

**Appendix 1:** Level and quality of evidence with relevant references for EMA-approved orphan drugs

<b>Orphan drug</b>	<b>Active ingredient</b>	<b>†Level</b>	<b>‡Quality</b>	<b>Reference</b>
Adcetris	Brentuximab vedotin	3	L	[1,2]
Adempas	Riociguat	2	M	[3]
Arzerra	Ofatumumab	1	L	[4]
Atriance	Nelarabine	3	L	[5,6,7]
Bosulif	Bosutinib (monohydrate)	3	L	[8]
Bronchitol	Inhaled mannitol	1	M	[9]
Carbaglu	Carglumic acid	3	VL	[10]
Cayston	Aztreonam	1	M	[11]
Ceplene	Histamine dihydrochloride	2	L	[12]
Cholic Acid FGK	Cholic acid	3	VL	[13]
Cometriq	Cabozantinib	2	L	[14]
Cystadane	Betaine anhydrous	3	VL	[15,16]
Dacogen	Decitabine	2	M	[17,18,19]
Defitelio	Defibrotide	1	L	[20]
Diacomit	Stiripentol	2	M	[21]
Elaprase	Idursulfase	1	M	[22]
Esbriet	Pirfenidone	1	M	[23]
Evoltra	Clofarabine	3	VL	[24,25]
Exjade	Deferasirox	1	M	[26,27]
Firazyr	Icatibant acetate	1	M	[28]
Firdapse	Amifampridine	1	L	[29]
Gliolan	5-aminolevulinic acid	2	M	[30]
Glybera	Alipogene tiparvovec	2	M	[31,32]
Iclusig	Ponatinib	3	L	[33]
Increlex	Mecasermin	2	M	[34]
Inovelon	Rufinamide	1	M	[35]
Jakavi	Ruxolitinib	2	M	[36,37]
Kalydeco	Ivacaftor	1	M	[38]
Kuvan	Sapropterin	1	M	[39]
Litak	Cladribine	2	M	[40,41,42,43,44]
Lysodren	Mitotane	2	M	[45,46]
Mepact	Mifamurtide	2	L	[47]
Mozobil	Plerixafor	2	M	[48,49]
Myozyme	Alglucosidase alfa	1	M	[50]
Naglazyme	Gasulfase	1	L	[51]
Nexavar	Sorafenib	1	M	[52,53,54,55]
Nexobrid	Bromelain	3	L	[56,57]
Nplate	Romiplostim	2	M	[58,59]
Onsenal	Celecoxib	2	M	[60,61]
Orfadin	Nitisinone	3	M	[62,63,64]
Pedea	IV Ibuprofen	1	M	[65]
Peyona	Caffeine citrate	2	M	[66,67]
Photobarr	Porfimer sodium	2	M	[68,69]
Plenadren	Hydrocortisone	2	M	[70,71]
Prialt	Ziconotide	2	M	[72,73]
Procysbi	Mercaptamine bitartrate	2	L	[74]
Revatio	Sildenafil	I	M	[75,76]
Revestive	Teduglutide	2	M	[77,78]
Revlimid	Lenalidomide	2	M	[79,80,81]

Rilonacept Regeneron	Rilonacept	2	M	[82]
Savene	Dexrazoxane	3	M	[83]
Signifor	Pasireotide	3	M	[84]
Siklos	Hydroxycarbamide	1	M	[85]
Sirturo	Bedaquiline fumarate	2	M	[86]
Soliris	Eculizumab	2	M	[87,88,89]
Sprycel	Dasatinib	1	L	[90]
Tasigna	Nilotinib	1	L	[90]
Tepadina	Thiotepa	2	M	[91,92,93,94,95]
Thalidomide Celgene	Thalidomide	1	M	[96]
Thelin	Sitaxentan sodium	1	H	[97,98,99,100]
Tobi Podhaler	Tobramycin	1	M	[101]
Torisel	Temsirolimus	1	M	[55,102,103]
Tracleer	Bosentan	1	M	[75,76,104,105]
Trisenox	Arsenic Trioxide	2	M	[106,107,108]
Ventavis	Iloprost	1	M	[75,76,109]
Vidaza	Azacitidine	1	M	[110,111]
Volibris	Ambrisentan	2	M	[112]
Votubia	Everolimus	2	M	[17,18]
Vpriv	Velaglucerase alfa	2	M	[113,114]
Vyndaqel	Tafimidis	2	M	[115]
Wilzin	Zinc acetate dihydrate	3	L	[116,117,118]
Xagrid	Anagrelide	2	M	[119,120]
Xaluprine	Mercaptopurine	2	M	[121,122]
Yondelis	Trabectedin	2	M	[123,124,125,126]
Zavesca	Miglustat	2	M	[127,128,129,130,131]

† Adapted from the Oxford Centre for Evidence-Based Medicine tool kit. **1:** Systematic review of randomized trials or *n*-of-1 trials; **2:** Randomized trial or observational study with dramatic effect; **3:** Non-randomized controlled cohort/follow-up study; **4:** Case-series, case-control studies, or historically controlled studies; **5:** Mechanism-based reasoning

‡ Adapted from GRADE tool kit. **H:** high quality - Further research is very unlikely to change our confidence in the estimate of effect; **M:** moderate quality - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **L:** low quality - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **VL:** Very low quality - Any estimate of effect is very uncertain

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