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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

09-11 December 2019

Opinions on paediatric investigation plans

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

- (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;
- Anti-CD7 mAb conjugated to ricin toxin A chain / anti-CD3 mAb conjugated to ricin toxin A chain (T-Guard), EMEA-002087-PIP01-16, from Xenikos BV, for the treatment of acute Graft versus Host Disease;
- Atogepant, EMEA-002530-PIP01-18, from Allergan Pharmaceuticals International Limited, for the prevention of migraine headaches;
- Norursodeoxycholic acid, EMEA-002485-PIP01-18, from Dr. Falk Pharma GmbH, for the treatment of primary sclerosing cholangitis and treatment of autoimmune sclerosing cholangitis;
- Human immunoglobulin G2 isotype antibody to IL-33R, EMEA-002515-PIP01-18, from GlaxoSmithKline Trading Services Limited, for the treatment of asthma;
- Asciminib, EMEA-002347-PIP01-18, from Novartis Europharm Limited, for the treatment of chronic myeloid leukaemia;
- Factor VIII Fc – von Willebrand factor – XTEN fusion protein (rFVIIIFc-VWF-XTEN), EMEA-002501-PIP01-18, from Bioverativ Therapeutics, Inc., a Sanofi Company, for the treatment of congenital haemophilia A;
- Anti-IL-17A/F Nanobody (MK1095), EMEA-002568-PIP01-19, from Bond Avillion 2 Development LP, for the treatment of psoriasis;
- 2-[[8-chloro-3-[(4-chlorophenyl)methyl]-4-(difluoromethoxy)-2-ethyl-5- quinolinyl]oxy]acetic acid L-lysine salt (GB001), EMEA-002484-PIP01-18, from GB001, Inc (A wholly-owned subsidiary of

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Gossamer Bio, Inc.), for the treatment of asthma;

- Mecasermin rinfabate, EMEA-000534-PIP03-17, from Premacure AB, a member of the Shire group of companies, for the prevention of chronic lung disease of prematurity;
- Budesonide, EMEA-002500-PIP01-18, from Calliditas Therapeutics AB, for the treatment of primary IgA nephropathy.

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

- Dupilumab, EMEA-001501-PIP04-19, from Regeneron Ireland DAC, for the treatment of eosinophilic esophagitis.

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 a PIP with Deferral and waiver adopted on 18 October 2019 for 3-[5-[(1R,2S)-2-(2,2-difluoropropanoylamino)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propoxy]indazol-1-yl]-N-[(3R)-tetrahydrofuran-3-yl]benzamide (AZD7594), EMEA-001976-PIP02-18, , from AstraZeneca AB, for the treatment of asthma, the PDCO adopted a revised positive opinion and agreed to the changes regarding measures and timelines of the paediatric investigation plan 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:

- Ripasudil, EMEA-002676-PIP01-19, from Kowa Pharmaceutical Europe Co. Ltd., for the treatment of corneal dystrophy;
- Autologous dendritic cells activated by transient exposure to killed prostate cancer cells *ex vivo* (DCVAC/PCa), EMEA-002679-PIP01-19, from SOTIO a.s., for the treatment of prostate cancer;
- Benzocaine, EMEA-002654-PIP02-19, from Johnson and Johnson, for the treatment of oropharyngeal pain;
- Levocetirizine / montelukast, EMEA-002646-PIP01-19, from Abbott Laboratories Limited, for the

treatment of allergic rhinitis;

- Futibatinib, EMEA-002647-PIP01-19, from Taiho Pharma Europe Lt, for the treatment of cholangiocarcinoma;
- 3-[4-(4-Aminopiperidin-1-yl)-3-(3,5-difluorophenyl)quinolin-6-yl]-2-hydroxybenzonitrile (CRN00808), EMEA-002682-PIP01-19, from Crinetics Pharmaceuticals Inc, for the treatment of acromegaly and treatment of pituitary gigantism;
- Glibenclamide, EMEA-002651-PIP01-19, from Biogen Idec Limited, for the treatment of large hemispheric infarction;
- Modified human papillomavirus capsid protein conjugated to the near-infrared dye silicate(5-),bis[N-[3-[(hydroxy-.kappa.O)dimethylsilyl]propyl]-3-sulfo-N,N-bis(3-sulfopropyl)-1-propanaminiumato(4-)][6-[[[3-[(29H,31H-phthalocyanin-yl-.kappa.N29,.kappa.N30,.kappa.N31,.kappa.N32)oxy]propoxy]carbonyl]amino]hexanoato(3-)]-, sodium (1:5), EMEA-002658-PIP01-19, from Aura Biosciences Inc, for the treatment of ocular melanoma;
- rhPSMA-7.3 (18F), EMEA-002657-PIP01-19, from Blue Earth Diagnostics Ltd, for the visualisation of prostate-specific membrane antigen in adenocarcinoma of the prostate;
- Hyoscine / physostigmine, EMEA-002678-PIP01-19, from Defence Science Technology Laboratory, for the prevention of organophosphate poisoning;
- Canakinumab, EMEA-000060-PIP08-19, from Novartis Europharm Limited, for the treatment of lung carcinoma;
- Humanized immunoglobulin (Ig) G4 proline, alanine, alanine (IgG4 PAA) based bispecific antibody directed against cluster of differentiation (CD) 3 receptor complex and B-cell maturation antigen (BCMA), EMEA-002650-PIP01-19, from Janssen-Cilag International N.V., for the treatment of multiple myeloma.

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:

- Vamorolone, EMEA-001794-PIP02-16-M02, from ReveraGen BioPharma Ltd., for the treatment of Duchenne muscular dystrophy;
- Fosnetupitant / palonosetron, EMEA-001198-PIP03-17-M03, from Helsinn Birex Pharmaceuticals Limited, for the prevention of chemotherapy-induced nausea and vomiting;
- Zoledronic acid, EMEA-000057-PIP01-07-M07, from Novartis Europharm Limited, for the treatment of Paget's disease of the bone and treatment of osteoporosis;
- (RS)-Baclofen / Naltrexone HCl /D-Sorbitol (PXT3003), EMEA-002164-PIP01-17-M02, from Pharnext S.A., for the treatment of Charcot-Marie-Tooth disease Type 1A;
- 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) /

Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H1N1), EMEA-001715-PIP01-14-M03, from Seqirus Netherlands B.V., for the prevention of influenza infection;

- Albutrepenonacog alfa, EMEA-001107-PIP01-10-M04, from CSL Behring GmbH, for the treatment of hereditary factor IX deficiency;
- Cannabidiol (CBD), EMEA-001964-PIP01-16-M01, from GW Pharma (International) B.V., for the treatment of seizures associated with Dravet Syndrome (DS), treatment of seizures associated with infantile spasms (IS), treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) and treatment of seizures associated with Tuberous Sclerosis Complex (TSC);
- Vosoritide (BMN 111), EMEA-002033-PIP01-16-M01, from BioMarin International Limited, for the treatment of achondroplasia;
- Nivolumab, EMEA-001407-PIP01-12-M02, from Bristol-Myers Squibb Pharma EEIG, for the treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue);
- Nivolumab, EMEA-001407-PIP02-15-M03, from Bristol-Myers Squibb Pharma EEIG, for the treatment of malignant neoplasms of lymphoid tissue and treatment of malignant neoplasms of the central nervous system;
- Lipegfilgrastim, EMEA-001019-PIP01-10-M05, from UAB ”Sicor Biotech“, for the prevention of chemotherapy-induced febrile neutropenia and treatment of chemotherapy-induced neutropenia;
- Lenvatinib, EMEA-001119-PIP02-12-M06, from Eisai GmbH, for the treatment of papillary thyroid cancer, treatment of follicular thyroid cancer and treatment of osteosarcoma;
- Bupivacaine, EMEA-000877-PIP03-17-M01, from Pacira Ltd, for postsurgical analgesia.

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

- Fluticasone furoate / umeclidinium bromide / vilanterol trifenatate /, EMEA-002153-PIP01-17-M01, from GlaxoSmithKline Trading Services Limited, for the treatment of asthma.

Opinion on compliance check

The PDCO adopted positive opinions on full compliance check for:

- Lurasidone (hydrochloride), EMEA-C-001230-PIP01-11-M05, from Aziende Chimiche Riunite Angelini Francesco -ACRAF S.p.A, for the treatment of schizophrenia;
- Vestronidase alfa, EMEA-C-001540-PIP01-13-M01, from Ultragenyx Germany GmbH, for the treatment of mucopolysaccharidosis type VII;
- Octenidine (dihydrochloride), EMEA-C-001514-PIP01-13-M01, from Cassella-med GmbH & Co. KG, for the treatment of upper respiratory tract infections;
- Glecaprevir / Pibrentasvir, EMEA-C-001832-PIP01-15-M02, from AbbVie Ltd, for the treatment of chronic hepatitis C;
- Sodium thiosulfate (STS), EMEA-C-002147-PIP02-17-M01, from Fennec Pharmaceuticals, Inc., for the prevention of platinum-induced ototoxic hearing loss.

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 5 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 28-31 January 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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