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Inspections, Human Medicines Pharmacovigilance and Committees Division

PDCO monthly report of opinions on paediatric investigation plans and other activities

25-28 June 2019

Opinions on paediatric investigation plans

The Paediatric Committee (PDCO) adopted opinions agreeing paediatric investigation plans (PIPs) for the following medicines:

- Recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein, EMEA-002435-PIP01-18, from PTC Therapeutic International Limited, for the treatment of aromatic L-amino acid decarboxylase deficiency;
- 6-cyclopropaneamido-4-{[2-methoxy-3-(1-methyl-1H-1,2,4 triazol-3-yl)phenyl]amino}-N-(2H3)methylpyridazine-3-carboxamide, EMEA-002350-PIP01-18, from Bristol-Myers Squibb International Corporation, for the treatment of psoriasis;
- Human immunoglobulin (Ig) G4-variant monoclonal antibody that binds and neutralizes soluble human interleukin- (IL-) 33, EMEA-002464-PIP01-18, from Eli Lilly and Company, for the treatment of atopic dermatitis;
- Bulevirtide, EMEA-002399-PIP01-18, from MYR GmbH, for the treatment of chronic hepatitis D infection;
- Vedolizumab, EMEA-000645-PIP03-18, from Takeda Pharma A/S, for the prevention of acute graft-versus-host disease;
- Oxalobacter formigenes Strain HC-1, EMEA-000370-PIP02-18, from OxThera AB, for the treatment of hyperoxaluria;
- Humanized anti-CD19, Fc engineered, monoclonal antibody, EMEA-002414-PIP01-18, from Xencor, Inc., for the treatment of immunoglobulin G4-related disease

The PDCO adopted an opinion on the **refusal** of a PIP for:

- Hydrogen peroxide (45%), EMEA-001884-PIP03-18, from Aclaris Therapeutics Inc., for the treatment of common warts (verrucae vulgaris)

For this medicine the PDCO granted a product-specific waiver on its own motion for all subsets of the paediatric population in the specified condition, on the grounds that the specific medicinal product does

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not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The PDCO adopted an opinion on the **refusal** of a PIP and deferral for:

- Relugolix / estradiol / norethisterone acetate, EMEA-002428-PIP02-18, from Myovant Sciences Ireland Limited, for the treatment of endometriosis

For this medicine the PDCO granted a product-specific waiver on its own motion for all subsets of the paediatric population in the specified condition, on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified subset(s) of the paediatric population, and Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

A PIP sets out a programme for the development of a medicine in the paediatric population. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages. These data have to be submitted to the European Medicines Agency, or national competent authorities, as part of an application for a marketing authorisation for a new medicine, or for one covered by a patent. In some cases, a PIP may include a waiver of the studies in one or more paediatric subsets, or a deferral.

Adoption of an opinion following re-examination

The PDCO adopted opinions for the following products:

Following the re-examination of the negative opinion on a PIP adopted on 26 April 2019 for

- Genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII, EMEA-002472-PIP02-19, from Krystal Biotech, Inc., for the treatment of dystrophic epidermolysis bullosa, the PDCO recommended to maintain its opinion and to refuse the paediatric investigation plan in accordance with Article 17(1) of Regulation (EC) No 1901/2006 as amended, as the measures and the timelines are not appropriate to ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or some subsets, nor to adapt a paediatric formulation, or do not bring expected significant therapeutic benefit.

A re-examination of the opinion can be requested by the applicant within 30 days following receipt of the opinion of the PDCO. The grounds for the re-examination should be based only on the original information and scientific data provided in the application that were previously available to the PDCO and on which the initial opinion was based. This may include new analysis of the same data or minor protocol amendments to a previously proposed study. Significant changes to the previous plan cannot be part of the re-examination process.

Opinions on product-specific waivers

The PDCO adopted positive opinions for product-specific waivers, recommending that the obligation to submit data obtained through clinical studies with children be waived in all subsets of the paediatric population, for the following medicines:

- Mifepristone, EMEA-001437-PIP02-19, from Laboratorios Litaphar S.L., for the treatment of endometriosis;
- Botulinum toxin type A, EMEA-002521-PIP01-18, from Allergan Pharmaceuticals International Limited, for the treatment of skin wrinkling;

- Istradefylline, EMEA-002540-PIP01-18, from Kyowa Kirin Limited, for the treatment of Parkinson's disease;
- Ciclosporin, EMEA-002491-PIP02-19, from Sun Pharmaceutical Industries Europe BV, for the treatment of dry eye disease;
- Tafasitamab, EMEA-002499-PIP02-19, from MorphoSys AG, for the diffuse large B-cell lymphoma (DLBCL);
- Human chorionic gonadotrophin, EMEA-002547-PIP01-19, from Regulis Consulting Europe Ltd, for the treatment of female infertility;
- (cis)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide, EMEA-002575-PIP01-19, from Blueprint Medicines (Netherlands) B.V., for the treatment of lung cancer (small cell and non-small cell lung cancer);
- EGFR-cMET bispecific antibody, EMEA-002573-PIP01-19, from Janssen-Cilag International N.V., for the treatment of lung carcinoma;
- Anti-neonatal Fc receptor human monoclonal antibody, EMEA-002559-PIP01-19, from Momenta Pharmaceuticals, Inc., for the prevention of haemolytic disease of the foetus and newborn;
- Gallium 68-labelled Prostate-Specific Membrane Antigen-11 (^{68}Ga-PSMA-11), EMEA-002577-PIP01-19, from Endocyte, Inc., for the visualisation of prostate specific membrane antigen in prostate cancer

Opinions on modifications to an agreed PIP

The PDCO also adopts, every month, opinions on modifications to an agreed PIP, which can be requested by the applicant when the plan is no longer appropriate or when there are difficulties that render the plan unworkable. The PDCO adopted positive opinions, agreeing change(s), for the following products:

- Octenidine (dihydrochloride), EMEA-001514-PIP01-13-M01, from Cassella-med GmbH & Co. KG, for the treatment of upper respiratory tract infections;
- Delamanid, EMEA-001113-PIP01-10-M06, from Otsuka Pharmaceutical Development & Commercialisation Europe GmbH, for the treatment of multi drug resistant tuberculosis;
- Fosnetupitant / palonosetron , EMEA-001198-PIP03-17-M02, from Helsinn Birex Pharmaceuticals Limited, for the prevention of chemotherapy-induced nausea and vomiting;
- Ixazomib, EMEA-001410-PIP02-17-M02, from Takeda Pharm A/S, for the treatment of lymphoid malignancies (excluding multiple myeloma) and treatment of multiple myeloma;
- Saxagliptin, EMEA-000200-PIP01-08-M08, from AstraZeneca AB, for the treatment of type 2 diabetes mellitus;
- Daunorubicin / cytarabine, EMEA-001858-PIP02-16-M03, from Jazz Pharmaceuticals Ireland Limited, for the treatment of acute myeloid leukaemia;
- Tezepelumab, EMEA-001613-PIP01-14-M03, from AstraZeneca AB, for the treatment of asthma;
- Eslicarbazepine (acetate), EMEA-000696-PIP02-10-M06, from BIAL - Portela & Ca, SA, for the treatment of epilepsy with partial onset seizures;

- Ixekizumab, EMEA-001050-PIP02-18-M01, from Eli Lilly Nederland B.V., for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis and juvenile idiopathic arthritis);
- Bosutinib, EMEA-000727-PIP01-09-M03, from Pfizer Europe MA EEIG, for the treatment of chronic myeloid leukaemia;
- Belatacept, EMEA-000157-PIP01-07-M04, from Bristol-Myers Squibb Pharma EEIG, for the prevention of rejection of transplanted kidney;
- Fluciclovine (^{18}F), EMEA-001644-PIP02-14-M01, from Blue Earth Diagnostics Ireland Ltd, for the diagnosis of amino acid metabolism in solid malignant tumours;
- Reslizumab, EMEA-001202-PIP02-13-M03, from Teva Pharmaceuticals Europe, for the treatment of asthma;
- Selumetinib, EMEA-001585-PIP01-13-M03, from AstraZeneca AB, for the treatment of neurofibromatosis type 1, treatment of thyroid cancer and treatment of melanoma;
- Eteplirsen, EMEA-001722-PIP01-14-M02, from Sarepta Therapeutics Ireland Limited, for the treatment of Duchenne muscular dystrophy;
- Recombinant human monoclonal antibody to GM-CSF, EMEA-001882-PIP02-16-M01, from GlaxoSmithKline Trading Services Limited, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis and juvenile idiopathic arthritis);
- Lasmiditan, EMEA-002166-PIP01-17-M02, from Eli Lilly and Company Limited, for the treatment of migraine headaches

The PDCO adopted opinions on the **refusal** of modifications to an agreed PIP for the following applications:

- Mirabegron, EMEA-000597-PIP02-10-M07, from Astellas Pharma Europe B.V., for the treatment of idiopathic overactive bladder

Opinion on compliance check

The PDCO adopted positive opinions on full compliance check for:

- Etravirine, EMEA-C-000222-PIP01-08-M09, from Janssen-Cilag International NV, for the treatment of HIV-1 virus infection

A compliance check is performed to verify that all the measures agreed in a PIP and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Full compliance with all studies/measures contained in the PIP is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.

Before the submission of a request for a compliance check, applicants are encouraged to consult the Agency's Procedural advice for validation of a new marketing authorisation application or extension/variation application and compliance check with an agreed PIP.

Withdrawals

The PDCO noted that 6 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

The PDCO also noted that the application leading to the opinion adopted during the May 2019 PDCO meeting for tabelecleucel, EMEA-002025-PIP02-16, from Atara Biotherapeutics, Inc., for the treatment of Epstein-Barr virus associated post-transplant lymphoproliferative disorder, was withdrawn before the decision was adopted by the Agency.

Other matters

The next meeting of the PDCO will be held on 23-25 July 2019.

– END –

Notes:

1. As of 26 January 2009, pharmaceutical companies that submit an application for a marketing authorisation for a medicinal product, or those that submit an application for an extension of indication, a new route of administration, or a new pharmaceutical form of a medicinal product already authorised in the European Union, have to provide either the results of studies in children conducted in accordance with an approved PIP, or an Agency's decision on a waiver or on a deferral.

2. PDCO opinions on PIPs and waivers are transformed into Agency's decisions within the timeframe laid down by the Paediatric Regulation (Regulation (EC) No 1901/2006, as amended). The decisions can be found on the Agency's website at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d129

3. More information about the PDCO and the Paediatric Regulation is available in the Regulatory section of the Agency's website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cd

4. This meeting report, together with other information on the work of the Agency's, can be found on the Agency's website: http://www.ema.europa.eu

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