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Human Medicines Division

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

22-25 June 2021

Opinions on paediatric investigation plans

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

- Human, recombinant, non-fucosylated IgG1k monoclonal antibody targeting OX-40 receptor on activated T cells (KHK4083), EMEA-002886-PIP01-20, from Kyowa Kirin Pharmaceutical Development Limited, for the treatment of atopic dermatitis;
- Infigratinib, EMEA-002594-PIP02-20, from QED Therapeutics Inc., for the treatment of achondroplasia;
- (1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxamide, EMEA-002863-PIP01-20, from Alexion Europe SAS, for the treatment of paroxysmal nocturnal haemoglobinuria;
- Fenebrutinib, EMEA-002349-PIP03-20, from Roche Registration GmbH, for the treatment of multiple sclerosis;
- Deucravacitinib, EMEA-002350-PIP03-20, from Bristol-Myers Squibb International Corporation, for the treatment of systemic lupus erythematosus;
- Cefepime/zidebactam, EMEA-002892-PIP01-20, from Wockhardt Bio AG, for the treatment of complicated urinary tract infections;
- Vatiquinone, EMEA-001238-PIP02-20, from PTC Therapeutics International Limited, for the treatment of mitochondrial disease;
- Ublituximab, EMEA-002889-PIP02-20, from CambPharma Solutions (CY) Ltd, for the treatment of multiple sclerosis;
- Afamitresgene autoleucel, EMEA-002867-PIP01-20, from Adaptimmune Ltd, for the treatment of soft tissue sarcoma;
- Allogeneic anti-CD19 CAR T cells produced using CRISPR/Cas9 to disrupt the T cell receptor alpha

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constant (TRAC) and β2-microglobulin (B2M) genomic loci and a recombinant adeno-associated viral vector to deliver donor template for insertion of the anti-CD19 CAR expression cassette into the TRAC locus, EMEA-002881-PIP01-20, from CRISPR Therapeutics AG, for the treatment of B-lymphoblastic leukaemia/lymphoma and treatment of mature B cell neoplasms;

- Iptacopan, EMEA-002705-PIP03-20, from Novartis Europharm Limited, for the paroxysmal nocturnal haemoglobinuria;
- Bardoxolone (methyl), EMEA-002488-PIP01-18, from Reata Pharmaceuticals Inc., for the treatment of Alport syndrome;
- Human Immunoglobulin G1 constant region – human ectodysplasin-A1 receptor-binding domain fusion protein (ER004), EMEA-002995-PIP01-21, from EspeRare Foundation, for the treatment of X-linked hypohidrotic ectodermal dysplasia (XLHED).

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:

- No item

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:

- Ramipril / amlodipine / hydrochlorothiazide, EMEA-002998-PIP01-21, from Swyssi AG, for the treatment of hypertension;
- Empagliflozin, EMEA-000828-PIP07-21, from Boehringer Ingelheim International GmbH, for the treatment of ischaemic heart disease;
- Semaglutide / insulin icodec, EMEA-002988-PIP01-21, from Novo Nordisk A/S, for the treatment of type 2 diabetes mellitus;
- Aldafermin, EMEA-003005-PIP01-21, from NGM Biopharmaceuticals, Inc., for the treatment of non-alcoholic steatohepatitis (NASH);
- Immunoglobulin G1 anti-SORT1 human monoclonal antibody, EMEA-002997-PIP01-21, from Alector, Inc., for the treatment of clinically symptomatic or pre-symptomatic frontotemporal dementia;

- Cetrelimab, EMEA-003006-PIP01-21, from Janssen-Cilag International NV, for the treatment of urothelial carcinoma;
- Gemcitabine (hydrochloride), EMEA-003007-PIP01-21, from Janssen-Cilag International NV, for the treatment of urothelial carcinoma;
- Sivopixant, EMEA-003010-PIP01-21, from Shionogi B.V., for the treatment of unexplained or refractory chronic cough;
- In vitro expanded autologous human articular chondrocytes, EMEA-002217-PIP01-17-M02, from TETEC Tissue Engineering Technologies AG, for the treatment of cartilage disorders;
- Gabapentin, EMEA-002994-PIP01-21, from Alvogen Malta Out-licensing Ltd., for the treatment of postherpetic neuralgia;
- Datopotamab deruxtecan, EMEA-002976-PIP02-21, from Daiichi Sankyo Europe GmbH, for the treatment of breast cancer;
- Temelimab, EMEA-002127-PIP01-17-M01, from GeNeuro SA, for the treatment of multiple sclerosis.

The PDCO adopted 1 opinion on the **refusal** of a request for waiver for:

- Bentracimab, EMEA-002766-PIP02-21, from PhaseBio Pharmaceuticals Inc.; for the treatment of ticagrelor associated haemorrhage/prevention of ticagrelor associated haemorrhage.

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:

- Sacubitril/valsartan, EMEA-000316-PIP02-11-M05, from Novartis Europharm Ltd., for the treatment of heart failure;
- Baricitinib, EMEA-001220-PIP03-16-M02, from Eli Lilly and Company Limited, for the treatment of atopic dermatitis;
- Dupilumab, EMEA-001501-PIP01-13-M07, from Regeneron Pharmaceuticals, Inc, for the treatment of atopic dermatitis;
- Ligelizumab, EMEA-001811-PIP02-15-M04, from Novartis Europharm Limited, for the treatment of chronic spontaneous urticaria;
- Tralokinumab, EMEA-001900-PIP02-17-M05, from LEO Pharma A/S, for the treatment of atopic dermatitis;
- Lebrikizumab, EMEA-002536-PIP01-18-M01, from Eli Lilly and Company Limited, for the treatment of atopic dermatitis;
- Liraglutide, EMEA-000128-PIP02-09-M04, from Novo Nordisk A/S, for the treatment of obesity;

- Ferric maltol, EMEA-001195-PIP01-11-M05, from Norgine BV, for the treatment of iron deficiency;
- Rurioctocog alfa pegol, EMEA-001296-PIP01-12-M04, from Baxalta Innovations GmbH, for the treatment of congenital factor VIII deficiency;
- Giroctocogene fitelparvovec, EMEA-002724-PIP01-19-M01, from Pfizer Europe MA EEIG, for the treatment of haemophilia A;
- Tocilizumab, EMEA-000309-PIP04-17-M03, from Roche Registration GmbH, for the treatment of cytokine release syndrome associated with chimeric antigen receptor (CAR) T cell therapy or T-cell-engaging bispecific antibody therapy;
- Ocrelizumab, EMEA-000310-PIP03-10-M05, from Roche Registration GmbH, for the treatment of multiple sclerosis;
- Phenobarbital, EMEA-002532-PIP01-18-M01, from Proveca Pharma Limited, for the treatment of Epilepsy;
- Cenobamate, EMEA-002563-PIP02-19-M01, from A.C.R.A.F. SpA, for the treatment of epilepsy;
- Cabozantinib, EMEA-001143-PIP01-11-M03, from Ipsen Pharma, for the treatment of malignant solid tumours;
- Ibrutinib, EMEA-001397-PIP03-14-M06, from Janssen-Cilag International N.V., for the treatment of mature B-cell neoplasm;
- Quizartinib, EMEA-001821-PIP01-15-M05, from Daiichi Sankyo Europe GmbH, for the treatment of acute myeloid leukaemia;
- Cemiplimab, EMEA-002007-PIP02-17-M01, from Regeneron Ireland DAC, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue);
- Sirolimus, EMEA-001416-PIP01-12-M03, from Santen Incorporated, for the treatment of non-infectious uveitis;
- Selexipag, EMEA-000997-PIP01-10-M05, from Janssen-Cilag International NV, for the treatment of pulmonary arterial hypertension;
- Xylitol / Procaine hydrochloride / Magnesium sulphate heptahydrate / Potassium chloride, EMEA-001171-PIP01-11-M02, from MIT Gesundheit GmbH, for cardioplegia;
- Lactobacillus reuteri (IBP-9414), EMEA-001895-PIP01-15-M01, from Infant Bacterial Therapeutics AB, for the prevention of necrotising enterocolitis;
- Fasinumab, EMEA-002059-PIP02-19-M01, from Regeneron Ireland D.A.C., for the treatment of chronic musculoskeletal pain and treatment of chronic non-musculoskeletal pain;
- Vortioxetine, EMEA-000455-PIP02-10-M08, from H. Lundbeck A/S, for the treatment of major depressive disorder;
- Seltorexant, EMEA-002746-PIP01-20-M01, from Janssen-Cilag International NV, for the treatment of major depressive disorder;
- Finerenone, EMEA-001623-PIP01-14-M04, from Bayer AG, for the treatment of chronic kidney disease;
- Hepatitis B (rDNA) surface antigen adjuvanted, EMEA-001127-PIP02-11-M01, from Dynavax GmbH,

for the prevention of Hepatitis B virus infection;

- Nirsevimab (MEDI8897), EMEA-001784-PIP01-15-M03, from AstraZeneca AB, for the prevention of lower respiratory tract infection caused by respiratory syncytial virus;
- Neisseria meningitidis serogroup A polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup C polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup Y polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup W polysaccharide conjugated to tetanus toxoid (MenACYW), EMEA-001930-PIP01-16-M03, from Sanofi Pasteur, for the prevention of invasive meningococcal disease;
- Multivalent, live, recombinant, non-replicating in human cells, Modified Vaccinia Ankara vectored vaccine, expressing the EBOV Mayinga glycoprotein, the Sudan virus Gulu GP, the Marburg virusMusoke GP, and the Taï Forest virus nucleoprotein [MVA-BN-Filo], EMEA-002308-PIP01-17-M02, from Janssen Cilag International NV, for the prevention of Ebola virus disease.

The following product(s) was/were granted a product-specific waiver in replacement of an agreed PIP:

- Monovalent, live, recombinant, replication-incompetent adenoviral serotype 26 vectored vaccine expressing the full length glycoprotein of the Ebola virus Mayinga variant (Ad26.ZEBOV), EMEA-002307-PIP01-17-M02, from Janssen Cilag International NV; for the prevention of Ebola virus disease.

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

- No item

Opinion on compliance check

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

- Enalapril maleate, EMEA-C-001706-PIP01-14-M03, from Proveca Pharma Limited, for the treatment of heart failure;
- Ticagrelor, EMEA-C-000480-PIP01-08-M14, from AstraZeneca AB, for the prevention of thromboembolic events;
- Secukinumab, EMEA-C-000380-PIP02-09-M04, from Novartis Europharm Ltd, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, spondylarthritis, psoriatic arthritis and juvenile idiopathic arthritis);
- Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide, EMEA-C-001460-PIP01-13-M05, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Brentuximab vedotin, EMEA-C-000980-PIP01-10-M07, from Takeda Pharma A/S; for the treatment of Hodgkin lymphoma and the treatment of anaplastic large cell lymphoma;
- Ceftolozane / Tazobactam, EMEA-C-001142-PIP01-11-M04, from Merck Sharp & Dohme (Europe), Inc., for the treatment of urinary tract infection and the treatment of intra-abdominal infections;
- Cobimetinib, EMEA-C-001425-PIP01-13-M05, from Roche Registration GmbH, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue) with Ras, Raf or MEK pathway activation;
- Dimethyl fumarate, EMEA-C-000832-PIP01-10-M05, from Biogen Idec Ltd., for the treatment of

multiple sclerosis.

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

Other matters

The PDCO welcomed the renewed alternate member from Germany, Yuansheng Sun, who has been nominated by Paul-Ehrlich-Institut .

The next meeting of the PDCO will be held on 20-23 July 2021.

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: https://www.ema.europa.eu/en/medicines/ema_group_types/ema_pip
3. More information about the PDCO and the Paediatric Regulation is available in the Regulatory section of the Agency's website: _https://www.ema.europa.eu/en/committees/paediatric-committee-pdco
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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