APPENDIX 2: Summary of evidence tables and annual costs of orphan drugs approved by the EMA

Table 1: Summary of evidence and main results of orphan drugs for the management of cancers

Orphan drug	Active ingredient	Indication	[1]Level of evidence	[2]Quality of evidence	Annual cost per patient (£)	Summary of main results	Severe adverse events (SAEs)
Adcetris	Brentuximab vedotin	$CD30^+$ Hodgkins & ALCL	3	Low	42,500	Median OS for Hodgkins was 40.5 mos (95% CI: 28.7, – [range, 1.8 to 48.3+ mos]) and the estimated 36-mo survival rate was 54% (44 to 64). Median OS not reached for ALCL	Anaemia, neutropenia, thrombocytopenia, peripheral sensory neuropathy
Arzerra	Ofatumumab	Resistant CLL	1	Low	40,586	Insufficient evidence; impact on OS unclear	Infections, neutropenia
Atriance	Nelarabine	T-ALL & T-LBL	3	Low	50,000	Response rates 31-50%; insufficient evidence on OS; severe toxicities	Neurotoxicity, thrombocytopenia, neutropenia
Bosulif	Bosutinib	Ph+ CML	3	Low	44,799	PFS at 2 years was 79%; overall survival at 2 years was 92%	Thrombocytopenia, neutropenia, anemia, diarrhea, vomitting, rash, increased AST
Ceplene	Histamine dihydrochloride	Acute myeloid leukemia	2	Low	35,450	Over 3 years, sig ↑ leukaemia-free survival vs control group ($p < 0.01$). No sig effects on OS	Headache, pyrexia
Cometriq	Cabozantinib	Metastatic medullary thyroid CA	2	Low	70,664	PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (HR= 0.28; 95% CI, 0.19 to 0.40; $p < 0.001$); no statistically sig difference in OS (HR= 0.98; 95% CI: 0.63 to 1.52)	Diarrhea, palmarplantar erythrodysesthesia, and fatigue, GIT perforations, fistula development, and hemorrhage, mucosal inflammation, hypocalcemia, pulmonary embolism, hypertension
Dacogen	Decitabine	Acute myeloid leukemia	2	Moderate	58,300	Sig ↑ in PFS vs control (3.7 months: 2.7 to 4.6). No sig effect on OS compared with controls ($p = 0.11$). 1 RCT discontinued due to ↑d relapse rates	Sig ↑ in risk of SAE compared with placebo ($p = 0.002$)
Evoltra	Clofarabine	Acute lymphoblastic leukemia	3	Very low	43,200	Response rates of 30-44%; no data on PFS; limited data on OS	Infections, multiorgan failure, hepatotoxicity, death
Gliolan	5-ALA	Malignant glioma	2	Moderate	2,630	Sig diff in number of complete resections compared with conventional white light ($p < 0.0001$). Higher 6 month PFS compared with white light ($p = 0.0003$); sig ↑ in OS	None
Iclusig	Ponatinib	Chronic myeloid leukemia	3	Low	68440	PFS 55% at 12 months; OS 84% at 12 months	Pancreatitis, abd pain, increased lipase, diarrhea, fever, MI, thrombocytopenia, anemia, neutropenia, febrile neutropenia, pancytopenia. 18 deaths in study; 5 of which were attributed to ponatinib
Imnovid	Pomalidomide	Multiple myeloma	2	Moderate	105600	Median PFS vs dexamethasone was 4 vs 1.9 months (HR = 0.48; 95% CI: 0.39 to 0.60; $p < 0.0001$); Median OS 12.7 vs 8.1 months (HR=0.74; 95% CI: 0.56 to 0.97; p=0.0285)	Significant increase in risk of neutropenia and pneumonia

Jakavi	Ruxolitinib	Primary myelofibrosis	2	Moderate	43,200	Sig ↓ in reduction of splenic vol compared with placebo ($p < 0.001$); trend towards ↑d OS ($p = 0.076$; 0.009 at 3 yrs)	Anemia, neutropenia, thrombocytopenia; ↑d in risk of hematologic SAEs compared with placebo ($p < 0.0001$)
Litak	Cladribine	Hairy cell leukemia	2	Moderate	35,000	Improved rates of OS. 12 year survival rate of 79% in one study	Asthenia, fever, rigor
Lysodren	Mitotane	Adrenocortical CA	2	Moderate	51,900	Improvement on the duration of tumor regression. Estimate on overall survival not precise (no studies comparing lysodren with placebo or other supportive therapies)	Fever, rigor
Mepact	Mifamurtide	Osteosarcoma	2	Low	92,000	Did not improve 3-year EFS rate compared with standard chemotherapy	↑d ALT
Mozobil	Plerixafor	Multiple myeloma & NHL	2	Moderate	34,179	Sig ↑ in median $CD34^+$ count compared with placebo ($p < 0.001$); no sig diff in OS	Diarrhea, fatigue
Nexavar	Sorafenib	Liver CA & Advanced RCC	1	Moderate	38,852	Improvement in PFS; sig improvement in OS compared with placebo	Hand & foot syndrome, sig ↑in risk of hypertension compared with placebo ($p < 0.0001$)
Onsenal	Celecoxib	Familial adenomatous polyposis	2	Moderate	1,800	Sig ↓ in incidence of adenoma compared with placebo at 5 years ($p < 0.001$); reverse was the case at 2 years ($p < 0.0001$)	Sig ↑ in risk of CVS and GI disorders compared with placebo ($p = 0.034$)
Revlimid	Lenalidomide	Multiple myeloma	2	Moderate	53,363	PFS significantly greater in revlimid compared with placebo ($p < 0.0001$); no sig diff in median OS	Sig ↑ in risk of hematological and thrombotic SAE ($p < 0.0001$)
Savene	Dexrazoxane	Anthracycline extravasation	3	Moderate	6,750	Almost 100% ↓ in the need for surgical debridment	Wound infection, neutropenia
Sprycel	Dasatinib	CML & resistant ALL	1	Low	32,000	Sig ↑ in PFS compared with imatinib in CML ($p = 0.0012$); ≥90% complete remission in 2 non-RCTs for ALL; impact on OS unclear	Fluid retention, dyspnea, pleural effusion, cytopenia, hemorrhage
Tasigna	Nilotinib	Chronic phase CML	1	Low	30,000	Rates of molecular and cytogenetic response significantly greater compared with imatinib ($p < 0.001$); impact on OS unclear	Thrombocytopenia, anemia, neutropenia, and asthenia
Tepadina	Thiotepa	HPCT	2	Moderate	20,608	Results from phase III RCTs have been mixed	Cytopenia, hemorrhagic cystitis, acute and chronic GvHD
Thalidomide Celgene	Thalidomide	Multiple myeloma	1	Moderate	25,200	Improved PFS & OS when combined with standard therapy ($p = 0.05$)	Sig ↑ in risk of VTE compared with control ($p < 0.0001$)
Torisel	Temsirolimus	RCC & mantle cell lymphoma	1	Moderate	36,000	Sig ↑ in OS & PFS compared with interferon in RCC; no sig effect on median OS in mantle cell lymphoma	Bowel perforation, neutropenia, anemia, dyspnea, hyperglycemia
Vidaza	Azacitidine	Myelodysplastic syndromes	1	Moderate	45,000	Sig. improvement in OS compared with placebo	Neutropenia, thrombocytopenia, anemia
Votubia	Everolimus	SECA assoc with TSC	2	Moderate	15,000	↓d primary SECA vol by ≥ 50% in 35% of patients compared with placebo ($p < 0.0001$)	Pneumonia, bronchitis, abscess

Xaluprine	Mercaptopurine	Acute lymphoblastic leukemia	2	Moderate	2,100	Sig diff in duration of remission vs placebo ($p < 0.01$); no sig diff in median OS	Hypersensitivity, thrombocytopenia
Yondelis	Trabectedin	STS & ovarian neoplasm	2	Moderate	24,898	Improved OS compared with standard care ($p = 0.02$). Analyses for platinum-resistant not specified	Rhabdomyolysis, neutropenia, ↑bilirubin, congestive heart failure

Abbreviations:

ALCL: Anaplastic large cell lymphoma; FVC: forced vital capacity; 6MWD: 6-minute walk distance; CLL: chronic lymphocytic leukemia; OS: overall survival; T-ALL: T-cell acute lymphoblastic leukemia; T-LBL: T-cell lymphoblastic lymphoma; 5-ALA: 5-aminolevulinic acid; PFS: progression-free survival; CML: chronic myeloid leukemia; ALT: alanine transaminase; AST: aspartate transaminase; NHL: non-hodgkins lymphoma; RCC: renal cell carcinoma; HPCT: haematopoietic progenitor cell transplant; GvHD: graft versus host disease; VTE: venous thromboembolism; SECA: subependymal giant cell astrocytoma; TSC: tuberous sclerosis complex; STS: soft tissue sarcoma

Table 2: Summary of evidence and main results of orphan drugs for management of inborn errors of metabolism and immune disorders

Orphan drug	Active ingredient	Indication	[1]Level of evidence	[2]Quality of evidence	Annual cost per patient (£)	Summary of main results	Severe adverse events (SAE)
Bronchitol	Inhaled mannitol	Cystic Fibrosis	1	Moderate	6,040	Sig ↑ in FEV1 vs placebo in adults ($p < 0.001$). No sig reduction in pulmonary exacerbations	Nasopharyngeal pain, bronchospasm
Carbaglu	Carglumic acid	Hyperammonaemia	3	Very low	245,000	↓d blood ammonia conc. , ↓ in metabolic decompensation, ↓d neurological sequelae	None
Cayston	Aztreonam	Cystic Fibrosis	1	Moderate	15,399	Sig ↓ in Pseudomonas spp. density compared with placebo; no sig diff on CFQ-RRS	None-related
Cholic acid FGK	Cholic acid	IEM in primary bile acid synthesis due to Sterol 27-hydroxylase	3	Very low	N/A	No statistically significant changes in urinary bile acids and transaminases	No formal preclinical safety studies have been conducted
Cystadane	Betaine anhydrous	Homocystinuria	3	Very low	46,580	No sig benefit on BMD; evidence from several case series very limited	Cerebral edema
Elaprase	Idursulfase	Hunter syndrome	1	Moderate	309,660	Sig ↑ in 6MWD vs placebo ($p =0.013$); sig ↓ in spleen vol vs placebo ($p < 0.0001$); no sig diff in FVC	Carpal tunnel syndrome, airway obstruction, sleep apnea
Exjade	Deferasirox	Iron overload in beta-thalassemia	1	Moderate	25,000	Comparable in efficacy with deferoxamine	Transient transaminitis
Firazyr	Icatibant acetate	Hereditary angioedema	1	Moderate	16740	Sig ↓ in recovery times from attacks vs placebo ($p < 0.001$)	None
Glybera	Alipogene tiparvovec	Lipoprotein lipase deficiency	2	Moderate	216,150	Sig ↓ in serum TG's and chylomicrons compared with pre-treatment levels; sig ↓ in incidence of pancreatitis episodes compared with pre-treatment levels	Fever
Increlex	Mecasermin	Insulin growth factor-1 deficiency	2	Moderate	18,000	Growth at 6 months was > 3 times that achieved with placebo	Papilledema
Kalydeco	Ivacaftor	Cystic Fibrosis	1	Moderate	182,625	The mean difference in change in % of predicted FEV1 was 10.5 (95% CI: 8.5 to 12.5) % points in the adults' study and 10.0 (95% CI 4.5 to 15.5) %points in the children's study at 48 weeks	Epistaxis, diarrhea, asthenia
Kuvan	Sapropterin	Hyperphenylalaninaemia	1	Moderate	36,336	Sig ↓ in serum PHA conc compared with placebo ($p < 0.001$)	None
Myozyme	Alglucosidase alfa	Pompe disease	1	Moderate	230,000	≥67% of patients were stabilized or had improvement in muscular and respiratory function; sig ↑ in 6MWT, FVC & maximum expiratory pressure compared with placebo	Tracheal hemorrhage, emphysema, pneumothorax
Naglazyme	Gasulfase	Mucopolysaccharidosis VI	1	Low	170,000	No statistical difference compared with placebo in both 12MWT and 3MSCT	Anaphylaxis
Orfadin	Nitisinone	Hereditary tyrosinemia 1	3	Moderate	24,744	Sig ↓ in number of hospitalisations and liver transplantation compared with controls ($p < 0.001$)	Corneal opacities, convulsion, GI hemorrhage

Orphacol	Cholic acid	IEM in primary bile acid synthesis due to Sterol 27-hydroxylase	3	Low	N/A	500-fold ↓ in 3β -HSD; 30-fold ↓ in Δ4-3-oxo-R deficiency	Well tolerated
Procysbi	Mercaptamine bitartrate	Nephropathic cystinosis	2	Low	148659	Sig ↓in peak WBC cyctine level compared with conventional Cystagon 0.08±0.04 nmol 1/2 cystine/mg protein (95.8% CI: 0–0.16)	GI AEs were 3-fold greater with procysbi
Siklos	Hydroxycarbamide	Sickle cell disease	1	Moderate	6,085	Sig ↓ in no & severity of crises yearly compared with placebo ($p < 0.001$)	Neutropenia
Soliris	Eculizumab	PNH & aHUS	2	Moderate	378,000	Sig diff in stabilization of Hb levels in the absence of transfusion compared with placebo in PNH ($p < 0.0001$); complete reversal of aHUS post-transplantation	Abdominal distension, renal impairment
Tobi Podhaler	Tobramycin	Pseudomonas in cystic fibrosis	1	Moderate	1540 (28 days)	Sig ↑in FEV1 compared with placebo ($p = 0.002$)	Exacerbation of cystic fibrosis
Vpriv	Velaglucerase alfa	Gaucher's disease type 1	2	Moderate	146,660	Sustained maintenance of Hb conc, and platelet counts, as well as liver and spleen volumes; sig ↑ in BMD ($p < 0.01$)	Anaphylaxis
Vyndaqel	Tafimidis	Transthyretin amyloidosis	2	Moderate	112,051	Trend toward more NIS-LL responders in the tafamidis group than in the placebo group ($p = 0.068$)	Urinary tract infection
Wilzin	Zinc acetate dihydrate	Wilson's disease	3	Low	726	Sig ↑ in urinary copper excretion at 4 wks; slight ↓ in ALT, AST and ϒ-GTP	Safer compared with penicillamine
Zavesca	Miglustat	Type 1 Gaucher disease & Niemann-Picks Disease Type C	2	Moderate	58,400	Sig ↑ in BMD ($p < 0.001$), no sig diff in Hb conc, as well as liver and spleen vol b/w groups in Gauchers; no sig diff between groups for HSEM for NPD-C ($p=0·091$)	Diarrhea, weight loss

Abbreviations:

FVC: forced vital capacity; 6MWD: 6-minute walk distance; FEV1: forced expiratory volume in one minute; CFQ-RRS : cystic fibrosis questionnaire-revised respiratory score; BMD: bone mineral density; NIS-LL: Neuropathy Impairment Score-Lower Limbs; ALT: alanine transaminase; AST: aspartate transaminase; TG: triglycerides; IGF-1 : Insulin growth factor-1; PHA: phenylalanine; 12MWT: 12-minute walk test; WBC: White blood cell count; 3MSCT: 3-minute stair climb test; 3β-HSD: 3β-hydroxy-Δ^5-C_{27}-steroid oxido reductase ; PNH: paroxysmal nocturnal hemoglobinuria; aHUS: atypical haemolytic uremic syndrome; ϒ-GTP: gamma-glutamyl transpeptidase; NPD-C: Niemann-Pick's disease type C; HSEM: horizontal sadistic eye movement.

Table 3: Summary of evidence and main results of orphan drugs for managing other conditions

Orphan drug	Active ingredient	Indication	[1]Level of evidence	[2]Quality of evidence	Annual cost per patient (£)	Summary of main results	Severe adverse events (SAE)
Adempas	Riociguat	PAH Class II to III	2	Moderate	53495	Sig ↑ in 6MWD vs placebo MD: 46m; 95% CI: 25 to 67; p < 0.001; Sig ↓ in pulm vascular resistance vs placebo MD: –246 dyn · sec · cm–5; 95% CI, –303 to –190; P<0.001	Syncope, gastritis, acute renal failure, hypotension
Revatio	Sildenafil	PAH Class II & III	1	Moderate	4482	Sig improvement in 6MWD compared with placebo (p < 0.001)	Left ventricular dysfunction, postural hypertension
Tracleer	Bosentan	PAH III; digital ulcers	1	Moderate	19463	Sig ↑in 6MWD compared with placebo; sig ↓ in the number of new digital ulcers compared with placebo	↑LFTs
Opsumit	Macitentan	PAH Class II to III	2	Moderate	27,979	Sig ↑ in 6MWD vs placebo (3mg macitentan: 16.8 m; 97.5% CI, −2.7 to 36.4; P = 0.01) 10mg macitentan: 22.0 m; 97.5% CI, 3.2 to 40.8; P = 0.008). Time to death: 3mg HR=0.70; 97.5% CI: 0.52 to 0.96; p = 0.01 and 10 mg HR = 0.55; 97.5% CI: 0.39 to 0.76; p < 0.001	Haematemesis, sudden cardiac death, cardiorespiratory failure, nasopharyngitis, anemia
Volibris	Ambrisentan	PAH III & III	2	Moderate	20088	Sig ↑in 6MWT compared with placebo (p < 0.005)	Gastroenteritis, intracranial bleeding, headache, facial edema
Diacomit	Stiripentol	SMEI, Dravet's syndrome	2	Moderate	7600	Sig ↓ in freq of seizures vs placebo (p < 0.0001)	Drowsiness
Defitelio	Defibrotide	Veno-occlusive disease (VOD)	1	Low		Overall mean incidence of VOD compared with other was 4.7% vs 13.7% (p < 0.005); no sig difference in severity (0.8% 95% CI, 0.2–1.4) or RR (0.31; 95% CI, 0.09–1.06) of VOD	None
Esbriet	Pirfenidone	Idiopathic Pulm Fibrosis	1	Moderate	26172	Sig ↓ in risk of disease progression vs placebo (p = 0.002); sig improvement in FVC and VC vs placebo (p = 0.0006). No evidence on OS	Cardiotoxicity, respiratory infections
Firdapse	Amifampridine	LEMS in adults	1	Low	47000	Sig improvements in QMG score & (CMAP); p < 0.0001)	Rare
Inovelon	Rufinamide	Lennox Gastaut syndrome	1	Moderate	3000	Efficacious in doses up to 45mg/kg/day when used as adjunct; sig ↓ in the incidence of seizures compared with placebo (p < 0.0001)	Convulsion, weight loss
Nexobrid	Bromelain	Debridement	3	Moderate	?	Sig ↓ in perceived full-thickness wound area & skin-graft use (p < 0.0001)	Fever
Nplate	Romiplostim	Idiopathic thrombocytopenic purpura	2	Moderate	40102	Sig ↑ in platelet response rate compared with placebo (p < 0.0001)	Thrombosis
Pedea	IV Ibuprofen	Patent ductus arteriosus	1	Moderate	6575	No advantage in closure rates compared with oral ibuprofen	Comparable to oral ibuprofen
Peyona	Caffeine citrate	Primary apnea	2	Moderate	6300	Sig ↑ in rate of survival compared with placebo (p = 0.008); sig ↓in the incidence of severe retinopathy compared with placebo (p = 0.017)	NEC, seizures

Plenadren	Hydrocortisone	Adrenal insufficiency	2	Moderate	2920	Sig ↓ in body weight, blood pressure and heart rate compared with thrice daily hydrocortisone; limited evidence	Gastroenteritis, intracranial bleeding, headache, facial edema
Prialt	Ziconotide	Intractable chronic pain	2	Moderate	20000	Sig ↓in pain compared with placebo ($p < 0.04$); sig ↑ in risk of SAE compared with placebo ($p = 0.006$)	Dizziness, confusion, urinary retention, possible suicide link
Revestive	Teduglutide	Short-bowel syndrome	2	Moderate	200000 (US estimates)	Sig improvement in graded response score (GRS) compared with placebo at high dose ($p = 0.007$)	Catheter-site infection and sepsis
Rilonacept Regeneron	Rilonacept	Cryopyrin-associated periodic syndrome (CAPS)	2	Moderate	212000 (US estimates)	Sig improvement in symptom score compared with placebo ($p < 0.0001$)	None
Signifor	Pasireotide	Cushing's disease	3	Moderate	47000	Sig ↓ in urinary cortisol levels at medium and high does ($p < 0.001$)	Hyperglycemia, diabetes mellitus
Sirturo	Bedaquiline fumarate	Multi-drug resistant TB	2	Moderate	N/A	Sig ↓ in time to conversion to a -ve sputum culture compared with PLA, HR= 11.8; 95% CI: 2.3 to 61.3; P = 0.003	Diabetic ketoacidosis
Xagrid	Anagrelide	High risk essential thrombocythemia	2	Moderate	5000	Significantly more patients in the hydroxyurea group reached the primary end point at 39 months ($p = 0.04$)	Arterial and venous thrombosis, hemorrhage

Abbreviations:

PAH: pulmonary arterial hypertension; FVC: forced vital capacity; 6MWD: 6-minute walk distance; FEV1: forced expiratory volume in one minute; SMEI: severe myoclonic epilepsy in infancy; LEMS: Lambert-Eaton myoclonic syndrome; QMG: Quantitative Myasthenia Gravis; CMAP: compound muscle action potential

[1] Based on the Oxford Centre for Evidence-Based Medicine criteria [16]. 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

[2] Based on the GRADE criteria [17]. High quality - Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; 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; Very low quality - Any estimate of effect is very uncertain