25 March 2014
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Paediatric Committee (PDCO)

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

19-21 March 2014

Opinions on paediatric investigation plans

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

- Recombinant human alpha-mannosidase, from Zymenex, for the treatment of alpha-mannosidosis;
- Febuxostat, from Menarini International Operations Luxembourg S.A., for the treatment of hyperuricaemia and prevention of hyperuricaemia;
- Enalapril (maleate), from Pharmathen S.A., for the treatment of hypertension;
- Fentanyl (hydrochloride), from Incline Therapeutics Europe Ltd., for the treatment of acute pain;
- 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, from Sanofi Pasteur SA, for the prevention of dengue;
- Pradigastat, from Novartis Europharm Limited, for the treatment of familial chylomicronaemia syndrome (type I hyperlipoproteinaemia);
- Atazanavir / cobicistat, from Bristol-Myers Squibb International Corporation, for the treatment of HIV-1 infection;
- Drospirenone, from Laboratorios León Farma, S.A., for the prevention of pregnancy;
- Chimeric anti-disialoganglioside (GD2) monoclonal antibody (ch14.18/CHO) (APN311), from APEIRON Biologics AG, for treatment of neuroblastoma;
- N-{2-(2,3-Difluorobenzylthio)-6-[(2R,3S)-3,4-dihydroxybut-2-yloxy]pyrimidin-4-yl}azetidine-1-sulfonamide (AZD5069), from AstraZeneca AB, for the treatment of asthma;
- Lumacaftor / ivacaftor, from Vertex Pharmaceuticals (Europe) Ltd., for the treatment of cystic fibrosis.

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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 product:

- Following the re-examination of the positive opinion on a PIP adopted on 14 February 2014 for RNA,[2'-O-(2-methoxyethyl)](P-thio)(m5U- m5C-A- m5C-m5U-m5U-m5U- m5C-A-m5U-A-A-m5U-G- m5C-m5U-G-G) (ISIS 396443), from Isis Pharmaceuticals, for the treatment of spinal muscular atrophy, the PDCO adopted a revised positive 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:

- Anastrozole / levonorgestrel, from Bayer Pharma AG, for the treatment of endometriosis;
- Amlodipine / rosuvastatin, from Krka, d.d., Novo mesto, for the treatment of dyslipidaemia, treatment of hypertension, treatment of ischemic coronary artery disorders and prevention of cardiovascular events;
- Alirocumab, from Sanofi-aventis recherche & développement, for the treatment of mixed dyslipidaemia.

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:

- Tiotropium bromide (monohydrate), from Boehringer Ingelheim International GmbH, for the treatment of asthma;
- Naloxegol, from AstraZeneca AB, for the treatment of opioid-induced constipation;

- Human coagulation Factor VIII / von Willebrand Factor, from CSL Behring, for the treatment of hereditary factor VIII deficiency (Haemophilia A) and treatment of von Willebrand disease;
- Poly(oxy-1,2-ethanediyl),alpha-hydro-omega-methoxy-133 ester with granulocyte colony-stimulating factor [methionyl,133-[O-[2-(acetylamino]-6-O-[N-[N-carboxyglycyl)amino]-alpha neuraminosyl]-2-deoxy-alpha-D-galactopyranosyl]-L-threonine]] (human) (XM22), from Teva Pharma B.V., for the treatment of chemotherapy-induced neutropenia and prevention of chemotherapy-induced febrile neutropenia;
- Atazanavir (sulphate), from Bristol-Myers Squibb Pharma EEIG, for the treatment of human immunodeficiency virus (HIV-1) infection;
- Methyl aminolevulinate hydrochloride, from Photocure ASA, for the treatment of acne vulgaris;
- Teriflunomide, from Sanofi-aventis recherche & développement, for the treatment of multiple sclerosis;
- Corifollitropin alfa, from Merck Sharp & Dohme Limited, for the treatment of hypogonadotrophic hypogonadism;
- Canagliflozin, from Janssen-Cilag International N.V., for the treatment of type 2 diabetes mellitus;
- Eribulin, from Eisai Europe Ltd, for the treatment of soft tissue sarcoma;
- Ipilimumab, from Bristol-Myers Squibb Pharma EEIG, for the treatment of melanoma;
- Ipilimumab, from Bristol-Myers Squibb Pharma EEIG, for all the conditions included in the category of malignant neoplasms (except melanoma, nervous system, haematopoietic and lymphoid tissue);
- Octocog alfa, from Bayer Pharma AG, for the treatment of hereditary factor VIII deficiency;
- Romiplostim, from Amgen Europa B.V, for the treatment of immune thrombocytopenia (idiopathic thrombocytopenic purpura) and treatment of disease-related thrombocytopenia in myelodysplastic syndrome;
- Octadecasodium hexakis(4-{[(1S,3R)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate) hexakis(N-pentanoyl-N-{[2´-(1H-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15) (LCZ696), from Novartis Europharm Ltd., for the treatment of heart failure;
- Human normal immunoglobulin, from LFB Biotechnologies, for the treatment of primary immunodeficiency (PID) and treatment of idiopathic thrombocytopenic purpura (ITP);
- Everolimus, from Novartis Europharm Limited, for the prevention of rejection of transplanted kidney, prevention of rejection of transplanted heart and prevention of rejection of transplanted liver;
- Tapentadol (hydrochloride), from Grünenthal GmbH, for the treatment of chronic pain.

Opinion on compliance check

The PDCO adopted a positive opinion on (full) compliance check for the following procedures:

- Bosentan, from Actelion Registration Ltd, for the treatment of pulmonary arterial hypertension (PAH), treatment of systemic sclerosis and treatment of interstitial pulmonary fibrosis;
- Rupatadine fumarate, from J. Uriach y Compañía, S.A., treatment of allergic rhinitis and treatment of chronic idiopathic urticaria;

- Raltegravir / lamivudine, from Merck Sharp & Dohme (Europe), Inc., for the treatment of human immunodeficiency virus (HIV-1) 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/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 1 application was withdrawn during the late stages of the evaluation (30 days or less before opinion).

Other matters

The PDCO welcomed the new alternate from Cyprus, Andreas Teloudes.

The PDCO thanked Stefanos Christodoulou for his work.

The next meeting of the PDCO will be held on 23-25 April 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

Enquiries to: AskEMA
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid=)

Annex of the March PDCO 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	41	1561[1]
Applications submitted for a product not yet authorised *(Article 7[2])*	149	176	37	1212 *(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	4	322 *(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	44	2071

Number of Paediatric Committee (PDCO) opinions	2012	2013	2014	Cumulative total (2007 to present)
Positive on full waiver	47	52	12	332
Positive on PIP, including potential deferral	87	97	29	726
Negative opinions adopted	3	4	0	34
Positive opinions adopted on modification of a PIP	165	186	54	720
Negative opinions adopted on modification of a PIP	1	3	0	9
Positive opinions on compliance with a PIP	4	16	6	57
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 412 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	1
Uro-nephrology	5	9	1
Gastroenterology-hepatology	8	17	4
Pneumology-allergology	9	10	5
Infectious diseases	19	20	8
Cardiovascular diseases	34	21	5
Diagnostics	3	3	0
Endocrinology-gynaecology-fertility-metabolism	27	32	4
Neonatology-paediatric intensive care	2	3	0
Immunology-rheumatology-transplantation	15	11	2
Psychiatry	0	9	0
Pain	9	6	1
Haematology-haemostaseology	9	14	0
Otorhinolaryngology	1	3	1
Oncology	19	27	4
Dermatology	14	12	3
Vaccines	2	5	1
Ophthalmology	5	6	1
Anaesthesiology	2	0	0
Nutrition	0	0	0
Other	16	11	2

** One PIP can cover several therapeutic areas*