

#### Appendix 4: Mechanisms of action, approval dates, clinical effectiveness and annual costs for drugs approved for same orphan disease

##### Pulmonary Arterial Hypertension

Drug	Active ingredient	Mechanism of action	Approval date	Main results of effectiveness	Serious adverse events	Annual cost (£)
Adempas	Riociguat	Soluble guanylate cyclase (sGC) stimulator	27/03/2014	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 <sup>-5</sup> ; 95% CI, -303 to -190; p<0.001	Syncope, gastritis, acute renal failure, hypotension	53,495
Opsumit	Macitentan	Endothelin-receptor antagonist	20/12/2013	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	NS	27,979
Revatio	Sildenafil	Phosphodiesterase inhibitor	28/10/2005	Sig ↑ in 6MWD compared with placebo (p < 0.001); sig ↓ in clinical worsening compared with placebo (p = 0.02)	Left ventricular dysfunction, postural hypertension	4,482
Tracleer	Bosentan	Endothelin-receptor antagonist	15/05/2002	Two RCTs showed sig ↑ in 6MWD (p < 0.001; 0.021) and time to clinical worsening compared with placebo (0.03 and 0.01)	↑LFTs	19,463
Volibris	Ambrisentan	Endothelin-receptor antagonist	21/04/2008	Sig ↑ in 6MWT compared with placebo (p < 0.005); sig ↓ in clinical worsening (p < 0.001)	Gastroenteritis, intracranial bleeding, headache, facial edema	20,088

##### Multiple myeloma

Drug	Active ingredient	Mechanism of action	Approval date	Main results of effectiveness	Serious adverse events	Annual cost (£)
Imnovid	Pomalidomide	Direct inhibition of angiogenesis and myeloma growth	05/08/2013	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	Significant increase in risk of neutropenia and pneumonia	105,600
Mozobil	Plerixafor	Blocks 'CXCR4 chemokine receptor' activity	31/07/2009	Sig ↑ in number of patients collecting ≥ 6 x 10 <sup>6</sup> CD34 <sup>+</sup> cells/kg compared with placebo (p < 0.001); no sig diff in OS; several adverse effects	Diarrhea, fatigue	34,179
Revlimid	Lenalidomide	Immunomodulation (IL-2, IL-6, NK-cells)	14/06/2007	PFS significantly greater in revlimid compared with placebo (p < 0.0001). No sig diff between groups on median OS; sig ↑ in risk of hematologic and thrombotic SAE	Sig ↑ in risk of hematological and thrombotic SAE (p < 0.0001)	53,363
Thalidomide	Thalidomide	Immunomodulation (IL-2, IL-6, NK-cells)	16/04/2008	Improved median and overall survival when combined with standard therapy (p = 0.05); sig ↑ in risk of hematologic and thrombotic SAE	Sig ↑ in risk of VTE compared with control (p < 0.0001)	25,200

### Acute lymphoblastic leukemia

Drug	Active ingredient	Mechanism of action	Approval date	Main results of effectiveness	Serious adverse events	Annual cost (£)
Atriance	Nelarabine	Cytotoxicity via DNA synthesis inhibition	22/08/2007	Response rates 31-50%; insufficient evidence on OS; severe toxicity	Neurotoxicity, thrombocytopenia, neutropenia	50,000
Evoltra	Clofarabine	Cytotoxicity via DNA synthesis inhibition	29/05/2006	30-44% response rates; limited data on OS; patient deaths due to drug-related adverse events reported	Infections, multiorgan failure, hepatotoxicity, death	43,200
Sprycel	Dasatinib	Protein kinase inhibition	20/11/2006	Sig ↑ in PFS compared with imatinib (p = 0.0012). No evidence of greater benefit on OS	Fluid retention, dyspnea, pleural effusion, cytopenia, hemorrhage	32,000
Xaluprine	Mercaptopurine	Competes for hypoxanthine and guanine for HGPRTase	09/03/2012	Sig diff in duration of remission vs placebo (p < 0.01); no sig diff in median OS	Hypersensitivity, thrombocytopenia	2,100

### Chronic myeloid leukemia

Drug	Active ingredient	Mechanism of action	Approval date	Main results of effectiveness	Serious adverse events	Annual cost (£)
Bosulif	Bosutinib	Tyrosine kinase inhibitor	27/03/2013	PFS at 2 years was 79%; overall survival at 2 years was 92%	Thrombocytopenia, neutropenia, anemia, diarrhea, vomiting, rash, increased AST	44,799
Iclusig	Ponatinib	Tyrosine kinase inhibitor	01/07/2013	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	68,440
Sprycel	Dasatinib	Protein kinase inhibition	20/11/2006	Sig ↑ in PFS compared with imatinib (p = 0.0012). No evidence of greater benefit on OS	Fluid retention, dyspnea, pleural effusion, cytopenia, hemorrhage	32,000
Tasigna	Nilotinib	Protein kinase inhibition	19/11/2007	Rates of molecular and cytogenetic response significantly greater compared with imatinib (p < 0.001). No evidence on OS	Thrombocytopenia, anemia, neutropenia, and asthenia	30,000

### Acute myeloid leukemia

Drug	Active ingredient	Mechanism of action	Approval date	Main results of effectiveness	Serious adverse events	Annual cost (£)
Ceplene	Histamine dihydrochloride	Immunomodulator; combined with IL-2	07/10/2008	Over 3 years, leukaemia free survival was 40% for HDC/IL-2 vs 26% in control group. No results for OS	Headache, pyrexia	35,450
Dacogen	Decitabine	Inhibition of DNA methyltransferases	20/09/2012	RCTs show no sig improvement in OS compared with controls. Sig ↑ in risk of SAE compared with placebo (p = 0.002). 1 RCT was discontinued due to SAE	Sig ↑ in risk of SAE compared with placebo (p = 0.002)	58,300

### Pseudomonas in Cystic Fibrosis

Drug	Active ingredient	Mechanism of action	Approval date	Main results of effectiveness	Serious adverse events	Annual cost (£)
Cayston	Aztreonam	Bactericidal	21/09/2009	Modest effects on respiratory symptoms; sig improvements in FEV1 compared with placebo	Sig ↓ in Pseudomonas spp. density compared with placebo; no sig diff on CFQ-RRS	2567 (28 days)
TobiPodhaler	Tobramycin	Bactericidal	20/07/2011	Sig ↑ in FEV1 compared with placebo (p = 0.002)	Sig ↑ in FEV1 compared with placebo (p = 0.002)	1540 (28 days)