EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Paediatric Committee (PDCO)

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

15-17 January 2014

Opinions on paediatric investigation plans

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

- Ustekinumab, from Janssen-Cilag International NV, for the treatment of Crohn disease;
- Human normal immunoglobulin, from Baxter Innovations GmbH, for the treatment of primary immunodeficiency (PID);
- Enalapril (maleate), from Proveca Limited, for the treatment of heart failure;
- Citric acid (as citric acid anhydrous) / sodium chloride / simeticone / macrogol 4000 / sodium citrate / sodium sulfate (as sodium sulfate anhydrous) / potassium chloride, from ALFA WASSERMANN S.p.A., for the diagnosis of large intestine disorders;
- Clazakizumab, from Bristol-Myers Squibb International Corporation, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis and juvenile idiopathic arthritis);
- Idarucizumab, from Boehringer Ingelheim International GmbH, for the prevention and treatment of dabigatran associated haemorrhage;
- Elobixibat, from Ferring Pharmaceuticals A/S, for the treatment of chronic constipation.

The PDCO adopted an opinion on the **refusal** of a PIP, including a deferral, for Fluocinolone acetonide, from Laboratorios SALVAT, for the treatment of dermatitis and eczema.

The PDCO subsequently granted on its own motion a product-specific waiver for this medicine 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.

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Also, the PDCO adopted an opinion on the **refusal** of a PIP for recombinant human growth hormone modified by fusion with two hydrophilic polypeptide chains (VRS-317), from Versartis, Inc, for the treatment of growth hormone deficiency.

The PDCO subsequently granted on its own motion a product-specific waiver for this medicine for all subsets of the paediatric population in the specified condition, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population and 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.

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:

- Ocriplasmin, from ThromboGenics NV, for the treatment of symptomatic focal vitreomacular adhesion;
- Ertugliflozin / metformin, from Merck Sharp & Dohme (Europe), Inc., for the treatment of type II diabetes mellitus;
- Ertugliflozin / sitagliptin, from Merck Sharp & Dohme (Europe), Inc., for the treatment of type II diabetes mellitus;
- Telmisartan / amlodipine (besylate), from Zentiva k.s., for the treatment of essential hypertension;
- Diclofenac sodium / thiocolchicoside, from Epifarma Srl, for the treatment of musculoskeletal and connective tissue pain and discomfort;
- Amlodipine (besylate) / ramipril, from Brunifarma Research s.r.l., for the treatment of essential hypertension.

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:

- Cinacalcet hydrochloride, from Amgen Europe B.V., for the treatment of parathyroid carcinoma, treatment of primary hyperparathyroidism and treatment of secondary hyperparathyroidism in patients with end-stage renal disease;

- Telaprevir, from Janssen-Cilag International NV, for the treatment of chronic viral hepatitis C;
- Darbepoetin alfa, from Amgen Europe B.V., for the treatment of anaemia due to chronic disorders;
- Linagliptin, from Boehringer Ingelheim International GmbH, for the treatment of type 2 diabetes mellitus;
- Tofacitinib, from Pfizer Limited, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis);
- Tofacitinib, from Pfizer Limited, for the treatment of psoriasis;
- Lanthanum carbonate hydrate, from Shire Pharmaceutical Contracts Ltd, for the treatment of hyperphosphataemia;
- Trenonacog alfa (Coagulation Factor IX (recombinant)), from Cangene Europe Ltd., for the treatment of hereditary factor IX deficiency (Haemophilia B);
- Pneumococcal polysaccharide serotype 6B conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 1 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 18C conjugated to tetanus toxoid / Pneumococcal polysaccharide serotype 5 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 19F conjugated to diphtheria toxoid / Pneumococcal polysaccharide serotype 14 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 9V conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 4 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 23F conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 7F conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein, from GlaxoSmithKline Biologicals S.A., for the disease caused by streptococcus pneumoniae and acute Otitis media caused by Non-typeable Haemophilus influenzae;
- Dulaglutide, from Eli Lilly & Company, for the treatment of type 2 diabetes mellitus;
- Edoxaban (tosylate), from Daiichi Sankyo Development Limited, for the prevention of arterial thromboembolism, treatment of venous thromboembolism and prevention of venous thromboembolism;
- Rubidium (82Rb) chloride, from Jubilant DraxImage Inc., for the visualisation of myocardial perfusion for diagnostic purposes;
- Treosulfan, from medac Gesellschaft für klinische Spezialpräparate mbH, for the conditioning treatment prior to haematopoietic progenitor cell transplantation;
- Lenvatinib, from Eisai Europe Ltd, for the treatment of papillary thyroid cancer, treatment of follicular thyroid cancer and treatment of osteosarcoma;
- Glycopyrronium (bromide), from Proveca Limited, for the treatment of sialorrhoea.

Opinion on compliance check

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

- Human Papillomavirus Type 6 L1 protein / Human Papillomavirus Type 11 L1 protein / Human Papillomavirus Type 16 L1 protein / Human Papillomavirus Type 18 L1 protein / Human

Papillomavirus Type 31 L1 protein / Human Papillomavirus Type 33 L1 protein / Human Papillomavirus Type 45 L1 protein / Human Papillomavirus Type 52 L1 protein / Human Papillomavirus Type 58 L1 protein, from Sanofi Pasteur MSD S.N.C., for the prevention of infection by human papillomavirus;

- Nitisinone, from Swedish Orphan Biovitrum International AB, for the treatment of tyrosinemia type 1.

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/measured 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 3 applications were withdrawn during the late stages of the evaluation (30 days or less before opinion).

PDCO and Companies meeting on Paediatric trials in *Clostridium difficile* infections

Three companies with PIPs in the condition "Treatment of *Clostridium difficile* infections" initiated this meeting with the committee. The scope of the discussion was on which age groups should be included in the paediatric clinical trials for this condition. Three external experts with expertise in paediatric gastro-enterology and microbiology were invited by the Committee.

Other matters

The PDCO welcomed Dana Gabriela Marin in her new role as a member nominated by the CHMP to represent Romania.

The PDCO welcomed Nela Vilceanu in her new role as an alternate nominated by the CHMP to represent Romania.

The PDCO thanked Peter Bauer, who is retiring, for his outstanding work as an expert at PDCO meetings.

The next meeting of the PDCO will be held on 12-14 February 2014.

– 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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Annex of the January 2014 PDCO meeting report

	2012 (January to December)	2013 (January to December)	2014 (January to current month)	Cumulative total (2007 to present)
Total number of validated PIP/waiver applications	178	198	16	1536[1]
Applications submitted for a product not yet authorised *(Article 7[2])*	149	176	14	1189 *(77%)*
Applications submitted for a product already authorised and still under patent, in view of a submission of a variation/extension for a new indication, pharmaceutical form or route of administration *(Article 8[2])*	28	22	2	320 *(21%)*
Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation *(Article 30[2])*	1	0	0	27 *(2%)*
PIPs and full waiver indications covered by these applications	218	225	18	2045

Number of Paediatric Committee (PDCO) opinions	2012	2013	2014	Cumulative total (2007 to present)
Positive on full waiver	47	52	8	328
Positive on PIP, including potential deferral	87	97	7	704
Negative opinions adopted	3	4	0	34
Positive opinions adopted on modification of a PIP	165	186	15	681
Negative opinions adopted on modification of a PIP	1	3	0	9
Positive opinions on compliance with a PIP	4	16	2	53
Negative opinions on compliance check with a PIP	0	1	0	2
Opinions adopted under Art. 14.2	0	0	0	2

[1] Of which 401 have been requests for a full waiver.
[2] Applications submitted in accordance with the referenced article of Regulation (EC) No 1901/2006, as amended.

Areas covered by PIPs/waiver applications	2012 *(Number of areas covered)**	2013 *(Number of areas covered)**	2014 *(Number of areas covered)**
Neurology	11	13	0
Uro-nephrology	5	9	1
Gastroenterology-hepatology	8	17	0
Pneumology-allergology	9	10	2
Infectious diseases	19	20	4
Cardiovascular diseases	34	21	3
Diagnostics	3	3	0
Endocrinology-gynaecology-fertility-metabolism	27	32	1
Neonatology-paediatric intensive care	2	3	0
Immunology-rheumatology-transplantation	15	11	1
Psychiatry	0	9	0
Pain	9	6	0
Haematology-haemostaseology	9	14	0
Otorhinolaryngology	1	3	0
Oncology	19	27	2
Dermatology	14	12	0
Vaccines	2	5	1
Ophthalmology	5	6	0
Anaesthesiology	2	0	0
Nutrition	0	0	0
Other	16	11	0

** One PIP can cover several therapeutic areas*