6 March 2018
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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

20 – 23 February 2018

Opinions on paediatric investigation plans

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

- Fevipiprant, EMEA-001315-PIP02-16, from Novartis EuroPharm Ltd., for the treatment of asthma;
- Influenza virus H1 haemagglutinin / influenza virus H3 haemagglutinin / influenza virus haemagglutinin from strain B Victoria lineage / influenza virus haemagglutinin from strain B Yamagata lineage (expressed as virus-like particle [VLP]), EMEA-002220-PIP01-17, from Medicago Inc., for the prevention of influenza;
- Ixazomib, EMEA-001410-PIP02-17, from Takeda Pharm A/S, for the treatment of multiple myeloma and treatment of lymphoid malignancies (excluding multiple myeloma);
- Obeticholic Acid, EMEA-001304-PIP03-17, from Intercept Pharma Ltd., for the treatment of non-alcoholic steatohepatitis;
- Plazomicin (sulfate), EMEA-001639-PIP02-17, from Achaogen Inc., for the treatment of complicated urinary tract infections and treatment of infections due to *Enterobacteriaceae*.

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 modification to an agreed PIP adopted on 15 December 2017 for midostaurin, EMEA-000780-PIP01-09-M04, from Novartis Europharm

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Ltd, for the treatment of acute myeloid leukaemia, treatment of malignant mastocytosis and treatment of mast cell leukaemia, the PDCO adopted a revised positive opinion and agreed to the changes regarding the measures and the timelines of the deferral in the scope set out in the Annex I of the opinion.

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:

- Calcium,N,N'-1,2-ethanediylbis[N-[[3-(hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methyl]glycine] manganese complexes, EMEA-002293-PIP01-17, from PledPharma AB, for the prevention of oxaliplatin induced peripheral neuropathy;
- Enfortumab vedotin, EMEA-002299-PIP01-17, from Astellas Pharma Europe B.V., for the treatment of urothelial carcinoma;
- Ezetimibe / rosuvastatin, EMEA-001344-PIP02-17, from Zentiva, k.s., for the prevention of cardiovascular events;
- Humanized recombinant IgG4 anti-human tau antibody, EMEA-002226-PIP02-17, from AbbVie Ltd, for the progressive supranuclear palsy;
- Polatuzumab vedotin, EMEA-002255-PIP01-17, from Roche Registration Limited, for the treatment of mature B cell neoplasms;
- Rovalpituzumab tesirine, EMEA-002292-PIP01-17, from AbbVie Ltd, for the treatment of lung carcinoma (small cell and non-small cell carcinoma).

Waivers can be issued if there is evidence that the medicine concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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:

- Abatacept, EMEA-000118-PIP02-10-M03, from Bristol-Myers Squibb Pharma EEIG, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis);
- Andexanet alfa, EMEA-001902-PIP01-15-M02, from Portola Pharma UK Limited, for the treatment

of factor Xa inhibitor associated haemorrhage and prevention of factor Xa inhibitor associated haemorrhage;

- Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor, EMEA-001995-PIP01-16-M01, from Celgene Europe Limited, for the treatment of B-lymphoblastic leukemia/lymphoma and treatment of mature B-cell neoplasms;
- Benralizumab, EMEA-001214-PIP01-11-M07, from AstraZeneca AB, for the treatment of asthma;
- Crisaborole, EMEA-002065-PIP01-16-M01, from Pfizer Ltd, for the treatment of atopic dermatitis;
- Dalbavancin, EMEA-000016-PIP01-07-M06, from Allergan Pharmaceuticals International Limited, for the treatment of acute bacterial skin and skin structure infections;
- Dopamine, EMEA-001105-PIP01-10-M04, from BrePco Biopharma Limited, for the treatment of vascular hypotensive disorders;
- Evolocumab, EMEA-001268-PIP01-12-M05, from Amgen Europe B.V., for the treatment of elevated cholesterol and treatment of mixed dyslipidaemia;
- Lanadelumab, EMEA-001864-PIP01-15-M02, from Shire Pharmaceuticals Ireland Limited, for the treatment of hereditary angioedema attacks;
- Luspatercept, EMEA-001521-PIP01-13-M02, from Celgene Europe Ltd, for the treatment of beta-thalassaemia and treatment of myelodysplastic syndromes;
- Methoxyflurane, EMEA-000334-PIP01-08-M07, from Medical Developments UK Ltd, for the treatment of acute pain;
- Nusinersen, EMEA-001448-PIP01-13-M03, from Biogen Idec Ltd, for the treatment of spinal muscular atrophy;
- Palovarotene, EMEA-001662-PIP01-14-M02, from Clementia Pharmaceuticals Inc., for the treatment of fibrodysplasia ossificans progressiva;
- Peginterferon beta-1a, EMEA-001129-PIP01-11-M02, from Biogen Idec Ltd, for the treatment of multiple sclerosis;
- Ponesimod, EMEA-000798-PIP01-09-M01, from Actelion Registration Limited, for the treatment of multiple sclerosis;
- Quizartinib, EMEA-001821-PIP01-15-M01, from Daiichi Sankyo Europe GmbH, for the treatment of acute myeloid leukaemia;
- Tapentadol, EMEA-000325-PIP01-08-M09, from Grünenthal GmbH, for the treatment of chronic pain;
- Tilmanocept, EMEA-001255-PIP01-11-M03, from Norgine BV, for the visualisation of lymphatic drainage of solid malignant tumours for diagnostic purposes;
- Vedolizumab, EMEA-000645-PIP01-09-M06, from Takeda Pharma A/S, for the treatment of Crohn's disease and treatment of ulcerative colitis;

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

- Concentrate of proteolytic enzymes in bromelain, EMEA-000142-PIP02-09-M06, from MediWound Germany GmbH, for the treatment of burns.

Opinion on compliance check

The PDCO adopted positive opinions on (full) compliance check for:

- Dasatinib, EMEA-C-000567-PIP01-09-M05, from Bristol-Myers Squibb Pharma EEIG, for the treatment of Philadelphia chromosome (BCR-ABL translocation)-positive acute lymphoblastic leukaemia and treatment of Philadelphia chromosome (BCR-ABL translocation)-positive chronic myeloid leukaemia;
- Tocilizumab, EMEA-C-000309-PIP01-08-M07, from Roche Registration Limited, for the treatment of chronic idiopathic arthritis (including rheumatioid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile arthritis).

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 4 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

New submissions deadlines

From August 2018, the PDCO meeting in August will be held by written procedure. Therefore, the EMA has synchronised the submission deadlines for paediatric procedures, to streamline the process for applicants and the PDCO. A new submission deadline document replaces the three pre-existing ones. The dates are published on the Agency's website at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91&jsenabled=true

Other matters

The next meeting of the PDCO will be held on 20 – 23 March 2018.

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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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