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Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP) meeting report on the review of applications for orphan designation

January 2018

The Committee for Orphan Medicinal Products held its 196th plenary meeting on 16-18 January 2018.

Orphan medicinal product designation

Positive opinions

The COMP adopted 17 positive opinions recommending the following medicines for designation as orphan medicinal products to the European Commission:

1. Opinion(s) adopted at the second COMP discussion, following the sponsor's response to the COMP list of questions:

- 6-{[(1R,2S)-2-aminocyclohexyl]amino}-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridine-3-one monocitrate for treatment of acute myeloid leukaemia, Takeda Pharma A/S;
- Allogeneic CD4+ and CD25+ T lymphocytes ex vivo incubated with GP120 for treatment in haematopoietic stem cell transplantation, Universitätsmedizin der Johannes Gutenberg-Universität Mainz;
- Flucytosine for treatment of glioma, Richardson Associates Regulatory Affairs Ltd;
- Human monoclonal IgG2 antibody against tissue factor pathway inhibitor for treatment of haemophilia A, Bayer AG;
- Mertansine functionalised gold nanoconjugate for treatment of hepatocellular carcinoma, Midatech Pharma Plc;
- Vocimagene amiretrorepvec for treatment of glioma, Richardson Associates Regulatory Affairs Ltd.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

2. Opinions adopted at the first COMP discussion:

- (R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate for treatment of cystic fibrosis, Chiesi Farmaceutici S.p.A.;
- 1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yl]oxy]methyl]cyclopropanamine-dihydrochloride for treatment of soft tissue sarcoma, CATS Consultants GmbH;
- 2'-O-(2-methoxyethyl)-modified antisense oligonucleotide targeting exon 13 in the *USH2A* gene for treatment of retinitis pigmentosa, ProQR Therapeutics IV BV;
- Adenovirus-associated viral vector serotype 8 containing the human *RPGR* gene for treatment of retinitis pigmentosa, Nightstar Therapeutics plc;
- Cannabidivarin for treatment of fragile X syndrome, GW Research Ltd;
- Levosimendan for treatment of amyotrophic lateral sclerosis, Orion Corporation;
- N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide for treatment of pulmonary arterial hypertension, ATXA Therapeutics Limited;
- Pyridoxal 5'-phosphate for treatment of pyridoxamine 5'-phosphate oxidase deficiency, Medicure Pharma Europe Limited;
- Recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2 for treatment of primary IgA nephropathy, Omeros London Limited;
- Rusalatide acetate for treatment of acute radiation syndrome, Raremoon Consulting Ltd;
- Seletalisib for treatment of activated phosphoinositide 3-kinase delta syndrome, UCB Biopharma SPRL.

3. Opinion(s) following appeal procedures:

None

Public summaries of opinions will be available on the EMA website following adoption of the respective decisions on orphan designation[1] by the European Commission. Please also refer to the Community Register of orphan medicinal products for human use.

Negative opinion(s)

1. Opinion(s) adopted following the sponsor's response to the COMP list of questions:

None

2. Opinion(s) following appeal procedures:

- Melatonin for treatment of partial deep dermal and full thickness burns, Therapicon Srl.

[1] Details of all orphan designations granted to date by the European Commission are entered in the EU Register of Orphan Medicinal Products

Lists of questions

The COMP adopted 15 lists of questions on initial applications. These applications will be discussed again at the next COMP meeting prior to the adoption of an opinion.

Oral hearings

7 oral hearings took place.

Withdrawals of applications for orphan medicinal product designation

The COMP noted that 11 applications for orphan medicinal product designation were withdrawn by the sponsor before adoption of the COMP opinion.

Detailed information on the orphan designation procedures

An overview of orphan designation procedures since 2000 is provided in Annex 1.

The list of medicinal products for which decisions on orphan designation have been granted by the European Commission since the last COMP meeting is provided in Annex 2.

Re-assessment of orphan designation at time of marketing authorisation

(Article 5(12) (b) of Regulation (EC) No 141/2000 of the European Parliament and of the Council)

When a designated orphan medicinal product receives a positive opinion for marketing authorisation from EMA's Committee for Medicinal Products for Human Use (CHMP), the COMP has the responsibility to review whether or not the medicinal product still fulfils the designation criteria prior to the granting of a marketing authorisation.

1. Opinion(s) adopted at time of CHMP opinion:

The COMP adopted opinions recommending to the European Commission that the following orphan medicinal products be kept in the Community Register of orphan medicinal products for human use:

- Crysvita (burosumab) for treatment of hypophosphataemic rickets, Kyowa Kirin Limited (EU/3/14/1351). The opinion was adopted by written procedure after the December meeting.
- Lamzede (velmanase alfa) for treatment of alpha-Mannosidosis, Chiesi Farmaceutici S.p.A. (EU/3/04/260). The opinion was adopted by written procedure after the January meeting.

2. Opinion(s) following appeal procedures:

Following an appeal procedure, the COMP adopted an opinion recommending the following orphan medicinal product to be kept in the Community Register of orphan medicinal products for human use:

- Alofisel – darvadstrocel for treatment of anal fistula TIGENIX, S.A.U. (EU/3/09/667)[2].

3. Revised opinion:

[2] On 20 December 2017, the COMP had first adopted by written procedure an opinion recommending removal of Alofisel from the Community Register of orphan medicinal products for human use.

Following receipt of a request for clarification by the European Commission, the COMP adopted a revised final opinion recommending to the European Commission that the following orphan medicinal product be removed from the Community Register of orphan medicinal products for human use:

• Verkazia (ciclosporin) for treatment of vernal keratoconjunctivitis, Santen Oy (EU/3/06/360)[3].

Details of the designated orphan medicinal products that have been subject of a new European Union (EU) marketing authorisation application since the last COMP monthly report are provided in Annex 3.

Details on the authorised orphan medicinal products can be found on the EMA website.

Other matters

The main topics addressed during the meeting related to:

- Protocol assistance advice

Upcoming meetings

- The 197th meeting of the COMP will be held on 13-15 February 2018.

Note

This monthly report, together with other information on the work of the European Medicines Agency, can be found on the EMA website: www.ema.europa.eu

Contact details of our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu

[3] The initial COMP opinion was adopted on 27 November 2017.

Annex 1

Overview for orphan medicinal product designation procedure since 2000

Please also refer to the Community Register of orphan medicinal products for human use.

Year	Applications submitted	Applications discussed in reporting year	Positive COMP opinions	Applications withdrawn[4]	Negative COMP opinions	EC designations	Orphan medicinal products[5] authorised	Orphan designations included in authorised therapeutic indication[6]
2018	3	26	17 (65%)	8 (31%)	0 (0%)	17	2	2
2017	260	245	144 (59%)	100 (41%)	3 (1%)	147	14	15
2016	330	304	220 (72%)	82 (27%)	3 (1%)	209	14	14
2015	258	272	177 (65%)	94 (35%)	1 (1%)	190	14	21
2014	329	259	196 (76%)	62 (24%)	2 (1%)	187	15	16
2013	201	197	136 (69%)	60 (30%)	1 (1%)	136	7	8
2012	197	192	139 (72%)	52 (27%)	1 (1%)	148	10	12
2011	166	158	111 (70%)	45 (29%)	2 (1%)	107	5	5
2010	174	176	123 (70%)	51 (29%)	2 (1%)	128	4	4
2009	164	136	113 (83%)	23 (17%)	0 (0%)	106	9	9
2008	119	118	86 (73%)	31 (26%)	1 (1%)	73	6	7
2007	125	117	97 (83%)	19 (16%)	1 (1%)	98	13	13
2006	104	103	81 (79%)	20 (19%)	2 (2%)	80	9	11
2005	118	118	88 (75%)	30 (25%)	0 (0%)	88	4	4
2004	108	101	75 (74%)	22 (22%)	4 (4%)	73	6	6
2003	87	96	54 (56%)	37 (40%)	1 (1%)	55	5	5

[4] Revision of the figures for 2015, 2014, 2003, 2002, 2001 and 2000
[5] The number of orphan medicinal products authorised includes the products for which the market exclusivity has expired.
[6] The market authorisation of an orphan medicinal product may cover more than one orphan designation.

Year	Applications submitted	Applications discussed in reporting year	Positive COMP opinions	Applications withdrawn	Final negative COMP opinions	EC designations	Orphan medicinal products authorised	Orphan designations included in authorised therapeutic indication
2002	80	75	43 (57%)	32 (42%)	2 (3%)	49	4	4
2001	83	90	62 (70%)	26 (29%)	1 (1%)	64	3	3
2000	72	32	26 (81%)	3 (10%)	0 (0%)	14	0	0
Total	**2978**	**2810**	**1988 (71%)**	**797 (28%)**	**27 (1%)**	**1969**	**144**	**159**

Annex 2

Designations granted by the European Commission following COMP opinion on the fulfilment of the orphan designation criteria since last COMP plenary meeting

Please also refer to the Community Register of orphan medicinal product for human use.

The list includes designation decisions that were revised following the amendment of an existing designated condition (identified by * when applicable)

Active substance	Orphan indication	Sponsor	COMP opinion date	EC designation date
(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidine-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridine-2-yl)-4-fluoropyrrolidine-2-carboxamide	Treatment of paroxysmal nocturnal haemoglobinuria	FGK Representative Service GmbH	31 October 2017	12 December 2017
Pyrazolo[1,5-a]pyrimidine, 3-[4-chloro-2-(4-morpholinyl)-5-thiazolyl]-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,3-a]pyrimidine	Treatment of congenital adrenal hyperplasia	RegIntel Limited	7 December 2017	17 January 2018
2-isopropyl-3H-naphtho[1,2-d]imidazole-4,5-dione	Treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes	NeuroVive Pharmaceutical AB	31 October 2017	12 December 2017
4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl	Treatment of familial cerebral cavernous malformation	Premier Research Group Limited	31 October 2017	12 December 2017
Acetylleucine	Treatment of GM2 gangliosidosis	IntraBio Ltd	31 October 2017	12 December 2017
Adeno-associated viral vector serotype 2/6 encoding zinc-finger nucleases and the human alpha L-iduronidase gene	Treatment of mucopolysaccharidosis type I	Quintiles Ireland Limited	7 December 2017	17 January 2018
Adeno-associated viral vector serotype 2/6 encoding zinc-finger nucleases and the human iduronate 2-sulfatase gene	Treatment of mucopolysaccharidosis type II (Hunter's syndrome)	Quintiles Ireland Limited	7 December 2017	17 January 2018

Active substance	Orphan indication	Sponsor	COMP opinion date	EC designation date
Adeno-associated viral vector serotype 5 encoding a microRNA targeted to human huntingtin gene	Treatment of Huntington's disease	uniQure biopharma B.V.	7 December 2017	17 January 2018
Adenovirus-associated viral vector serotype 8 containing the human *AIPL1* gene	Treatment of Leber's congenital amaurosis	MeiraGTx UK II Limited	31 October 2017	12 December 2017
Agammaglobulinaemia tyrosine kinase	Treatment of pemphigus	Clinical Network Services (UK) Ltd	31 October 2017	12 December 2017
Allogeneic umbilical cord blood CD34+ cells cultured ex vivo with Notch ligand Delta1	Treatment in haematopoietic stem cell transplantation	Voisin Consulting S.A.R.L.	7 December 2017	17 January 2018
Cannabidiol	Treatment of tuberous sclerosis	GW Research Ltd;	7 December 2017	17 January 2018
Ciclopirox	Treatment of congenital erythropoietic porphyria	Atlas Molecular Pharma S.L.	7 December 2017	17 January 2018
Gilteritinib	Treatment of acute myeloid leukaemia	Astellas Pharma Europe B.V.	7 December 2017	17 January 2018
Humanised Fc-engineered monoclonal antibody against CD19	Treatment of IgG4-related disease	MWB Consulting Ltd	7 December 2017	17 January 2018
Hydroxychloroquine sulphate	Treatment of LIPIN1 disease	Professor Pascale De Lonlay	7 December 2017	17 January 2018
Itacitinib	Treatment of graft-versus-host disease	Incyte Biosciences UK Ltd	7 December 2017	17 January 2018
Metformin and L-citrulline	Treatment of Duchenne muscular dystrophy	Duchenne UK	7 December 2017	17 January 2018
Modified messenger ribonucleic acid encoding human argininosuccinate lyase enzyme encapsulated into lipid nanoparticles	Treatment of argininosuccinic aciduria	PhaseRx Ireland, Ltd	31 October 2017	12 December 2017
N-(bromoacetyl)-3,3-dinitroazetidine	Treatment of small cell lung cancer	Sirius Regulatory	7 December 2017	17 January 2018

Active substance	Orphan indication	Sponsor	COMP opinion date	EC designation date
		Consulting Limited		
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea , hydrochloride salt	Treatment of congenital adrenal hyperplasia	Millendo Therapeutics Ltd	7 December 2017	17 January 2018
Pegunigalsidase alfa	Treatment of Fabry disease	Protalix B.V.	31 October 2017	12 December 2017
Recombinant adeno-associated viral vector serotype 2/1 encoding human beta-hexosaminidase alpha and beta subunits	Treatment of GM2 gangliosidosis	University of Cambridge	7 December 2017	17 January 2018
Sirolimus	Treatment of sickle cell disease	Rare Partners srl Impresa Sociale	7 December 2017	17 January 2018
Vatiquinone	Treatment of RARS2 syndrome	Edison Orphan Pharma BV	7 December 2017	17 January 2018
Venetoclax	Treatment of mantle cell lymphoma	Abbvie Ltd	31 October 2017	12 December 2017

Annex 3

Designated orphan medicinal products that have been subject of a new European Union marketing authorisation application under the centralised procedure since the last COMP monthly report

Please also refer to the Community Register of orphan medicinal products for human use.

Active substance	Designated orphan indication	Sponsor/applicant	EU designation number
Avacopan	Treatment of microscopic polyangiitis	ChemoCentryx Ltd	EU/3/14/1372
Avacopan	Treatment of granulomatosis with polyangiitis	ChemoCentryx Ltd	EU/3/14/1373