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Commentary

Orphan drug development is not taking off

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Although, by definition, rare diseases involve few patients, there are so many – about 7000 (http://www.orpha.net/testor/cgi-bin/OTmain.php?&UserCell=publications) – that their epidemiological impact is impressive: 6–8% of the population is affected worldwide, with 30–40 million patients in the European Union (EU). This makes rare diseases a major public health issue [1]. However, the fragmented market means it is an area of little commercial interest for pharmaceutical companies, and the high price of orphan drugs tends to put them out of reach for the National Health Service [2].

Pinning-up measures

In the EU the European Medicines Agency (EMEA) recognizes the orphan drug status on the basis of epidemiological data (prevalence of the rare disease $\leq$5/10 000), medical plausibility, and potential benefit [3]. Orphan status designation implies incentives for pharmaceutical companies to develop orphan drugs, including 10 years of market exclusivity in the EU, protocol assistance to optimize development, guidance on preparing the dossier according to regulatory requirements, direct access to and fee reduction for the EMEA centralized procedures, including applications for marketing authorization, inspections, variations, and eligibility for grants from EU and Member State programmes and initiatives supporting research and development.

Has the long-term implementation of these facilities been really effective?

How many orphan drugs?

Since 2000, when the *ad hoc* legislation [3] came into force, up to 2007, out of 528 designated orphan indications related to 400 orphan medicinal products (OMPs) (http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm), only 45 (44 drugs) were approved (8.5%) after a mean of 34.8 months (range 6–76 months); out of the 70 OMP marketing authorization applications, 44 were approved (62.9%), 21 withdrawn (30%) and five rejected (7.1%). In the same period, out of 334 applications submitted for 'non-orphan' drugs, 236 (70.7%) were licensed (http://www.emea.europa.eu/htms/human/epar/a.htm).

Were orphan drugs developed properly?

Although preclinical data in the dossiers were fairly satisfactory (Table 1), repeated-dose toxicity studies were not always done in the two recommended animal species [4] for 10 OMPs or with long enough exposure [5] for 24. Lack of genotoxicity, carcinogenicity and reproduction toxicity studies was acceptable for recombinant products mimicking human enzymes (agalsidase alfa, agalsidase beta, aglucosidase alpha, galsulfase, idursulfase, laronidase) or anticancer agents (sorafenib, sunitinib, temsirolimus, trabectedin). In view of the nature of certain compounds, an incomplete toxicological dossier was also justifiable for drugs already on the market for more common indications (e.g. busulfan, ibuprofen and mitotane).

Table 2 reports the main characteristics of the clinical studies in the dossier. Out of 44 approved OMPs, 24 (54.5%) received protocol assistance from the EMEA, 16 (36.4%) were authorized under exceptional circumstances, and two had a conditional marketing authorization, which means that the dossier was not complete and the EMEA required additional studies in order to maintain the authorization. Randomized controlled trials were done for 25 products (56.8%). In all the trials but three (5-aminolevulinic acid, deferasirox and porfimer) placebo was the comparator. It was used inappropriately in the case of anagrelide (hydroxyurea), arsenic trioxide (retinoic acid being an adequate control), bosentan, sidenafil and sitaxentan (epoprostenol), cladribine [interferon (IFN)-alpha], imatinib (IFN-alpha), ibuprofen (indomethacin), lenalidomide (bortezomib), miglustat (imiglucerase), pegvisomant (somatostatin), rufinamide (benzodiazepines or newer anti-epileptic drugs such as lamotrigine, topiramate or

Table 1

Pre-clinical data in orphan drugs' dossiers

DRUG	REPEATED DOSE TOXICOLOGY	EXPOSURE	GENOTOXICITY	CARCINOGENICITY	REPRODUCTION TOXICITY
Agalsidase alpha	Rabbits; rats; monkeys	2–26 wks	N.A.	N.A.	YES (not conclusive)
Agalsidase beta	Rats	27 wks	N.A.	N.A.	N.A.
Aglucosidase alfa	Rat, mice, Cynomolgous monkey	4–26 wks	N.A.	N.A.	YES (positive)
5-aminolevulinic acid hydrochloride	Mice, rats, dogs	1–7 wks	YES (negative in the dark and positive in the light)	N.A.	N.A.
Anagrelide	Rats; Monkeys; Dogs;	12–52 wks	YES (negative)	N.R.	YES (negative)
Arsenic trioxide	Mice, rats, dogs, monkeys	not specified	YES (positive)	N.R.	N.R.
Betaine hydrochloride	Rat	2–12 wks	YES (negative)	N.R. (natural component of mammalian cells)	N.R.
Bosentan	Rats; dogs; marmosets	1–4 wks	YES (negative)	YES (negative)	YES (+ in rats, – in rabbits)
Busulfan	Dogs	<1 wk	N.A.	N.R.	YES (positive)
Carglumic acid	Rats	2–18 wks	YES (positive)	YES (negative)	YES (not conclusive)
Celecoxib	Rats; dogs	24–52 wks	YES (negative)	YES (not conclusive)	YES (positive)
Cladribine	Mice	4 wks	YES (positive)	N.R.	YES (positive)
Clofarabine	Mice, rats, dogs	not specified	YES (positive)	N.A.	YES (positive)
Dasatinib	Rat, Cynomolgus monkeys	4–36 wks	YES (positive)	N.A.	YES (negative)
Deferasirox	Rats, marmosets	2–39 wks	YES (– in vitro; +/– in vivo)	YES (negative)	YES (negative)
Dexrazoxane	Rats, rabbits, mice, dogs, swine	1–22 wks	YES (positive)	N.A.	N.A.
Eculizumab	Mice	4–26 wks	N.A.	N.A.	YES (negative)
Galsulfase	Cynomolgus monkeys	1–27 wks	N.R.	N.R.	A full package of reproductive toxicity studies has not been conducted. Post- authorisation commitments have been agreed for further reproductive toxicity studies with toxicokinetics and clinical monitoring of pregnant animals
Hydroxycarbamide	Rats; dogs; monkeys	1–12 wks	N.R.	N.A.	YES (positive)
Ibuprofen	N.R.	N.R.	YES (negative)	YES (negative)	YES (negative)
Idursulfase	Cynomolgus monkeys	26 wks	N.R.	N.R.	YES (negative)
Iloprost	Rats; dogs	24–52 wks	YES (negative)	YES (negative)	YES (positive)
Imatinib	Monkeys	39 wks	YES (+ in vitro and – in vivo)	ongoing	YES (positive)
Laronidase	Dogs; monkeys	8–26 wks	N.A.	N.A.	YES (not conclusive)
Lenalidomide	Rats; monkeys	26–52 wks	YES (negative)	N.R.	YES (positive) additional investigations requested
Mecasermin	Rats; dogs	4–26 wks	YES (negative)	YES (positive)	YES (negative)
Miglustat	Rats; monkeys	4–52 wks	YES (negative)	YES (negative)	YES (positive)
Mitotane	N.A.	N.A.	N.A.	N.A.	N.A.
Nelarabine	Mice, Cynomolgus monkeys	1–4 wks	YES (positive)	N.A.	YES (positive)
Nilotinib	Mice, rats, dogs, monkeys	26–39 wks	YES (negative)	N.A.	YES (negative)
Nitisinone	Mouse, rats, rabbist, dogs, Rhesus monkeys	12–48 wks	YES (+ in vitro; – in vivo)	N.A.	YES (positive)
Pegvisomant	Rats; Monkeys	24 wks	YES (negative)	N.A.	YES (negative)
Porfimer	Rats; Dogs	13 wks	YES (positive)	N.A.	YES (negative)
Rufinamide	Mouse, rats, Beagles, Cynomolgus monkeys, wild-caught baboons	4–52 wks	YES (negative)	YES (positive)	YES (negative)
Sildenafil citrate	Mice, rats, Beagles	12–48 wks	YES (negative)	YES (negative)	YES (negative; but lack of data)
Sitaxentan sodium	Mice, rats, dogs	1–39 wks	YES (negative)	YES (positive)	YES (negative)
Sodium oxybate	Rats, dogs	12–48 wks	YES (negative)	YES (negative)	YES (negative)
Sorafenib tosylate	Mice, rat, Beagles	12–48 wks	YES (+ in vitro; +/– in vivo)	N.A.	YES (positive)
Stiripentol	Mouse, rats Cynomolgus monkeys	4–26 wks	YES (negative)	YES (positive)	YES (negative)
Sunitinib malate	Rats, monkeys	4–12 wks	YES (negative)	N.A.	YES (positive)
Temsirolimus	Mice, rats, monkeys	12–36 wks	YES (negative)	N.A.	YES (positive)
Trabectedin	Mice, rats, dogs, Cynomolgus monkeys	1–3 wks	YES (positive)	N.A.	N.A.
Ziconotide acetate	Rats, monkeys, dogs	2–24 wks	YES (negative)	N.A.	Not teratogenic; embryolethality observed
Zinc acetate	Rats	53 wks	YES (not conclusive)	YES (not conclusive)	YES (negative)

Legend to the table: N.A. = Not Available; N.R. = Not Requested.

Table 2

Orphan drugs' clinical research and development

ACTIVE PRINCIPLE	TRADE NAME	INDICATION	FREQUENCY OF INDICATION	PROTOCOL ASSISTANCE	DOSE FINDING	TYPE OF TRIAL	CONTROL	END-POINT	N. PATIENTS	DURATION	DESIGNATION DATE	MA DATE	NOTES	Δ months§
Agalsidase alpha	Replagal	Fabry disease	1/40,000	YES	YES	RCT	PLACEBO	Reduction of pain; reduction of GB3 (globotriaosylceramide); reduction of cardiac mass; improvement of renal function	41	18 wks; 24 wks; 18 wks; 18 mo	8/8/2000	04/05/2001**		9
Agalsidase beta	Fabrazyme	Fabry disease	1/40,000	YES	YES	RCT	PLACEBO	Reduction of GL-3 (globotriaosylceramide)	56	20 wks	8/8/2000	04/05/2001**		9
Aglucosidase alfa	Myozyme	Pompe disease (acid α-glucosidase deficiency)	0.137/10,000 EU population	NO	NO	1 = Phase II/III uncontrolled study; 2 = Phase II uncontrolleed study	NONE	1 = Percentage of patients alive and free of invasive ventilator support (endotracheal tube) at 12 months of age, when compared to a comparable historical untreated cohort derived from the Natural History study; 2 = survival	1 = 18; 2 = 21	1 = 52 wks; 2 = 52 + 52 wks	2/14/2001	3/29/2006	1 supportive study (extension)	61
5-aminolevulinic acid hydrochloride	Gliolan	Visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV)	1/10,000 EU population	YES	YES	Open label RCT	WHITE LIGHT	Percentage of patients without definite residual contrast-enhancing tumour seen on early (within 72 hours after surgery) postoperative MRI (Magnetic Resonance Imaging); progression-free survival six months after surgery	350	21 mo	11/13/2002	9/7/2007		58
Anagrelide	Xagrid	Essential thrombocythaemia	2–3/10,000	YES	YES	Open lable; non-randomized; uncontrolled	NONE	Platelet count less 600 × 109/L or reduction superior than 50% from baseline and maintenance of the reduction for at least 4 wks (= Complete Response)	1446	4–5 yrs	12/29/2000	16/11/ 2004**		47
Arsenic Trioxide	Trisenox	Acute promyelocytic leukemia	700–800/EU (yearly incidence)	NO	NO	Uncontrolled phase II	NONE	Complete response; overall survival	52	15 mo	10/18/2000	05/03/2002**		17
Betaine hydrochloride	Cystadane	Homocystinuria	1.65/100,000	NO	NO	Case reports*	NONE	Plasma homocysteine	140	N.A.	7/9/2001	2/15/2007		67
Bosentan	Tracleer	Pulmonary arterial hypertension	1–2/10^6 year	YES	NO	RCT	PLACEBO	Walk excercise	32	15 wks	2/14/2001	15/05/2002**		15
Busulfan	Busilvex	Conditioning haematopoietic progenitor cell transplantation	6.6/100,000	YES	NO	Uncontrolled phase II	NONE	Same effect of i.v. and oral busulfan	104	2,5 yrs	12/29/2000	7/9/2003		31
Carglumic acid	Carbaglu	N-acetyl glutamate synthase deficiency	0.00125/10,000	NO	NO	Retrospective study	NONE	Lower of ammonia level	20*	3,1 yrs	10/18/2000	24/01/2003**		27
Celecoxib	Onsenal	Familial adenomatons polyposis	03–1/10^4	NO	NO	RCT	PLACEBO	Decrease of colorectal polyps	970	6 mo	11/20/2001	10/17/2003		23
Cladribine	Litak	Nairy Cell Leukemia	4–5/10^6 year	NO	NO	Uncontrolled phase II (+ literature analysis)	NONE	Complete + partial responses	120		9/19/2001	4/14/2004		31
Clofarabine	Evoltra	Acute lymphoblastic leukaemia (ALL) in paediatric patients	1/29,000	NO	YES	Phase II, non-randomized, open-label, single-arm	NONE	Complete remission (CR); complete remission without platelet recovery (CRp), partial remission (PR)	61	N.A. (every 2-6 wks, max. 12 cycles)	2/5/2002	5/29/2006		51

Dasatinib	Sprycel	Chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL)	0.9/10,000 (CML) and 0.71/10,000 (ALL) EU population	YES	YES	Phase II open-label	NONE	1-5 = haematological and cytogenetic response rate	1 = 424 2 = 166 3 = 197 4 = 124 5 = 101	N.A.; mean follow-up = 6 mo	12/23/2005	11/20/2006	11
Deferasirox	Exjade	Transfusional haemosiderosis in patients aged >2 years	102,000 persons in the EU	YES	YES	1 = phase III RCT, active-contolled, open-label; 2 = phase II open-label trial	1 = Deferoxamine; 2 = NONE	Liver iron content	1 = 586 2 = 184	1/2 = 1 yrs	3/13/2002	8/28/2006	53
Dexrazoxane	Savene	Treatment of anthracycline extravasation	0.03/10,000	NO	NO	Open-label, single-arm studies, using an external control from the literature	NONE	1/2 = proportion of patients undergoing surgery	1 = 23 2 = 57	1 = 2 yrs; 2 = 3 yrs	9/19/2001	7/28/2006	58
Eculizumab	Soliris	Paroxysmal nocturnal haemoglobinuria (PNH) in patients with history of transfusions	0,01/100.000 EU population	YES	NO	1 = Phase III RCT; 2= Phase III open-label study	1° = PLACEBO	1= Co-primary endpoints: haemoglobin stabilization and number of packed red blood cell (PRBC) units transfused; 2= haemolysis as mesured by LDH (lactate dehydrogenase) area under the concentration curve (AUC)	1= 75; 2= 97	1= 26 wks 2= 52 wks	10/17/2003	6/20/2007	44
Galsulfase	Naglazyme	Maroteaux-Lamy Syndrome (Mucopolysaccharidosis VI)	0.024/10,000 EU population	NO	YES	1 = Phase III RCT; 2 = Phase II open-label study	1 = PLACEBO; 2 = NONE	1 = 12-minute walk test; 2 = 12-minute walk test; stair climb test; urinary GAG (glycosaminoglycans) levels; Shoulder ROM (Range of Movement)	1 = 39 2 = 10	1/2 = 24 wks	2/14/2001	1/24/2006	59
Hydroxycarbamide	Siklos	Prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic sickle cell syndrome	<0.5/10,000	YES	NO	1= Paediatric population: literature analysis 2 = Adults: RCT	1 =NONE 2 = PLACEBO	1 = Hospitalisation because pain episodes; number and lenght oh hospital admission; pain episodes 2 = mortality	1 = 378 2 = 299	1 = 6 mo – 7 yrs 2 = not clearly reported	7/9/2003	6/29/2007	47
Ibuprofen	Pedea	Patent ductus arteriosus (PDA) in preterm newborn infants (<34 weeks of gestational age)	42% in infants <1 kg at birth	YES	YES	RCT; controlled (+ metanalysis)	PLACEBO	Proportion of patients requiring surgical ligation of PDA after prophylactic vs. after curative administration of i.v. ibuprofen	131	36 wks	2/14/2001	7/29/2004	41
Idursulfase	Elaprase	Hunter syndrome (Mucopolysaccharidosis II, MPS II).	0.02/100,000 EU population	YES	YES	1 = Phase II/III RCT 2 = Phase I/II open-label extension study	1 = PLACEBO	1 = Sum of the ranks of the change from Baseline to week 53 in the total distance walked in the 6-minute walking test (6MWT) and in % predicted forced vital capacity (FVC)	1 = 96 2 = 12	1 = 12 mo 2 = 6 mo	12/11/2001	08/01/2007**	61

Table 2

Continued

ACTIVE PRINCIPLE	TRADE NAME	INDICATION	FREQUENCY OF INDICATION	PROTOCOL ASSISTANCE	DOSE FINDING	TYPE OF TRIAL	CONTROL	END-POINT	N. PATIENTS	DURATION	DESIGNATION DATE	MA DATE	NOTES	Δ months§
Iloprost	Ventavis	Primary Pulmonary Hypertension	1-2/10^6 year	YES	NO	RCT	PLACEBO	Improvement walk; Improvement of 1 NYHA (New York Heart Association) class	203	12 wks; 12 wks	12/29/2000	16/9/2003**		21
Imatinib	Glivec	Chronic Myeloid Leukemia (CML) Unresectable and Metastatic Malignant Gastrointestinal Stromal Tumours (GIST)	CML=1.09/100,000 EU population GIST= 1.1-1.5/100,000/year	YES	YES	Uncontrolled phase II	NONE	(CML) Hematological and cytogenetic response; (GIST) Tumor response	1= 1225; 2=147	254 days; 24 wks	2/14/2001	27/08/2001**		6
Laronidase	Aldurazyme	Mucopolysaccharidosis MPS-1	0.025/10,000	YES	NO	RCT	PLACEBO	Reduction of urinary GAG; reduction of hepatosplenomegaly; increase forced vital capacity (FVC); six-minute walk exercise tolerance test (6MWT)	45	3 yrs; 104 wks 26 wks 26 wks	2/14/2001	10/06/2003**		28
Lenalidomide	Revlimid	Multiple myeloma	21,500 new cases/year	YES	YES	1/2 = RCT	1/2 = PLACEBO	1/2 = time-to-progression (TTP)	1 = 353 2 = 351	1/2 = 12 mo	12/12/2003	6/14/2007		42
Mecasermin	Increlex	Severe primary insulin-like growth factor 1 deficiency (Primary IGFD)	<2/10,000 EU population	NO	YES	1 = Phase III RCT 2 = Phase III open-lable 3 = open-lable study	1 = PLACEBO	1/2/3 = linear growth rate	1 = 8 2 = 23 3 = 8	1 = 15 mo 2 = 24 mo 3 = 24 mo	8/26/2005	03/08/2007**		24
Miglustat	Zavesca	Gaucher disease Type 1	1/30,000	YES	NO	Uncontrolled phase II	NONE	Reduction of liver and spleen volume	28	2 yrs	10/18/2000	20/11/2002**		25
Mitotane	Lysodren	Adrenal cortical carcinoma	0.1/10,000	YES	NO	Literature analysis	NONE	Survival; remission time; tumour size reduction	500	various time period	6/12/2002	4/28/2004		22
Nelarabine	Atriance	T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)	1.1/10,000 EU population	YES	YES	Two Phase II open-label, non-comparative studies	NONE	1 = Complete and partial responses (paediatric); 2 = Complete and partial responses (adults)	1 = 70 paediatric pts. (≤21 ys); 2 = 39 adults (≥16 ys)	1 = 1 yr; 2 = 1 yr	6/16/2005	22/08/2007**		26
Nilotinib	Tasigna	Chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.	2.4/100,000 EU population	YES	YES	Uncontrolled, unblinded, non-randomised Phase IA/II study	NONE	Major (complete + partial) cytogenetic response (MCyR)	132	12 mo	5/22/2006	11/19/2007		18
Nitisinone	Orfadin	Hereditary tyrosinemia type 1 (HT-1)	0.1/10,000 EU population	NO	NO	Open-label, single-arm studies (based on compassionate use)	NONE	Survival, survival without transplantation, death due to liver failure, transplantation for liver failure and hepatocellular carcinoma	207	6,5 yrs	12/29/2000	21/02/2005**		50
Pegvisomant	Somavert	Resistant acromegaly	5–7/100,000	YES	NO	RCT	PLACEBO	Decrease in IGF-1 (Insulin-like Growth Factor-1)	112	12 wks	2/14/2001	11/13/2002		21
Porfimer sodium	Photobarr	Dysplasia in Barrett's oesophagus	>0,5% Barret's Oesophagus population annualy	YES	NO	RCT	OMEPRAZOLE	Complete responses	208	6 mo	3/6/2002	3/25/2004		2

Rufinamide	Inovelon	Lennox Gastaut syndrome in patients >4 years	1-2/100,000 (EU population)	N.A.	YES	RCT	PLACEBO	Combined endpoint: A. reduction in total seizure frequency per 28 days in double-blind phase relative to the baseline phase was significantly greater ($p < 0,025$; two-sided) for rufinamide than placebo; B. both of the following end points were met: – reduction in tonic-atonic seizure frequency per 28 days in the double-blind phase relative to the baseline phase was significantly greater $8p < 0,025$, two-tailed) for rufinamide than placebo; – the seizure severity rating from the Global Evaluation of the patient's condition was significantly greater ($p < 0,025$, two-tailed) for rufinamide than placebo	139	84 days	10/9/2004	1/16/2007	10 supportive study (3 extensions)	27
Sildenafil citrate	Revatio	Pulmonary arterial hypertension class III	1/10,000	NO	NO	RCT	PLACEBO	Six-minute walk exercise tolerance test (6MWT)	278	12 wks	12/12/2003	28/10/2005**	1 supportive study (extension)	22
Sitaxentan sodium	Thelin	Pulmonary arterial hypertension class III	2/100,000	NO	YES	RCT	1 = PLACEBO; 2 = PLACEBO (for descriptive comparison, an open-label bosentan arm was included); 3 = PLACEBO	1 = Change in percentage of predicted peak VO2 (oxygen uptake) from baseline to week 12 measured during cycle ergometry; 2/ 3 = change from baseline in six-minute walk exercise tolerance test (6MWT) at week 18	1 = 178 2 = 240 3 = 98	1/ 2 = 12 wks 3 = 18 wks	10/21/2004	8/10/2006		22
Sodium oxybate	Xyrem	Narcolepsy with cataplexy in adult patients.	5/10,000	NO	NO	RCT	1/2 = PLACEBO	1/ 2 = Total number of cataplexy attacks	1 = 136 2 = 55	1 = 2 and 4 wks; 2 = 2 wks	3/10/2005	7/19/2006	4 open-label supportive studies	16
Sorafenib tosylate	Nexavar	Hepatocellular carcinoma	3/10,000 EU population	YES	YES	RCT	PLACEBO	Overall survival	769	1 = 29 mo	7/29/2004	7/19/2006	supportive study (discontinuation phase II RCT)	24
Stiripemtol	Diacomit	Severe and uncontrolled myoclonic epilepsy in infancy (SMEI, Dravet's syndrome)	0.4/10,000	NO	NO	RCT	1°/2° = PLACEBO	1°/2° = Number of responders: subjects with > 50% reduction in the number of seizures during the treatment peiod (2 months)	1° = 41; 2° = 24	3 months	12/5/2001	04/12/2007***	4 supporting studies	72

Table 2

Continued

ACTIVE PRINCIPLE	TRADE NAME	INDICATION	FREQUENCY OF INDICATION	PROTOCOL ASSISTANCE	DOSE FINDING	TYPE OF TRIAL	CONTROL	END-POINT	N. PATIENTS	DURATION	DESIGNATION DATE	MA DATE	NOTES	Δ months§
Sunitinib malate	Sutent	Unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) Metastatic Renal Cell Carcinoma (MRCC)	64,400 in EU	N.A.	YES	GIST: RCT; MRCC: single-arm, open-labe	GIST: PLACEBO MRCC: NONE	GIST: Time to tumour progression (TTP) MRCC: complete and partial response (ORR)	GIST: 312 MRCC: 106	GIST: 2 yrs MRCC: 11 mo	2/3/2003	13/10/2005***	2 open-lable supportive studies	32
Temsirolimus	Torisel	First-line treatment of patients with advanced renal cell carcinoma	35/100,000 EU population	YES	YES	Phase II, randomised, blinded, dose-comparing, parallel-group	NONE	Complete and partial responses	111	8 wks	4/6/2006	11/19/2007		19
Trabectedin	Yondelis	Soft tissue sarcoma	2/10,000 EU population	NO	YES	Randomised open-lable study	DIFFERENT SCHEDULE	Time to progression (TTP)	260	24 mo	5/30/2001	17/09/2007**		76
Ziconotide acetate	Prialt	Severe, chronic pain in patients requiring intrathecal (IT) analgesia	N.A.	NO	YES	RCT	PLACEBO	1–3 = Percentage change in Visual Analogue Scale of Pain Intensity (VASPI)	1 = 112 2 = 257 3 = 220	1/2 = 5–6 days; 3 = 3 wks	7/9/2001	21/02/2005**	2 supportive studies (the first two studies were prolonged into a long-term open-label study)	43
Zinc acetate dihydrate	Wilzin	Wilson's disease	0.6/10,000	NO	YES	Open label; non-randomized; uncontrolled	NONE	Effects on copper metabolism [24 h copper excretion and non-coeruloplasmin plasma copper (NCPC); effect on speech and neurological function measured on integer scale; effect on liver function tests (liver enzymes, bilirubin, albumin)]	148	3.2 yrs in symptomatic adults; 3.1 yrs in pre-symptomatic adults	7/31/2001	10/13/2004		39

*reports retrieved from literature, **MA under exceptional circumstances, ***conditional MA, Δ months§ = difference between Designation date and MA date.

felbamate alone or as add-on to valproate), zinc acetate (tetrathiomolybdate, penicillamine or trientine), or ziconotide (morphin).

In 10 cases the approval was granted with an uncontrolled Phase II study; aglucosidase alpha, anagrelide, dexrazoxane, nitisinone and zinc acetate were authorized on the basis of open-label uncontrolled studies, and carglumic acid on the basis of a retrospective study; for mitotane and betaine only a literature analysis was submitted; this was also the case for hydroxylcarbamide in the paediatric population.

In 16 cases the number of study patients was <100, 10 drugs were tested in studies involving 100–200 patients, 13 in studies with 200–500 subjects, three in studies with 500–1000 and the remaining two drugs were studied in >1000 patients. Whereas for some very rare diseases the small number is justifiable, in other cases it is not: nelarabine was studied in about 100 patients out of 50 000 potential European cases of T-cell acute lymphoblastic leukaemia or T-cell lymphoblastic lymphoma; for Fabry disease the pivotal studies included 41 and 56 patients out of 10 000 potential cases in Europe. Similar figures apply to miglustat, tested on only 28 patients; and clofarabine, tested in 61 patients.

Has the clinical relevance of orphan drug benefit been proved (or even sought)?

Typically the primary end-points are surrogate. Biochemical parameters such as GL-3 (globotriaosylceramide), GB-3 (globotriaosylceramide), IGF-1 (insulin-like growth factor-1), GAG (glycosaminoglycans), homocysteine or ammonia are certainly relevant for the respective diseases, but there is very little proof that the extent of their change is clinically important, justifying long-term treatments. The same holds true for the short-term platelet count reduction by anagrelide. Similarly, the improvement in walking induced by drugs active in pulmonary arterial hypertension, and in mucopolysaccharidosis, although statistically significant, is of questionable clinical importance. The efficacy of anticancer drugs was measured through tumour responses or time to progression rather than survival or quality of life.

In some cases the trial was too short in relation to the natural history of the disease: 20 weeks for agalsidase-beta or 18 months for agalsidase-alpha in the treatment of Fabry disease; 12 weeks for pegvisomant acting on resistant acromegaly, for drugs active in pulmonary hypertension or in epilepsy; 4 weeks for anagrelide in essential thrombocythaemia or for sodium oxybate in narcolepsy all seem inadequate.

The dossiers of the 20 orphan drugs developed without protocol assistance always contain some deficiencies, but these are also present in 20 out of 24 seeking advice (Table 2).

Small numbers and poor evidence for a sizable public health burden

The epidemiological magnitude of rare diseases (7000) is possibly reflected by the number of orphan drug designations (528) but not by their approvals (44), and even less so by their availability on the market (only 26 in the Italian market, driven by a fairly generous national health service). Moreover, clinical and public health needs are poorly met by inadequately documented orphan drugs' efficacy and safety profiles. Limitations include frequent lack of dose-finding studies, often inappropriate clinical design or lack of active comparator where available, insufficient exposure to the treatment, surrogate end-points or weak proof of clinical benefit. The lack of reliable methods for evaluating the effect of drugs on small numbers of patients is also a factor in the general poor quality of the dossiers [6]. However, although less stringent criteria can be considered for orphan drugs than for drugs treating more common diseases, this cannot be an excuse not to guarantee the best possible treatments to patients with rare diseases. For a frequency from 5/10 000 to 5/100 000, at least 25 000–250 000 patients are to be found in the whole of Europe. This should allow adequately sized multicentre trials to test superiority over effective treatments, where available, in terms of clinically meaningful end-points. Longer marketing exclusivity should be granted in order to compensate the long-term follow-up of clinical outcome measures. Because of deficiencies in the documentation, the EMEA required follow-up studies for 18 drugs, which will not necessarily be done and in any case would take many years before the results are available.

It is a cause for concern that in spite of an ad hoc law, after 8 years orphan drugs in the EU are still few and poorly studied. Long-term data confirm previous evaluations in the early stages when measures aimed at promoting orphan drugs had still to be fully implemented [7–9], and cast doubt on the effectiveness of the current system.

It is not clear what discourages the pharmaceutical industry from developing so few orphan drugs out of the many designated, in spite of the market exclusivity, methodological facilities, and the willingness of the European health systems to pay the high costs and endure the possible low cost-effectiveness of these products.

Stakeholders need to reflect on these findings to foster new measures to providw an answer to this largely neglected clinical and social issue.

Competing interests

None to declare.

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