co-ordinators: V. Tillmann / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation and in particular to discuss the duration of the condition as used in the prevalence calculation.

The duration of treatment and the duration of the disease are different concepts and it is not justified why they might be used interchangeably for the prevalence calculation.

- Significant Benefit

The sponsor is invited to comment on the therapeutic impact of the pharmacokinetic profile of the weekly administration in particular with regards to the absence of daily peaks in plasma levels and to compare this with the pharmacokinetics profile of the daily administration with the authorised counterparts.

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 its December meeting.

2.2.12 Triheptanoin for treatment of Long-chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency, B. Braun Melsungen AG - EMA/OD/127/12
[Co-ordinators: V. Saano / S. Tsigkos]

The Committee agreed that the condition, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the proposed product can be considered justified on the basis of preliminary clinical data. The condition was estimated to be affecting not more than 0.17 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating and life-threatening in particular due to hypoglycaemia, cardiomyopathy, hepatomegaly, myopathy, encephalopathy, neuropathy and pigmentary retinopathy. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for triheptanoin, for treatment of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, was adopted by consensus.

2.2.13 Triheptanoin for treatment of Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency, B. Braun Melsungen AG - EMA/OD/126/12
[Co-ordinators: V. Saano / S. Tsigkos]

The Committee agreed that the condition, of very long-chain acyl-CoA dehydrogenase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the proposed product was considered justified on the basis of preliminary clinical data. The condition was estimated to be affecting not more than 0.32 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to fatigue, hypoglycaemia, muscle wasting, rhabdomyolysis and life-threatening in particular due to cardiomyopathy. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for triheptanoin, for treatment of very long-chain acyl-CoA dehydrogenase deficiency, was adopted by consensus.

2.2.14 For treatment of complex regional pain syndrome - EMA/OD/125/12
[Co-ordinators: L. Gramstad / L. Fregonese]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the product for the treatment of complex regional pain syndrome (CRPS), the sponsor is invited to further elaborate on:

-the extent and relevance of bone reabsorption and other osteoclastic mechanisms in CRPS;

- the methodology, the scientific validity and relevance of the two cited references in CRPS, as the only study on 24 CRPS patients has been published as an abstract , and never as a full article;

- the characteristics of the patients that responded to treatment with the product in the abstract , and in particular on whether the responders had local or generalized osteoporosis;

- the extrapolation of data from conditions other than CRPS in relation to the proposed action of the product in reducing pain;

- the possible extrapolation to the product of data from other products of the same pharmacological class tested in CRPS.

In addition the sponsor is invited to comment on the expected low bioavailability using the oral route of administration, and how this would influence the expected action of the product on pain and on bone reabsorption in CRPS.

- Prevalence

In order to correctly establish the prevalence of CRPS in the EU the sponsor is invited to elaborate on:

- the extrapolation of the data from the US survey to the EU population, taking into account the possible differences in the definition of the condition between the US and the EU, and across time;

- the impact on the prevalence of the cases characterized by long-term course of the disease, i.e. more than one year. The sponsor is invited to add these cases to the overall prevalence of the disease, taking into account the average duration in these cases.

- Development of Medicinal Product

It appears unclear to what extent the product is developed for oral administration. As yet the pharmaceutical formulation is briefly described in prospected terms.

The sponsor is invited to provide a description of the medicinal product as developed at this stage

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 its December meeting.

2.3. Evaluation on-going

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

2.4. Validation on-going

The Committee was informed that validation was on-going for twenty eight applications for orphan designation.

3. Requests for protocol assistance

3.1 Treatment of corneal cystine crystals deposits in cystinosis [Co-ordinator: R. Elbers]

The protocol assistance letter was adopted by the Committee.

3.2 Treatment of mercury poisoning [Co-ordinator: B. Bloechl-Daum]

The protocol assistance letter was adopted by the Committee.

4. Overview of applications

4.1 Update on applications for orphan medicinal product designation submitted/expected

COMP co-ordinators were appointed for sixteen upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

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

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

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

5.1.1 NexoBrid (purified bromelain) for treatment of partial deep dermal and full thickness burns; Teva Pharma GmbH (OD/012/02, EU/3/02/107) [Co-ordinators: J. Eggenhofer / S. Tsigkos].

As agreed during the October meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to elaborate on the justifications provided for significant benefit. In particular a clinically relevant advantage or a major contribution to patient care should be justified in comparison to currently authorised products and the current standard of care.

In its written response, and during an oral explanation before the Committee on 6 November 2012, the sponsor, in addition to describing the standard of care for burn patients and the results from the main phase III study, also listed the identified authorised enzymatic products in the EU (collagenase, fibrinolysin, streptokinase and streptodornase). The sponsor pointed out that Nexobrid is indicated for eschar removal, in contrast to the authorised enzymatic products which are usually used after debridement at later stages. The COMP agreed that the proposed therapeutic indication "removal of eschar in adults with deep partial- and full-thickness thermal burns" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product "treatment of partial deep dermal and full thickness burns". The prevalence of partial deep dermal and full thickness burns was estimated

to remain below 5 in 10,000 at the time of the review of the designation criteria. This was based on the annual number of hospitalisations for burns as reported in databases and literature searches, and the condition was estimated to affect approximately 1 in 10,000 people at the time of the review of the orphan designation. The condition is life-threatening and chronically debilitating in particular due to the development of sepsis, acute respiratory distress syndrome, hypovolaemia, and extensive scarring that might impair mobility. The condition has an overall mortality of 5%. Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Nexobrid may be of potential significant benefit to those affected by the orphan condition still holds on the grounds of a clinically relevant advantage. This is based on a phase III clinical study comparing the product to the standard of care, which shows a decrease in the need for excisional surgery and autografting, reducing trauma, pain and scarring for the patients.

An opinion not recommending the removal from the EC Register of Orphan Medicinal Products for NexoBrid (purified bromelain) EU/3/02/107 for the treatment of partial deep dermal and full thickness burns was adopted by consensus.

The public summary of the COMP opinion on the review of the orphan designation (EMA/COMP/631996/2012/2012) was adopted for publication on the EMA website.

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

5.2.1 Bosulif (Bosutinib) for treatment of chronic myeloid leukaemia; Pfizer Limited (OD/160/09, EU/3/10/762) [Co-ordinators: R. Elbers / S. Tsigkos].

5.2.2 Exjade (4-(3,5-bis(hydroxy-phenyl)-1,2,4) triazol-1-yl) benzoic acid) for treatment of chronic iron overload requiring chelation therapy; Novartis Europharm Limited (OD/061/01, EU/3/02/092) [Co-odinators: M. Mozina/ S. Mariz]
Type II variations – new indications:

- treatment of infrequently transfused beta-thalassemia major patients
- treatment of non-transfusion dependent thalassemia syndromes.

5.2.3 Jenzyl ((1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate); Merck Sharp & Dohme Limited [Co-ordinators: B. Dembowska-Baginska / L. Fregonese]

- treatment of soft tissue sarcoma (OD/050/05, EU/3/05/312)
- treatment of primary malignant bone tumours (OD/055/05, EU/3/05/321)

5.3. On-going procedures

5.3.1 Bedaquiline ((1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethano) for treatment of tuberculosis; Janssen-Cilag International N.V. (OD/024/05 , EU/3/05/314) [Co-ordinators: N. Sypsas / L. Fregonese]

5.3.2 Cholic Acid FGK for treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid; FGK Representative Service GmbH (OD/080/09, EU/3/09/683) [Co-ordinators: A. Magrelli / S. Tsigkos]

5.3.3 Cysteamine bitartrate [Cysteamine bitartrate (gastroresistant)] for treatment of cystinosis; Raptor Pharmaceuticals Europe B.V. (OD/034/10, EU/3/10/778) [Co-ordinators: V. Saano / S. Mariz]

5.3.4 Defitelio (Defibrotide); Gentium S.p.A. [Co-ordinators: J. Torrent-Farnell / S. Mariz]

- prevention of hepatic veno-occlusive disease (OD/025/04, EU/3/04/211)
- treatment of hepatic veno-occlusive disease (OD/026/04, EU/3/04/212)

5.3.5 Delamanid ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis (OD/094/07, EU/3/07/524); Otsuka Novel Products GmbH [Co-ordinators: V. Stoyanova / L. Fregonese]

5.3.6 Iclusig (benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-); ARIAD Pharma Ltd [Co-ordinators: K. Kubackova / L. Fregonese]

- treatment of chronic myeloid leukaemia (OD/121/09, EU/3/09/716)
- treatment of acute lymphoblastic leukaemia (OD/122/09, EU/3/09/715).

5.3.7 Istodax (previously Romidepsin) ((E)-(1S,4S,10S,21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23- tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone) for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated); Celgene Europe Limited (OD/056/05, EU/3/05/328) [Co-ordinators: D. O'Connor / L. Fregonese]

5.3.8 Kinaction (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (OD/063/09, EU/3/09/684) [Co-ordinators: B. Bloechl-Daum/ S. Tsigkos]

5.3.9 Loulla (Mercaptopurine) for treatment of acute lymphatic leukaemia, Only For Children Pharmaceuticals (OD/065/07, EU/3/07/496) [Co-ordinators: D. O'Connor / S. Tsigkos]

5.3.10 PAS-GR (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (OD/072/10, EU/3/10/826) [Co-ordinators: V. Stoyanova / S. Mariz]

5.3.11 Pheburane (Sodium phenylbutyrate) for treatment of carbamoyl-phosphate synthase-1 deficiency; Lucane Pharma SA (OD/098/11, EU/3/12/951) [Co-ordinators: J. Torrent-Farnell / L. Fregonese]

5.3.12 Pomalidomide Celgene (Pomalidomide) for treatment of multiple myeloma, Celgene Europe Ltd. (OD/053/09, EU/3/09/672) (Co-ordinators: R. Elbers/ S. Mariz]

5.3.13 Raxone (previously SAN Idebenone; Idebenone) for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (OD/076/06, EU/3/07/434) [Co-ordinators: J. Torrent-Farnell / S. Mariz]

5.3.14 Revlimid (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) for treatment of myelodysplastic syndromes; Celgene Europe Limited – UK (OD/083/03, EU/3/04/192) [Co-ordinators: L. Gramstad / S. Tsigkos]

5.3.15 Scenesse ([Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide) for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (OD/108/07, EU/3/08/541) [Co-ordinators: L. Gramstad / S. Mariz]

5.3.16 Masican N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (OD/061/04, EU/3/04/251) [Co-ordinators: D. O'Connor / S. Mariz]

5.3.17 Winfuran (-)-17(cyclopropylmethyl)-1,14 ß-dihydroxy-4,5 alpha-epoxy-6ß-[N-methyl-trans-3-(3-furyl) acrylamido] morphinan hydrochloride for treatment of uremic pruritus; Toray International U.K. Limited (OD/020/02, EU/3/02/115) [Co-ordinators: S. Thorsteinsson / S. Mariz]

6. Procedural aspects

6.1 European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP)

D. O'Connor was nominated as a new COMP representative in the PCWP.

7. Any other business

7.1 FDA/EMA Orphan Designation and Grant Workshop held on 12 October 2012 in Washington D.C.

The briefing from the Workshop was postponed to the next meeting.

7.2 COMP Work Programme 2013-2015

Detailed discussion will take place via teleconference on 13 November 2012.

7.3 COMP Informal meeting to be held on 22-23 November 2012 in Rome

The revised draft agenda was circulated for information.

7.4 Adaptive licensing

The Committee was briefed on the topic. B. Bloechl-Daum and P. Evers were nominated to represent the COMP in the Adaptive Licensing Discussion Group.

7.5 Managing Meeting Documents (MMD)

In preparation of the implementation of the system for the Committee the members were introduced to the technical aspects of the system.

7.6 Draft reflection paper on biomarkers

The revised document, EMA/COMP/9758/2012 was circulated for information.

7.7 Proposal for revision of fee reductions

The draft revision on the orphan products fee reduction policy EMA/662762/2012 was presented for information.

Date of next COMP meeting: on 5 - 6 December 2012

List of participants on 6 - 7 November 2012

Chair:
Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

André Lhoir	België/Belgique/Belgien
Irena Bradinova	България
Kateřina Kubáčková	Česká Republika
Rembert Elbers	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Annie Lorence	France
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Dainis Krievins	Latvija
Aušra Matulevičienė	Lietuva
Henri Metz	Luxembourg
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romãnia
Milica Molitorisová	Slovensko (present on 1st day only)
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Pauline Evers	Representing the European Genetic Alliances Network
Birthe Byskov Holm	Volunteer patient representative for Eurordis
János Borvendég	CHMP Representative
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative

Observers:

Ivana Martinovic	Croatia
Maria Mavris	Eurordis

European Commission:

Mirjam Soderholm	DG Health and Consumers

EMA Secretariat:

Jordi Llinares Garcia	Head of Orphan Medicines Section
Hans-Georg Eichler	Senior Medical Officer for 7.4
Laura Fregonese	Scientific Administrator

Segundo Mariz	Scientific Administrator (present on 2nd day only)
Stylianos Tsigkos	Scientific Administrator
Carla Paganin	EMA Expert
Daniel Glanville	Scientific Administrator (Medical Information) for 5.1.1
Agnieszka Wilk-Kachlicka	Assistant
Frederique Dubois	Assistant
Hanne Thisen	IT for 7.5
Helen Hansen	IT for 7.5

Apologies:

Members:

Dorthe Meyer	Danmark
Ioannis Kkolos	Κύπρος
Martin Možina	Slovenija

Observers:

Vesna Osrecki	Croatia
Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios