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SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

28-31 January 2020

Opinions on paediatric investigation plans

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

- Soticlestat, EMEA-002572-PIP01-19, from Takeda Pharma A/S, for the treatment of chromosome 15q duplication syndrome and treatment of cyclin-dependent kinase-like 5 deficiency disorder;
- Baricitinib, EMEA-001220-PIP05-19, from Eli Lilly and Company Limited, for the treatment of systemic lupus erythematosus;
- Efgartigimod alfa, EMEA-002597-PIP01-19, from argenx BVBA, for the treatment of myasthenia gravis;
- Zoliflodacin, EMEA-002599-PIP01-19, from Entasis Therapeutic Inc., for the treatment of gonococcal infection;
- Allogeneic, *ex vivo* expanded, umbilical cord blood-derived, haematopoietic CD34+progenitor cells (CF)/ allogeneic, non-expanded, umbilical cord blood-derived, haematopoietic mature myeloid and lymphoid cells (NF), EMEA-001913-PIP02-18, from Gamida Cell Ltd, for the treatment in haematopoietic stem cell transplantation;
- Timrepigene emparvovec, EMEA-002430-PIP01-18, from Nightstar Europa Limited, for the treatment of choroideremia;
- Autologous CD34+ haematopoietic stem cells transduced *ex vivo* with a lentiviral vector encoding for the human Beta 2 Integrin/CD18 gene, EMEA-002562-PIP01-19, from Rocket Pharmaceuticals, Inc., for the treatment of leukocyte adhesion deficiency type I;
- Tris(hydroxymethyl)aminomethane trihydrate (PF-05221304-82), EMEA-002552-PIP01-19, from Pfizer Europe MA EEIG, for the treatment of non-alcoholic steatohepatitis;
- Avatrombopag maleate, EMEA-001136-PIP02-19, from Dova Pharmaceuticals Ireland Limited, for the treatment of chemotherapy-induced thrombocytopenia;
- Autologous CD34+ enriched cells from patients with Fanconi anaemia subtype A (FA-A) transduced

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ex vivo with lentiviral vector carrying the FANCA gene (PGKFANCA-WPRE), EMEA-002578-PIP01-19, from Rocket Pharmaceuticals, Inc., for the treatment of Fanconi anaemia subtype A;

- Cannabidiol, EMEA-001964-PIP02-19, GW Pharma (International) B.V, for the treatment of Rett syndrome;
- Anti-neonatal Fc receptor human monoclonal antibody, EMEA-002559-PIP02-19, from Momenta Pharmaceuticals, Inc., for the treatment of myasthenia gravis;

The PDCO adopted an opinion(s) on the **refusal** of a PIP, including deferral for:

- Avapritinib, EMEA-002358-PIP03-19, from Blueprint Medicines (Netherlands) B.V., for the treatment of mastocytosis.

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 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 opinion on modification to an agreed PIP adopted on 18 October 2019 for Inotuzumab ozogamicin, EMEA-001429-PIP01-13-M03, from Pfizer Europe MA EEIG, for the treatment of B cell acute lymphoblastic leukaemia, the PDCO adopted a revised positive opinion and agreed to the changes regarding the measure and the timelines of paediatric investigation plan and the timelines of the deferral in the scope set out in the Annex I of this opinion;
- Following the re-examination of the opinion on modification to an agreed PIP adopted on 11 December 2019 for Vosoritide, EMEA-002033-PIP01-16-M01, from BioMarin International Limited, for the treatment of achondroplasia, the PDCO adopted a revised positive opinion and agreed to the changes regarding the measure and the timelines of paediatric investigation plan in the scope set out in the Annex I of this opinion;
- Following the re-examination of the opinion on modification of an agreed PIP with Deferral and waiver adopted on 11 December 2019 for Dupilumab, EMEA-001501-PIP04-19, from Regeneron Ireland DAC, for the treatment of eosinophilic esophagitis, the PDCO adopted a revised positive opinion on a paediatric investigation plan in accordance with Article 17(1) of said Paediatric Regulation (EC) No 1901/ 2006; granted a deferral in accordance with Article 21 of said Regulation; granted a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients;
- Following the re-examination of the opinion on modification to an agreed PIP with Deferral and a waiver adopted on 11 December 2019 for (R)-1-(3-(aminomethyl) phenyl)-N-(5-((3 cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-

carboxamide dihydrochloride (BCX7353), EMEA-002449-PIP02-18, from BioCryst UK, for the treatment of hereditary angioedema, the PDCO adopted a revised positive opinion and agreed to the paediatric investigation plan in accordance with Article 17(1) of said Paediatric Regulation (EC) No 1901/2006; to grant a deferral in accordance with Article 21 of said Regulation; to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(c) of said Regulation, that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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:

- 6 fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one, EMEA-002690-PIP01-19, from Amgen Europe BV, for the treatment of lung cancer;
- Zolbetuximab, EMEA-002695-PIP01-19, from Astellas Pharma Europe B.V., for the treatment of gastric cancer and gastro-oesophageal junction adenocarcinoma and treatment of pancreatic cancer;
- Gefapixant (citrate salt), EMEA-002267-PIP03-19, from Merck Sharp & Dohme (Europe), Inc., for the treatment of endometriosis;
- Parsaclisib, EMEA-002696-PIP01-19, from Incyte Biosciences Distribution B.V., for the treatment of mature B-cell malignancies;
- 5%-Δ9-Tetrahydrocannabinol standardised Cannabis extract, EMEA-002668-PIP01-19, from Vertanical GmbH, for the treatment of chronic pain;
- Eftilagimod alpha, EMEA-002698-PIP01-19, from Immutep SAS, for the treatment of breast cancer;
- Nemolizumab, EMEA-001624-PIP02-19, from Galderma International S.A., for the treatment of prurigo nodularis;
- Levodopa /carbidopa, EMEA-002687-PIP01-19, from Neuroderm Ltd, for the treatment of Parkinson’s disease;
- Brolucizumab, EMEA-002691-PIP01-19, from Novartis Europharm Limited, for the treatment of visual impairment due to macular oedema associated with retinal vein occlusion (branch RVO or central RVO);
- Rosuvastatin / ezetimibe, EMEA-002257-PIP02-19, from ELPEN Pharmaceutical Co. Inc., for the prevention of cardiovascular events;
- Verdiperstat, EMEA-002708-PIP01-19, from Biohaven Pharmaceuticals, Inc., for the treatment of multiple system atrophy;

- (2S)-2-[[2-[(4S)-4-(difluoromethyl)-2-oxo-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]amino]propanamide, EMEA-002686-PIP01-19, from Roche Registration GmbH, for the treatment of breast cancer;
- Daratumumab, EMEA-002152-PIP03-19, Janssen-Cilag International N.V. for the treatment of systemic light chain amyloidosis;

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:

- Anti-respiratory syncytial virus human IgG1κ monoclonal antibody (MEDI8897), EMEA-001784-PIP01-15-M02, from AstraZeneca AB, for the prevention of lower respiratory tract infection caused by respiratory syncytial virus;
- Vadadustat, EMEA-001944-PIP01-16-M01, from Akebia Therapeutics, Inc., for the treatment of anaemia due to chronic disorders;
- Burosumab, EMEA-001659-PIP01-15-M04, from Kyowa Kirin Holdings B.V., for the treatment of X-linked hypophosphataemia;
- Tenofovir alafenamide (as fumarate), EMEA-001584-PIP01-13-M05, from Gilead Sciences International Ltd., for the treatment of chronic viral hepatitis B;
- Split influenza virus, inactivated containing antigens equivalent to the A/H1N1-like strain, A/H3N2-like strain, B-like strain (Victoria lineage) and B-like strain (Yamagata lineage), EMEA-002359-PIP01-18-M01, from Sanofi Pasteur, for the prevention of influenza infection;
- Avacopan, EMEA-002023-PIP01-16-M04, from ChemoCentryx Ireland Ltd., for the treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis;
- Alogliptin, EMEA-000496-PIP01-08-M07, from Takeda Development Centre Europe Ltd, for the treatment of type 2 diabetes mellitus;
- Macimorelin, EMEA-001988-PIP01-16-M01, from Aeterna Zentaris GmbH, for the diagnosis of growth hormone deficiency;
- Entrectinib, EMEA-002096-PIP01-16-M02, from Roche Registration GmbH, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms);
- Sodium zirconium cyclosilicate, EMEA-001539-PIP01-13-M04, from AstraZeneca AB, for the treatment of hyperkalaemia;
- Ixekizumab, EMEA-001050-PIP01-10-M05, from Eli Lilly Nederland B.V., for the treatment of psoriasis;
- Eftrenonacog alfa, EMEA-000914-PIP01-10-M05, from Swedish Orphan Biovitrum AB (publ), for the treatment of hereditary factor IX deficiency;
- Eladocagene exuparvovec, EMEA-002435-PIP01-18-M01, from PTC Therapeutic International Limited, for the treatment of aromatic L-amino acid decarboxylase deficiency;

- Perampanel, EMEA-000467-PIP01-08-M13, from Eisai Europe Limited, for the treatment of treatment-resistant epilepsies;
- Sonidegib, EMEA-000880-PIP02-11-M04, from Sun Pharmaceutical Industries Europe B.V., for the treatment of medulloblastoma;
- Dapagliflozin, EMEA-000694-PIP01-09-M08, from AstraZeneca AB, for the treatment of type 2 diabetes mellitus;
- Eculizumab, EMEA-000876-PIP03-14-M04, from Alexion Europe SAS, for the treatment of neuromyelitis optica spectrum disorders;
- Bezlotoxumab, EMEA-001645-PIP01-14-M03, from Merck Sharp & Dohme (Europe), Inc., for the prevention of recurrence of *Clostridium difficile* infection;
- Denosumab, EMEA-000145-PIP02-12-M02, from Amgen Europe B.V., for the treatment of osteoporosis;
- Emapalumab, EMEA-002031-PIP01-16-M03, from Novimmune BV, for the treatment of haemophagocytic lymphohistiocytosis;
- Idasanutlin, EMEA-001489-PIP01-13-M02, from Roche Registration GmbH, for the treatment of acute lymphoblastic leukaemia and treatment of acute myeloid leukaemia;
- Bupivacaine / meloxicam (HTX-011), EMEA-002246-PIP01-17-M01, from Heron Therapeutics B.V., for the treatment of acute postoperative pain;
- Evinacumab, EMEA-002298-PIP01-17-M01, from Regeneron Ireland DAC, for the treatment of elevated cholesterol;
- Eluxadoline, EMEA-001579-PIP01-13-M03, from Allergan Pharmaceuticals International Limited, for the treatment of diarrhoea-predominant irritable bowel syndrome;
- Posaconazole, EMEA-000468-PIP02-12-M06, from Merck Sharp & Dohme (Europe), Inc. for the prevention and treatment of invasive fungal infections;
- Risdiplam, EMEA-002070-PIP01-16-M04, from Roche Registration GmbH, for the treatment of spinal muscular atrophy;
- Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H1N1) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H3N2) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Yamagata lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Victoria lineage) [QIVc], EMEA-002068-PIP01-16-M03, from Seqirus UK Limited; for the prevention of influenza;
- Live, attenuated, chimeric dengue virus, serotype 1 / Live, attenuated, chimeric dengue virus, serotype 2 / Live, attenuated, chimeric dengue virus, serotype 3 / Live, attenuated, chimeric dengue virus, serotype 4, EMEA-001545-PIP01-13-M02, from Sanofi Pasteur, for the prevention of dengue.

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

- Nemolizumab, EMEA-001624-PIP01-14-M02, from Galderma International S.A., for the treatment of atopic dermatitis;

Opinion on compliance check

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

- Adjupanrix: Purified antigen fractions of inactivated split virion influenza A/VietNam/1194/2004 (H5N1) like strain used (NIBRG-14) / Prepandrix: Purified antigen fractions of inactivated split virion influenza A/Indonesia/05/2005 like strain used (PR8-IBCDC-RG2), EMEA-C-000160-PIP01-07-M05, from GlaxoSmithKline Biologicals SA, for the prevention of influenza 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 9 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

Other matters

The next meeting of the PDCO will be held on 25-28 February 2020.

– 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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