EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Research and Development Support

This document was valid from 16 December 2014 to 9 January 2018. It is no longer valid.

No longer valid

Relevant sources for orphan disease prevalence data

Sponsors applying for orphan designation for a medicine under Article 3(1) a paragraph 1 of Regulation (EC) No 141/2000 on orphan medicinal products are requested to provide authoritative references to demonstrate that the condition, for which the medicine is intended, does not affect more than 5 in 10,000 people in the EU at the time the application is made. Possible sources include relevant scientific literature and databases.

After more than 10 years of the implementation of the Orphan Regulation the Agency has accumulated a considerable amount of data on sources of prevalence of rare diseases from the applications for orphan designation. In most cases those sources are publicly available but not easily accessible.

The Agency has decided to make the information collected so far publicly available. This will decrease the administrative burden for applicants for orphan designation and thus encourage the development of medicines for rare diseases. The information is provided in the table below will be updated regularly. The information provided herewith does not replace the obligation for the sponsor under the legislation to establish the prevalence (see Regulation (EC) No 141/2000 and the Guideline on the format and content of applications for designation as orphan medicinal product, ENTR/6283/00).

Sponsors are still obliged to submit an original, up-to-date prevalence calculation supported by data with their orphan designation application. In the Points to consider on the calculation and reporting on the prevalence of a condition for orphan designation, COMP/436/01, the Agency provides guidance for sponsors in establishing the prevalence for conditions and suggests sources of data, review methods and how to present results.

Of note, the references cited are not intended to substitute any epidemiological review of the prevalence of rare diseases and they have to be assessed by the Committee for Orphan Medicinal Products (COMP) in the regulatory context of orphan medicinal product designation. In this sense, it has to be stressed that sometimes the conclusions adopted reflect worst case scenarios that are adequate for regulatory purposes. It must also be emphasised that the prevalence that the sponsor is required to demonstrate is the prevalence at the time of the application for orphan designation, whereas prevalence can change over time.

If you have any comments on the table on prevalence sources do not hesitate to contact us on orphandrugs@ema.europa.eu

[1] Updated format, footer and links

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
Acromegaly	0.6	Publications: Alexander, L., et al., Epidemiology of acromegaly in the Newcastle region. Clin. Endocrinol (Oxf), 1980;12(1):71-9 Bengtsson, B.A., et al., Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta. Med. Scand., 1988;223(4):327-35 Ritchie, C.M., et al., Ascertainment and natural history of treated acromegaly in Northern Ireland. Ulster Med. J., 1990;59(1):55-62 Extabe, J., et al., Acromegaly: an epidemiological study. J. Endocrinol Invest., 1993;16(3):181-7	Somavert	EU/1/02/240 EMEA/H/C/000409	pegvisomant
Acute lymphoblastic leukaemia	0.4	Publications: Greaves M. Childhood leukaemia. BMJ 2002;324(7332):283-7 Pui CH, Mahmoud HH, Rivera GK, Hancock ML, Sandlund JT, Behm FG et al. Early Intensification of Intrathecal Chemotherapy Virtually Eliminates Central Nervous System Relapse in Children With Acute Lymphoblastic Leukemia. Blood 1998;92(2):411-5 Databases: EUCAN, GLOBOCAN 2000 and WHO Cancer Mortality data, Automated Childhood Cancer Information System -ACCIS-, and French National Registry of childhood Leukemia and Lymphoma	Evoltra	EU/1/06/334 EMEA/H/C/000613	clofarabine
Acute myeloid leukaemia	0.7	Publications: Redaelli A, Lee JM, Stephens JM and Pashos CL. Epidemiology and	Ceplene	EU/1/08/477 EMEA/H/C/000796	histamine dihydrochloride

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		clinical burden of acute myeloid leukaemia. *Expert Rev. Anticancer Ther.* 2003; 3(5): 695-710 Redaelli A, Stephens JM, Laskin BL, Pashos CL and Botteman MF. The burden and outcomes associated with four leukemias AML, ALL, CLL and CML. *Expert Rev. Anticancer Ther*. 2003; 3(3): 311-329 Järvisalo J, Tola S, Korkala M-L and Järvinen E. A cancer register-based case study of occupations of patients with acute myeloid leukaemia. *Cancer* 1984; 54:785-790 Langebrake C, Reinhardt D and Ritter J. Minimising the Long-Term Adverse Effects of Childhood Leukaemia. *Therap. Drug Safety* 2002; 25(15):1057-1077 Aul C, Gattermann N and Schneider W. Age-related incidence and other epidemiological aspects of myelodysplastic syndromes. *British Journal of Haematology* 1992; 82:385-367 Pagano L, Polsoni A, Tosti ME, Avvisati G, Mele L, Mele A *et al.* Clinical and biological features of acute myeloid leukaemia occurring as second malignancy: GIMEMA archive of adult acute leukaemia. *British Journal of Haematology* 2001; 112: 109-117 Pulsoni A, Stazi A, Cotichini R, Allione B, Cerri R, di Bona E *et al.* Acute promyelocytic leukaemia: epidemiology and risk factors. A report of the GIMEMA Italian archive of adult acute leukaemia. *Eur J Haematol* 1998; 61:327-332 Preiss BS, Kerndrup GB, Schmidt KG, Sørensen AG, Clausen NT, Gadeberg OV *et al.* Cytogenetic findings in adult *de novo* acute myeloid leukaemia. A population-based study of 303/337 patients.			

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		British Journal of Haematology 2003; 123:219-234 Aström M, Bodin L, Nilsson I and Tidefelt U. Treatment, long-term outcome and prognostic variables in 214 unselected AML patients in Sweden. *British Journal of Cancer* 2000; 82(8):1387-1392 Rådlund A, Thiede T, Hansen S, Carlsson M, Engquist L. Incidence of myelodysplastic syndromes in a Swedish population. *Eur J Haematol* 1995; 54:153-156 Hjalgrim LL, Rostgaard K, Schmiegelow K, Søderhăll S, Kolmannskog S, Verrenranta K *et al.* Age- and Sex-Specific Incidence of Childhood Leukemia by Immunophenotype in the Nordic Countries. J Natl Cancer Inst. 2003; 95(20):1539-44 Coebergh JW, van Steensel-Moll HA, Van Wering ER, van't Veer MB. Epidemiological and immunological characteristics of childhood leukaemia in The Netherlands: population-based data from a nationwide co-operative group of paediatricians. Leuk Res.1985;9(6):683-8 van Steensel-Moll HA, Valkenburg HA, van Zanen GE.. Incidence of childhood leukaemia in The Netherlands (1973-1980). Br J Cancer. 1983 Apr;47(4):471-5 McNally RJQ, Roman E and Cartwright RA. Leukemias and lymphomas: time trends in the UK, 1984-93. *Cancer Causes and Control* 1999;10:35-42 McNally RJQ, Rowland D, Roman E and Cartwright RA. Age and sex distributions of haematological malignancies in the UK. *Haematological Oncology* 1997; 15:173-189			

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		McNally RJQ, Cairns DP , Eden OB, Kelsey AM , Taylor GM and Birch JM. Examination of temporal trends in the incidence of childhood leukaemias and lymphomas provides aetiological clues. *Leukemia* 2001; 15:1612-1618 Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ; American Cancer Society. Cancer statistics, 2004. CA Cancer J Clin. 2004; 54(1):8-29 Kelleher C, Newell J, MacDonagh-White C, MacHale E, Egan E, Connolly E *et al.* Incidence and occupational pattern of leukaemias, lymphomas, and testicular tumours in Western Ireland over an 11 year period. *J Epidemiol Community Health* 1998; 52:651-656 S Schlieben, A Borkhardt, I Reinisch, J Ritterbach, JWG Janssen, R Ratei *et al.* Incidence and clinical outcome of children with CR/ABL-positive acute lymphoblastic leukaemia (ALL). A prospective RT-PCR study based on 673 patients enrolled in the German pediatric multicenter therapy trials ALL-BFM-90 and CoALL-05-92. *Leukemia* 1996; 10:957-963 Taylor PRA, Reid MM, Brown N, Hamilton PJ, and Proctor SJ. Acute lymphoblastic leukemia in patients aged 60 years and over: A population-based study of incidence and outcome. *Blood* 1992; 80(7):1813-1817 Groupe Francais de Morphologie Hematologique. Age distribution and hemogram analysis of the 4496 cases recorded during 1982-1983 and classified according to FAB criteria. *Cancer* 1987; 60:1385-1394 Sant M, Aareleid T, Berrion F, Bielska Lasota M, Carli PM, Faivre J,			

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		rosclaude P *et al.* Eurocare-3: survival of cancer patients diagnosed 1990-94-results and commentary. *Annals of Oncology* 2003; 14(Supplement 5): v61-v118 Capocaccia R, Colonna M, Carazzuari I, De Angelis R, Francisci S, Micheli A *et al.* Measuring cancer prevalence in Europe: the EUROPREVAL Project. *Annals of Oncology 2002*; 13:831-839 Micheli A, Mugno E, Krogh V, Quinn MJ, Coleman M, Hakulinen T *et al.* Cancer pervalence in European registry areas. *Annals of Oncology* 2002; 13:840-865 Clavel J, Goubin A, Auclerc MF, Auvrignon A, Waterkeyn C, Patte C, *et al.* Incidence of childhood leukaemia and non-Hodgkin's lymphoma in France: National registry of childhood leukaemia and lymphoma, 1990-1999. Eur J Cancer Prev. 2004; 13(2): 97-103			
Acute promyelocytic leukaemia	0.80	Publications: Black, R.J., F. Bray, J. Ferlay, and D.M. Parkin. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur. J. Cancer, 1997; 33:1075-1107 Lusis, M.K.P., C. Machado, A.E. Brito, D. Tabak, and M.S.P. de Oliveira. Leucemia M3 variante: aspectos clínicos e diagnósticos. Rev. Ass. Med. Brasil., 1993; 39:224-228 Pulsoni, A., A. Stazi, R. Cotichini, B. Allione, R. Cerri, E. Di Bona, A.M. Nosari, L. Pagano, A. Recchia, M. Ribersani, L. Rocchi, D. Veneri, G. Visani, F. Mandelli, and A. Mele. Acute promyelocytic leukaemia: epidemiology and risk factors. A report of the GIMEMA	Trisenox	EU/1/02/204 EMEA/H/C/000388	arsenic trioxide

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		Italian archive of adult acute leukaemia. Eur. J. Haematol.,1998; 61:327-332 Databases: Finnish Cancer Registry. Helsinki, Finland: Institute for Statistical and Epidemiological Cancer Research, 1997. The cell type distribution of leukaemias diagnosed by sex Swedish Medical Database. Stockholm, Sweden: Medicinsk Faktadatabas - MARS, 1998. Acute, adult, leukaemia registry (In Swedish)			
Adrenal cortical carcinoma	0.1	Publications: Kopf D, Goretzki PE, Lehnert H: Clinical management of malignant adrenal tumors: J. Cancer Res Clin Oncol 2001;127:143-155 Wooten MD, King DK: Adrenal cortical carcinoma, epidemiology and treatment with mitotane and a review of the literature. Cancer 1993; 72(11):3145-3155 Databases: Orphanet	Lysodren	EU/1/04/273 EMEA/H/C/000521	mitotane
Anthracycline extravasation	0.03 (incidence)	Publications: Laughlin RA, Landeen JM, Habal MB. The management of inadvertent subcutaneous adriamycin infiltration. Am J Surg 1979; 137:408-412 Linder RM, Upton J. Prevention of extravasation injuries secondary to doxorubicin. Postgrad Med 1985; 77(4):105-9 Larson DL. Treatment of tissue extravasation by antitumor agents. Cancer 1982; 49(9):1796-1799	Savene	EU/1/06/350 EMEA/H/C/000682	dexrazoxane

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		Wang JJ, Cortes E, Sinks LF, Holland JF. Therapeutic effect and toxicity of adriamycin in patients with antineoplastic disease. Cancer 1971; 28:837-843 Pitkanen J, Asko Seljavaara S, Grohn P, Sundell B, Heinonen E, Appelqvist P. Adriamycin extravasation: surgical treatment and possible prevention of skin and soft-tissue injuries. J Surg Oncol 1983; 23(4):259-262 Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M et al. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. J Clin Oncol 1995; 13(11):2851-2855 Barlock AL, Howser DM, Hubbard SM. Nursing management of Adriamycin extravasation. Am J Nursing 1979; 137:94-96 Other sources: IMS data for sales of packages of 5 different anthracyclines in 1997 Personal communications from experts			
Chronic iron overload	2.7	Publications: Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the Cancer Incidence and Mortality in Europe in 2006. Ann Oncol. 2007; 18(3):581-92. Ferlay J, Boyle P, Cancer Incidence and Mortality in Europe, 2004. Ann Oncol 2005; 16;481-488 Ferlay J, Bray F, Pisani P, Parkin DM. Cancer incidence, mortality and	Exjade	EU/1/06/356 EMEA/H/C/000670	deferasirox

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		prevalence worldwide, version 1.0. Lyon: IARC Press. IARC Cancer Base No. 5. 2001 Pisani, P., Bray, F., Parkin, D.M. Estimates of the worldwide prevalence of cancer for twenty-five sites in the adult population. Int. J. Cancer 2002; 97,72-81 Ferlay J, Bray F, Sankila R, et al. Cancer incidence, mortality and prevalence in the European Union. Lyon: IARC Press. 1999 Databases: GLOBOCAN 2002			
Chronic idiopathic thrombocytopenic purpura	1	Publications: Jacobson DL, Gange SJ, Rose NR, Graham NMH, Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol, 1997; 84(3): 223-243 Satia J, Acquavella J, Hollowell J, Rutstein, Descriptive epidemiology of immune thrombocytopenic purpura in three European countries. The 11th Congress of the European Hematology Association. Amsterdam: [poster presentation]; 2006 Segal JB, Powe NR, Prevalence of immune thrombocytopenia: analyses of administrative data. J Thromb Haemost., 2006; 4:2377-2383	Revolade	EU/1/10/612 EMEA/H/C/001110	eltrombopag
Chronic myelogenous leukaemia	0.4	Publications: Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with	Tasigna	EU/1/07/422 EMEA/H/C/000798	nilotinib

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		interferon alpha. J Natl Cancer Inst 1998;90(11):850-8 Marin D, Marktel S, Szydlo R, Klein JP, Bua M, Foot N, Olavarria E, Shepherd P, Kanfer E, Goldman JM, Apperley JF. Survival of patients with chronic- phase chronic myeloid leukemia on imatinib after failure on interferon alpha. Lancet 2003; 362(9384):617-9 Databases: GLOBOCAN 2002			
Chronic myeloid leukaemia	0.9	Databases: EUCAN; supported by data from EUROCARE-2	Glivec	EU/1/01/198/ EMEA/H/C/000406	imatinib
Conditioning treatment prior to conventional haematopoietic progenitor cell transplantation	1.6 to 0.7	Publications: A. Gratwohl, H. Baldomero. EBMT survey on Transplant activity 1998. Basel 2000 Apperley J, Gluckman E, Gratwohl A. Blood and Marrow Transplantation. ESH (European School of Hematology) and EBMT, 1998, p 18-24 Gratwohl A, Schmid O, Baldomero H, Horisberger B, Urbano-Ispizua A; Accreditation Committee of the European Group for Blood and Marrow Transplantation. Haematopoietic stem cell transplantation (HSCT) in Europe 2002. Changes in indication and impact of team density. A report of the EBMT activity survey.Bone Marrow Transplant. 2004;34(10):855-75	Busilvex Tepadina	EU/1/03/254 EMEA/H/C/000472 EU/1/10/622 EMEA/H/C/001046	busulfan thiotepa

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Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)	0.05	Publications: Cuisset L, Drenth JPH, Derthelop JM. Meyrier A, Vaudour G, Watts RA et al. Genetic linkage of the Muckle-Wells Syndrome to chromosome 1q44. Am. J. Hum Genet. 1999 65:1054-1059 Gerbig AW, Dahinden CA, Mullis P and Hunziker T. Circadian elevation of IL-6 levels in Muckel-Wells syndrome: a disorder of the neuro-immune axis? Q J Med 1998 91:489-492 Haas N, Küster W, Zuberbie r T, Henz BM. Muckle-Wells syndrome: clinical and histological skin findings compatible with cold air urticaria in a large kindred. Br J Dermatol 151 (1), 99–104 Databases: Orphanet: Hoffman, HM. Familial Cold Autoinflammatory Syndrome. Orphanet Encyclopedia. Grateau, G. Muckle-Wells syndrome: Orphanet Encyclopedia	Rilonacept Regeneron	EU/1/09/582 EMEA/H/C/001047	rilonacept
Cystic fibrosis	1.3	Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry Annual Data Report. 1998 Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992;326(18):1187-91 Doring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. Eur Respir J 2000;16(4):749-67 Rothman K, Greenland S. Modern Epidemiology. 2nd ed: Lippincott, Williams & Wilcott, 1998: 43-4 Bellon, G. (2006). About rare diseases - About orphan drugs - Disease: Cystic fibrosis. Orphanet	Cayston	EU/1/09/543 EMEA/H/C/000996	aztreonam lysine

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		Slieker, M. G., C. S. Uiterwaal, et al. (2005). "Birth prevalence and survival in cystic fibrosis: a national cohort study in the Netherlands." Chest 128(4): 2309-15 WHO (2002). The molecular genetic epidemiology of cystic fibrosis. Human Genetics Programme - Chronic Diseases and Health Promotion. W. H. Organization. Genoa Claustres, M., C. Guittard, et al. (2000). "Spectrum of CFTR mutations in cystic fibrosis and in congenital absence of the vas deferens in France." Hum Mutat 16(2): 143-56 Databases: Orphanet (2007). Prevalence of rare diseases: A bibliographic survey. Orphanet Reports Series. Orphanet			
Fabry disease (a-galactosidase A deficiency)	0.03	Publications: Davies JP, Eng CM, Hill JA, Malcolm S, MacdDermot K, Winchester B, Desnick RJ Fabry Disease: Fourteen α-Galactosidase A mutations in unrelated families from the united kingdom and other european countries.European Journal of Human Genetics 1996; 4: 219-224. Poorthuis, BJHM; Wevers, RA; Kleijer, WJ; Groener, JEM; de Jong, JGN; Van Weely, S; Niezen-Koning, KE; Van Diggelen, OP: The frequency of lysosomal storage disease in The Netherlands. Hum Gen	Fabrazyme	EU/1/01/188 EMEA/H/C/000370	agalsidase beta

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		1999; 105:151-156. Desnick, R.J., Ioannou, Y.A., and Eng, C.M. α-galactosidase A Deficiency: Fabry Disease in The Metabolic and Molecular Bases of Inherited Disease, 7th edition, C.R. Scriver, W.S. Sly, and D. Valle (eds), McGraw-Hill (New York, 1995). pp. 2741-2784. Meikle, P.J. et al. Prevalence of Lysosomal Disorders. JAMA 1999; 281: 249-254	Replagal	EU/1/01/189 EMEA/H/C/000369	agalsidase alfa
Gaucher disease	0.3 to 0.6	Publications: Beutler E and Grabowski GA, Gaucher Disease in; The Metabolic and Molecular Basis of Inherited Diseases, (Eds. Seriver CR, Beaudet Al, Sly WS and Valle D), p 2641-2670, McGraw Hill, New York, 1995 Cox T M and Schofield J P, Gaucher's disease: clinical features and natural history in; Ballière's Clinical Haematology, (Ed. A Zimran) Vol	Zavesca	EU/1/02/238 EMEA/H/C/000435	miglustat

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		10, No. 4 pp 657-689, Dec 1997 Erikson A et al, Neuronopathic forms of Gaucher's disease in; Ballière's Clinical Haematology, (Ed. A Zimran) Vol 10, No. 4 pp 711-723, Dec 1997 Beutler E, Gaucher Disease, Advances in Genetics, 1995; 32: 17-49 Bembi B et.al., Enzyme replacement treatment in type 1 and type 3 Gaucher's disease. Lancet, 1994; 344: 1679-1682 Beutler et.al., Failure of Alglucerase Infused into Gaucher Disease Patients to Localize in Marrow Macrophages. Molecular Medicine, 1995; 1 (3): 320-324, 1995 Belmatoug N, Caubel I, Stirnemann J, Billette de Villemeur T. Gaucher's disease, J Soc. Biol. 2002; 196: 141-149 Giraldo P, Pocovi M, Perez-Calvo J, Rubio-Felix D, Giralt M. Report of the Spanish Gaucher's disease registry: clinical and genetic characteristics. Haematologica 2000; 85: 792-799 Pregun I, Tulassay Z. Gaucher's disease: pathogenesis, diagnosis and therapy. Orv Hetil 2004; 145: 1883-1890	Vpriv	EU/1/10/646 EMEA/H/C/001249	velaglucerase alfa
Niemann Pick	0.1	Publications: Sokol J, Blanchetter-Mackie J, Kruth HS, et al. Type C Niemann-Pick disease. Lysosomal accumulation and defective intracellular mobilization of low density lipoprotein cholesterol. J Biol Chem 1988; 263: 3411–7 Steinberg SJ, Ward CP, Fensom AH. Complementation studies in Niemann-Pick disease, type C indicate the existence of a second	Zavesca	EU/1/02/238 EMEA/H/C/000435	Miglustat

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		group. J Med Genet 1994; 31: 317–20 Suzuki K, Parker CC, Pentchev PG, et al. Neurofibrillary tangles in Niemann-Pick disease, type C. Acta Neuropathol 1995; 89: 227–38 Tylki-Szymanska A, Czartoryska B, Lugowska A, Gorska D. The prevalence and diagnosis of lysosomal storage diseases in Poland. Eur J Pediatr 2001; 160: 261–2 Vanier MT, Duthel S, Rodriguez-Lafrasse C, et al. Genetic heterogeneity in Niemann-Pick disease: a study using somatic cell hybridization and linkage analysis. Am J Hum Genet 1996; 58: 118–25 Vanier MT, Suzuki K. Niemann-Pick diseases. In: Moser HW (editor). Neurodystrophies and neurolipidoses. Handbook of Neurology. Vol. 66. Amsterdam: Elsevier Science, 1996; 133–62 Vanier MT. Lipid changes in Niemann-Pick disease, type C brain: personal experience and review of the literature Neurochem Res 1999; 24: 481–9 Walkley 1998 Pinto R, Caseiro C, Lemos M, et al. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet 2004; 12: 87-92 Poorthuis BJ, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999; 105: 151–6 Tylki-Szymanska et al, 2001 Horowitz M, Pasmanik-Chor M, Borochowitz Z, et al. Prevalence of glucocerebrosidase mutations in the Israeli Ashkenazi Jewish population. Hum Mutat 1998; 12: 240–4			

No longer valid

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Malignant gastrointestinal stromal tumours	0.06	Publications: Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Miettinen M, Lasota J. Virchows Arch. 2001;438(1):1-12. Databases: SEER 1998	Glivec	EU/1/01/198/ EMEA/H/C/000406	imatinib
Hairy cell leukaemia	3.65	Databases: EUCAN and GLOBOCAN; supported by data from EUROCARE	Litak	EU/1/04/275 EMEA/H/C/000504	cladribine
Hereditary angioedema	3	Publications: Agostoni A., Cicardi M. Hereditary and Acquired C1-Inhibitor Deficiency: Biological and Clinical Characteristics in 235 Patients. Medicine 1992;71: 206-215 Bork K. Rezidivierende Angioödeme durch C1-Inhibitor-Mangel: Erstickungsrisiko. Deutsches Ärzteblatt 1997; 94: A-726-737 Bork K, Siedlecki K, Bosch S at al. Asphyxiation by Laryngeal Edema in Patients with Hereditary Angioedema. Mayo Clinic Proc 2000; 75: 349-354 Carreer FMJ. The C1 Inhibitor Deficiency- A Review. Eur J Clin Chem Biochem 1992; 30: 793-807 Göring HD, Bork K, Späth PJ et al. Untersuchungen zum hereditären Angioödem im deutschsprachigen Raum. Der Hautarzt 1998; 49: 114-122 Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema – A broad	Firazyr	EU/1/08/461 EMEA/H/C/000899	icatibant

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Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		review for clinicians. Arch Intern Med 2001; 161: 2417-2429 Späth PJ, Wüthrich B. Angioedema. A review on the acquired, allergic or non-allergic, and the hereditary forms. Recenti Progressi in Medicina 1990; 81: 515-531 Talavera A, Larraona JL, Ramos JL et al. Hereditary Angioedema: An Infrequent Cause of Abdominal Pain with Ascites. Am J Gastoenterol 1995; 90: 471-474			
Homocystinuria	0.17	Publications: De Franchis, R.,et al., Clinical aspects of cystathionine beta-synthase deficiency : how wide is the spectrum ? The Italian Collaborative Study Group on Homocystinuria. Eur J Pedatr, 1998; 157 (Suppl 2) : S67-70 Ogier de Baulny, H., et al., Remethylation defects : guidelines for clinical diagnosis and treatment Eur J Pediatr, 1998; 157 (Suppl 2) : S77-83 Naughten, E.R., S. Yap, and P.D. Mayne, Newborn screening for homocystinuria: Irish and world experience. Eur J Pediatr, 1998 ; 157 (Suppl 2) : S84-87	Cystadane	EU/1/06/379 EMEA/H/C/000678	betaine anhydrous

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
Hunter syndrome (Mucopolysaccharidosis II, MPS II)	0.02	Publications: Poorthuis, B.J.H.M. et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999: 105: 151-156 Meikle, P.J. et al. Prevalence of Lysosomal Disorders. JAMA 1999; 281: 249-254 Databases: UK Society for Mucopolysaccharide Diseases database	Elaprase	EU/1/06/365 EMEA/H/C/000700	idursulfase
Idiopathic Pulmonary Fibrosis	3	Publications: Hodgson U, Laitinen T and Tukiainen P. 2002. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. Thorax 57: 338-342 Thomeer MJ, Demedts M, Vandeurzen K et al. 2001. Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. Acta Clin Belg 56: 163-172 Scott J, Johnston, I and Britton J. 1990. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. BMJ 301: 1015-1017	Esbriet	EU/1/11/667 EMEA/H/C/002154	pirfenidone

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
Lambert-Eaton Myasthenic Syndrome	0.1	Publications: Goulon-Goëau C, Gajdos P, Goulon M. Myasthénie et syndromes myasthéniques. Encycl Méd Chir (Paris-France) Neurologie 1992;17-172-B-10 Henze T. Myasthenia gravis and myasthenic syndromes. Part II. Lambert-Eaton myasthenic syndrome, congenital myasthenic syndromes and botulism. Drugs of Today 1997;33(8):543-53 O'Neill JH, Murray MF, Newson-Davis J. The Lambert-Eaton myasthenic syndrome. A review of 50 cases. Brain 1988;111(1):577-596 Pascuzzi RM, Kim YI. Lambert-Eaton Syndrome. Semin Neurol 1990;10(1):35-41 Robertson NP, Deans J, Compston DAS. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. J Neurol Neurosurg Psychiatry 1998;65:492-6 Sanders DB. Lambert-Eaton myasthenic syndrome: clinical diagnosis, immune-mediated mechanisms, and update on therapies. Ann Neurol 1995;37(S1):S63-S73 Zenone T, Bady B, Souquet PJ, Bernard JP. Le syndrome de Lambert-Eaton. Rev Mal Resp 1992;9:483-90	Firdapse	EU/1/09/601 EMEA/H/C/001032	amifampridine
Lennox-Gastaut syndrome	2	Publications: Markand ON. Lennox-Gastaut syndrome (childhood epileptic encephalopathy). J Clin Neurophysiol 2003;20(6):426-41 Cowan LD, Bodensteiner JB, Leviton A, Doherty L. Prevalence of the	Inovelon	EU/1/06/378 EMEA/H/C/000660	rufinamide

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		epilepsies in children and adolescents. Epilepsia 1989;30(1):94-106 Sidenvall R, Forsgren L, Heijbel J. Prevalence and characteristics of epilepsy in children in northern Sweden. Seizure 1996;5(2):139-46 Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia 1997;38(12):1283-8 Eriksson KJ, Koivikko MJ. Prevalence, classification, and severity of epilepsy and epileptic syndromes in children. Epilepsia 1997;38(12):1275-82 Olafsson E, Hauser WA. Prevalence of epilepsy in rural Iceland: a population-based study. Epilepsia 1999;40(11):1529-34 Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993;34(4):592-6 Waaler PE, Blom BH, Skeidsvoll H, Mykletun A. Prevalence, classification, and severity of epilepsy in children in western Norway. Epilepsia 2000;41(7):802-10 Beilmann A, Napa A, Soot A, Talvik I, Talvik T. Prevalence of childhood epilepsy in Estonia. Epilepsia 1999;40(7):1011-9 Bauer B, Benke T, Bohr K. The Lennox-Gastaut Syndrome in Adults. In: Niedermeyer E, Degen R, editors. The Lennox-Gastaut Syndrome. New York: Liss,A, 1988:317-327 Rantala H, Putkonen T. Occurrence, outcome, and prognostic factors of infantile spasms and Lennox-Gastaut syndrome. Epilepsia 1999;40(3):286-9			

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		Oguni H, Hayashi K, Osawa M. Long-term prognosis of Lennox-Gastaut syndrome. Epilepsia 1996;37 Suppl 3:44-7 Yagi K. Evolution of Lennox-Gastaut syndrome: a long-term longitudinal study. Epilepsia 1996;37 Suppl 3:48-51 Trevathan E, Murphy C, Yeargin-Allsopp m. The Epidemiology of Lennox Gastaut Syndrome and Multiple Seizure Types in Atlanta Children (Abstract). Annals of Neurology 1996;40(2):300 Cowan LD. The epidemiology of the epilepsies in children. Ment Retard Dev Disabil Res Rev 2002;8(3):171-81			
Mucopolysaccharidosis I (MPS I; a [alpha]-L-iduronidase deficiency)	0.03	Publications: Lowry RB et al. An update on the frequency of mucopolysaccharide syndromes in British Columbia. . Hum. Genet. 1990;85:389-390 Meikle PJ et al. Prevalence of lysosomal storage disorders. JAMA, 1999;281:249-254 Poorthuis, B.J.H.M. et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999: 105: 151-156	Aldurazyme	EU/1/03/253 EMEA/H/C/000477	Laronidase

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
Mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome)	0.02	Publications: Meikle PJ et al. Prevalence of lysosomal storage disorders. JAMA, 1999;281:249-254 Poorthuis, B.J.H.M. et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999: 105: 151-156 ,1999 Nelson J. Incidence of mucopolysaccharidoses in Northern-Ireland. Hum. Genet. 1997;101:355-358	Naglazyme	EU/1/05/324 EMEA/H/C/000640	Galsulfase
Multiple myeloma	1.2	Publications: Singer, C.R.J., Clinical review ABC of clinical haematology: Multiple myeloma and related conditions BMJ 1997;314:960 'Epidemiology' by Olsen JH in Textbook of Malignant Haematology Degos L, Linch DC and Lowenberg B (eds) Martin Dunitz Ltd London 1999 Carli P.M, Coebergh J.W.W., Verdecchia A., and EUROCARE Working Group, Variation in survival of adult patients with haematological malignancies in Europe since 1978 . European Journal of Cancer 1998; 34, 14: 2253-2263 Stenbeck, M., Rosén M, Sparén P. Causes of increasing cancer prevalence in Sweden Lancet, 1999; 354,1093– 1094 Berrino F, Estève J and Coleman MP (1995). Basic issues in estimating and comparing the survival of cancer patients. In: Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T and Estève J (eds.) Survival of Cancer Patients in Europe. The EUROCARE Study. IARC Scientific Publications No. 132. Lyon: International Agency for	Thalidomide Celgene	EU/1/08/443 EMEA/H/C/000823	Thalidomide

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		Research on Cancer Databases: Globocan 2002, Eucan 1996			
Multiple myeloma	1.3	Publications: Ferlay J, Bray F, Pisani P et al. Globocan 2000 – cancer incidence, mortality and prevalence worldwide. IARC Press, Lyon 2001. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990.Int J Cancer 1999; 80: 827-841. Pisani P, Parkin DM, Bray F. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999; 83: 18-29. Databases: Globocan 2000	Revlimid	EU/1/07/391 EMEA/H/C/000717	lenalidomide
N-acetylglutamate synthase deficiency	0.001	Publications: Colombo JP (N-acetylglutamate deficiency : clinical and biochemical features. International Pediatrics 1995, 10, 109 - 113. Other: Expert statement	Carbaglu	EU/1/02/246 EMEA/H/C/000461	carglumic acid
Renal cell carcinoma	3 to 3.5	Databases: Eurostat European Community Estimated Annual Incidence of RCC (2000-2004)	Torisel	EU/1/07/424 EMEA/H/C/000799	temsirolimus
		Databases: GLOBOCAN 2002. Use of SEER data in extrapolation to EU data. Also	Afinitor	EU/1/09/538 EMEA/H/C/001038	everolimus

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		support from Scottish Cancer Registry Databases: EUROSTAT 2004; GLOBOCAN 2002	Nexavar	EU/1/06/342 EMEA/H/C/000690	sorafenib
Severe myoclonic epilepsy (Dravet's syndrome)	0.4	Publications: Cowan LD, Bodensteiner JB, Leviton A, Doherty L. Prevalence of the epilepsies in children and adolescents. Epilepsia 1989 ; 30 (1) : 94-106 Current Trends. Prevalence of Self-Reported Epilepsy - United States, 1986-1990. Morbidity and Mortality Weekly Report 1994 ; 43 (44) : 810-818 Dalla Bernardina B, Capovilla G, Gattoni MB, Colomaria V, Bondavalli S, Bureau M. Epilepsie myoclonique grave de la première année. Rev. EEG Neurophysiol. 1982 ; 12 : 21-25 Eriksson KJ, Koivikko MJ. Prevalence, classification and severity of epilepsy and epileptic syndromes in children. Epilepsia 1997 ; 38 (12) : 1275-1282 Hauser WA. Epidemiology of epilepsy in children. In Pediatric Epilepsy-Diagnosis and Therapy 2nd edition. J.W. Pellock, W.E. Dodson, B.F.D. Bourgeois ed. Demos Medical Publishing, Inc ; 2001 : 81-96 Sidenvall R, Forsgren L, Heijbel J. Prevalence and characteristics of epilepsy in children in Northern Sweden Seizure 1996 ; 5 : 139-146 Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence	Diacomit	EU/1/06/367 EMEA/H/C/000664	stiripentol

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		rates of treated epilepsy in an unselected population of 2.052.922 and age-specific fertility rates of women with epilepsy. The Lancet 1998 ; 352 : 1970-1973r Yacoub M, Dulac O, Jambaque I, Chiron C, Plouin P. Early diagnosis of severe myoclonic epilepsy in infancy. Brain Dev. 1992 ; 14 (5) : 299-303			
T-cell acute lymphoblastic leukaemia	1.1	Publications: EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Coleman MP, Gatta G, Verdecchia A, Estève J, Sant M, Storm H, Allemani C, Ciccolallo L, Santaquilani M, Berrino F; EUROCARE Working Group. Ann Oncol. 2003;14 Suppl 5:v128-49 Databases: EUROCARE-3 (published by Coleman et al., 2003)	Atriance	EU/1/07/403 EMEA/H/C/000752	nelarabine
Treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or	1.1	CML: Publications Ries LA. Influence of extent of disease, histology, and demographic factors on lung cancer survival in the SEER population-based data. Semin Surg Oncol 1994;10(1):21-30 Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of CML. N Engl J Med 1999;341(3):164-72 Lee SJ. Chronic myelogenous leukaemia. Br J Haematol	Sprycel	EU/1/06/363 EMEA/H/C/000709	dasatinib

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
intolerance to prior therapy. Treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate		2000;111(4):993-1009 Silver RT, Woolf SH, Hehlmann R, et al. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of CML: developed for the American Society of Hematology. Blood 1999;94(5):1517-36 Parkin DM, Whelan SL, Ferlay J, Storm H. Cancer Incidence in 5 Continents, Vol. I to VIII. Lyon; 1997 Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999;340(17):1330-40 Goldman J. ABC of clinical haematology. Chronic myeloid leukaemia. Bmj 1997;314(7081):657-60 Cortes J. Natural history and staging of CML. Hematol Oncol Clin North Am 2004;18(3):569-84, viii Databases : GLOBOCAN 2002 ALL: Publications Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL. A systematic literature review of the clinical and epidemiological burden of ALL. Eur J Cancer Care 2005;14(1):53-62 Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1975-2002, National Cancer Institute. Bethesda, MD; 2005, section 13. IARC. Cancer Incidence in Five Continents. Lyon, France; 1997. Report No.: 143			

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med 1998;339(9):605-15 IARC. Survival of Cancer Patients in Europe:the EUROCARE study. Lyon, France; 1995 Databases: European Network of Cancer Registries, Cancer Index, GLOBOCAN 2002			
Treatment of chronic lymphocytic leukemia (CLL)	3.5	CLL: Publications Cheson BD. The chronic lymphocytic leukemias. In: DeVite VT, Jr., Hellman S, Rosenberg SA, editors. Cancer principles & practice of oncology. Lippincott Williams & Wilkins, 2001: 2447-2465 Curado, M. P., B. Edwards, et al. (2007). Cancer Incidence in Five Continents, Vol. IX IARC Scientific Publications No. 160, Lyon, IARC Parkin, D. M., S. L. Whelan, et al. (2002). Cancer Incidence in Five Continents Vol. VIII, International Agency for research on Cancer Xie, Y., S. M. Davies, et al. (2003). "Trends in leukemia incidence and survival in the United States (1973-1998)." Cancer 97(9): 2229-35 Zenz TZ, DohnerHD, Stilgenbauer SS. Genetics and risk-stratifiec approach to therapy in chronic lymphocytic leukemia. Best Practice & Research Clinical Haematology. 2007;20:439	Arzerra	EU/1/10/625 EMEA/H/C/001131	ofatumumab
Visualisation of	1	Publications:	Gliolan	EU/1/07/413	5-

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
malignant tissue during surgery for malignant glioma (WHO grade III and IV)		Ahsan H, Neugut AI, Bruce JN. Trends in incidence of primary malignant brain tumors in USA, 1981-1990. Int J Epidemiol 1995;24:1078-1085 Fine HA, Dear KBG, Loeffler JS, Black PM, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. Cancer 1993;71:2585-2597 Greig NH, Ries LG, Yancik R, Rapoport SI. Increasing annual incidence of primary malignant brain tumors in the elderly. J Natl Cancer Inst 1990;82:1621-1624 Kleihues P, Cavenee WK. World Health Organization Classification of Tumours. Pathology & Genetics. Tumours of the Nervous System. IARC Press, Lyon 2000 Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8-31 Levi F, La Vecchia C, Te VC. Descriptive epidemiology of malignant brain tumors in the Swiss canton of Vaud. Neuroepidemiology 1990;9:135-142 Ries LAG, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, Vernon SW, Cronin K, Edwards BK. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer 2000;88:2398-2424 Scrip 2587 October 7th 2000 Van der Sanden GAC, Schouten LJ, Coebergh JWW, on behalf of specialists in Neuro-Oncology in southeastern Netherlands. Incidence of primary cancer of the central nervous system in southeastern		EMEA/H/C/000744	aminolevulinic acid hydrochloride

No longer valid

Designated condition	Prevalence per 10,000 in the EU as accepted in the designation	Prevalence sources at time of orphan designation	Medicine Name	EU Decision n. Product n.	Active Substance
		Netherlands during the period 1980-1994. Cancer Causes Control 1998;9:225-228 Databases: EUCAN			

No longer valid