

Supplementary Online Content

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eMethods

eFigure 1. Annual Number of Pediatric Exclusivity Awards, 1998 – 2016

eFigure 2. Time periods used when calculating net economic return

eTable 1. Consumer Price Index, All Urban Consumers, 2003-2017 (Source: <https://www.bls.gov/cpi/data.htm>)

eTable 2. Estimated Locally-Based Per Patient Costs by Selected Disease Areas and Phase

eTable 3. Average annual growth rates of clinical trial costs: alternative models and periods, 1989-2011 (in percent)

eTable 4. Components of Total Trials Conducted for Each Drug in Conjunction with Pediatric Written Request

eTable 5. Pediatric Exclusivity grants, Food and Drug Administration, September 27, 2007 – December 31, 2012

eTable 6. Estimated Cost to Consumers (Net Return) and Ratio of Net Return to Cost of Investment for 48 Pediatric Exclusivity Extensions with Revenue Data (Listed in Order of Pediatric Exclusivity Grant Date)

This supplementary material has been provided by the authors to give readers additional information about their work.

APPENDIX

Labeling Changes and Costs Emerging from Clinical Trials Performed under the FDA Pediatric Exclusivity Extension from 2007 to 2012

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INDEX OF ITEMS

Pg 2: Methodology details

Pg 5: eFigure 1: Annual Number of Pediatric Exclusivity Awards, 1998 – 2016

Pg 6: eFigure 2. Time periods used when calculating net economic return

**Pg 7: eTable 1: Consumer Price Index, All Urban Consumers, 2003-2017 (Source:
<https://www.bls.gov/cpi/data.htm>)**

**Pg 8: eTable 2: Estimated Locally-Based Per Patient Costs by Selected Disease Areas
and Phase**

**Pg 9: eTable 3: Average annual growth rates of clinical trial costs: alternative models
and periods, 1989-2011 (in percent)**

**Pg 10: eTable 4: Components of Total Trials Conducted for Each Drug in Conjunction
with Pediatric Written Request**

**Pg 12: eTable 5: Pediatric Exclusivity grants, Food and Drug Administration,
September 27, 2007 – December 31, 2012**

**Pg 18: eTable 6: Estimated Cost to Consumers (Net Return) and Ratio of Net Return
to Cost of Investment for 48 Pediatric Exclusivity Extensions with Revenue Data
(Listed in Order of Pediatric Exclusivity Grant Date)**

Methodology details

Exceptions to Clinical Trial Data:

We obtained clinical trial data from FDA Clinical Review documents for the respective written requests:

- Pediatric trial phase was not adequately described in clinical review documents for twelve drugs (anastrozole [Arimidex], aripiprazole [Abilify], bivalirudin [Angiomax], clopidogrel [Plavix], colesevelam [Welchol], famciclovir [Famvir], levocetirizine [Xyzal], olmesartan [Benicar], olopatadine [Patanol], quetiapine [Seroquel], rizatriptan [Maxalt], and saquinavir [Fortovase]). For each, we queried ClinicalTrials.gov for phase information using the study or protocol number listed in the clinical review document.
- Five drugs (bendamustine [Treanda], tenofovir [Viread], lopinavir-ritonavir [Kaletra], technetium Tc99m sestamibi [Cardiolite] and temsirolimus [Torisel]) conducted at least one unified Phase 1/2 study; these were coded as Phase 2 for our analysis unless enrollment differed between Phase 1 and Phase 2 (bendamustine [Treanda] and temsirolimus [Torisel]).
- Supplemental studies, conducted and submitted by the sponsor but not originally requested in the PWR, were excluded. This included studies for eight drugs.
 - Four referenced previous studies (gatifloxacin [Zymar] referenced a study submitted for its NDA; levetiracetam [Keppra] referenced previously submitted studies; olopatadine [Patanol] referenced studies of an earlier formulation of the drug; and rizatriptan [Maxalt] referenced five previously-completed Phase 3 trials in adolescents).
 - Four drugs conducted additional studies not requested in the PWR (clopidogrel [Plavix] conducted an additional Phase 1 study; fosamprenavir [Lexiva] conducted an additional Phase 2 study; nitric oxide [INOMax] conducted an additional Phase 3 study; and pantoprazole [Protonix] conducted four additional Phase 2 studies).
- Trials consisting entirely of adults, submitted for pediatric exclusivity determinations, were excluded. This was the case for four drugs (alfuzosin [Uroxatral], bicalutamide [Casodex], candesartan [Atacand], and darunavir [Prezista]).
- Lansoprazole [Pepcid] received pediatric exclusivity based on four trials conducted over a period of 6 years; in the absence of information on the previous trials, we consider only the pivotal Phase 3 trial identified in the FDA review documents.
- Sildenafil [Revatio] completed one Phase 3 trial and was partway through an open-label phase 3 trial when the research protocol was terminated to due adverse events. We consider only enrollees of this first trial (the same patients were continued in the subsequent open-label trial).
- The original Written Request for aripiprazole [Aricept] detailed 4 studies, but only three were reviewed in the initial Clinical Review; we include all four studies (Studies 31-03-238, 31-03-239, 31-03-240 and 31-03-241).

Exceptions to Pediatric Exclusivity Period:

In the case of litigation and settlements redefining the date of generic entry, that date became the final day of brand exclusivity, defining a new end date of the six-month window for our calculations. We focused on generic entry for the base drug; this does not include reformulations or combination products, for which exclusivity periods may be longer.

Exceptions to Revenue Data Determinations:

We obtained drug revenue data from publicly available corporate annual reports, including filings with the US Securities and Exchange Commission and quarterly financial results from brand manufacturers.

- Six drugs did not have readily available revenue figures (ixabepilone [Ixempra], loteprednol/tobramycin [Zylet], rocuronium [Zemuron], saquinavir [Invirase], temsirolimus [Torisel], and tipranavir [Aptivus]) and were excluded.
- For five drugs (almotriptan [Axert],¹ gatifloxacin [Zymar],² olmesartan [Benicar],³ olopatadine [Patanol],⁴ and tamsulosin [Flomax]⁵), we extracted information on revenues from press releases by generic manufacturers entering the market, which provided IMS Health revenue data.
 - IMS revenues for olmesartan [Benicar] exclude revenues for olmesartan-HCTZ [Benicar-HCT], which earned an additional \$805 million over the same time period.
- For valacyclovir [Valtrex], the market exclusivity end-date was close enough to the end of the calendar year (December 23) to justify using that year's revenue data.
- Recent corporate revenue filings grouped two or more of the drugs with combination drugs that included the same base compound (bendamustine [Treanda], darunavir [Prezista], and quetiapine [Seroquel]).
 - Annual revenues for 2016 included two formulations of bendamustine [Treanda & Bendeka], while darunavir's 2016 revenues included revenues for 2 formulations of darunavir/cobicistat [Prezcobix & Rezolsta]. We also combined revenues from ER and IR formulations of quetiapine.
- For eplerenone [Inspra], we used 2014 revenues (later revenues were unavailable).
- In 2010, both Bristol-Myers Squibb and Sanofi-Aventis generated revenue from clopidogrel [Plavix]. Rather than pooling the two, we used 2010 revenues from Bristol-Myers Squibb, the primary patent holder and funder of pediatric research.
- Finally, for technetium Tc99m sestamibi [Cardiolite], revenues were extrapolated from first quarter through third quarter revenues (just prior to divestment of the product by Bristol-Myers Squibb).

¹ <http://newsroom.mylan.com/2015-11-17-Mylan-Launches-Generic-AXERT-Tablets>

² <http://www.prnewswire.com/news-releases/lupin-launches-generic-zymaxid-ophthalmic-solution-in-the-us-226301061.html>

³ <http://newsroom.mylan.com/2016-10-26-Mylan-Launches-First-Generics-of-Benicar-and-Benicar-HCT-Tablets>

⁴ <http://www.pharmacytimes.com/product-news/generic-patanol-for-seasonal-allergic-conjunctivitis-approved>

⁵ <https://www.fiercepharma.com/pharma/actavis-launches-generic-version-of-flomax-r-u-s>

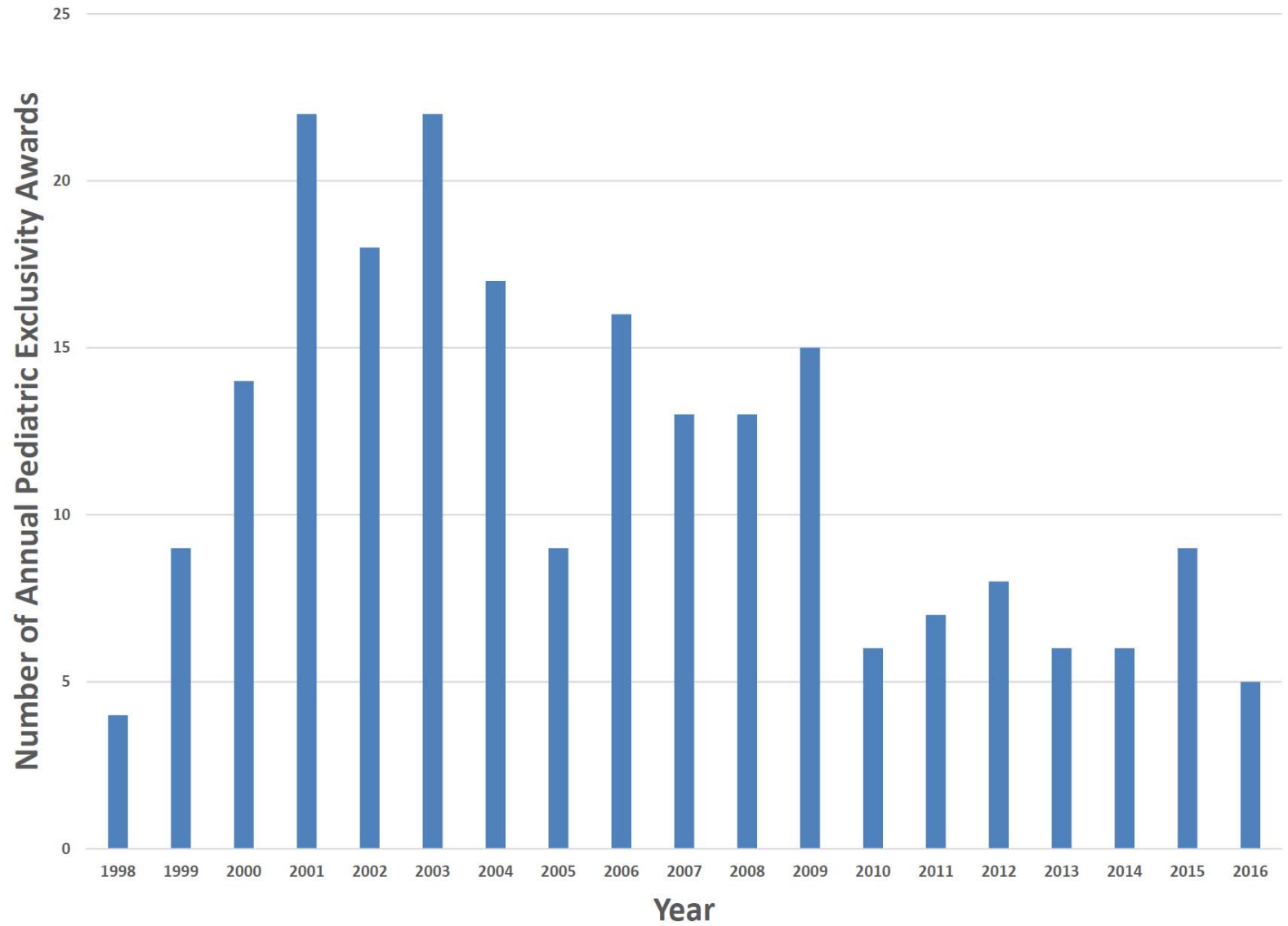
For 10 drugs, corporate revenues were reported in foreign currencies, so we converted to US dollars using the conversion rate on January 1 of the year pediatric exclusivity ended using the website X-Rates.com (<http://www.x-rates.com/historical/>). Relevant drugs and their original revenue currencies:

GBP: fosamprenavir [Lexiva], valacyclovir [Valtrex], albuterol [Ventolin HFA]

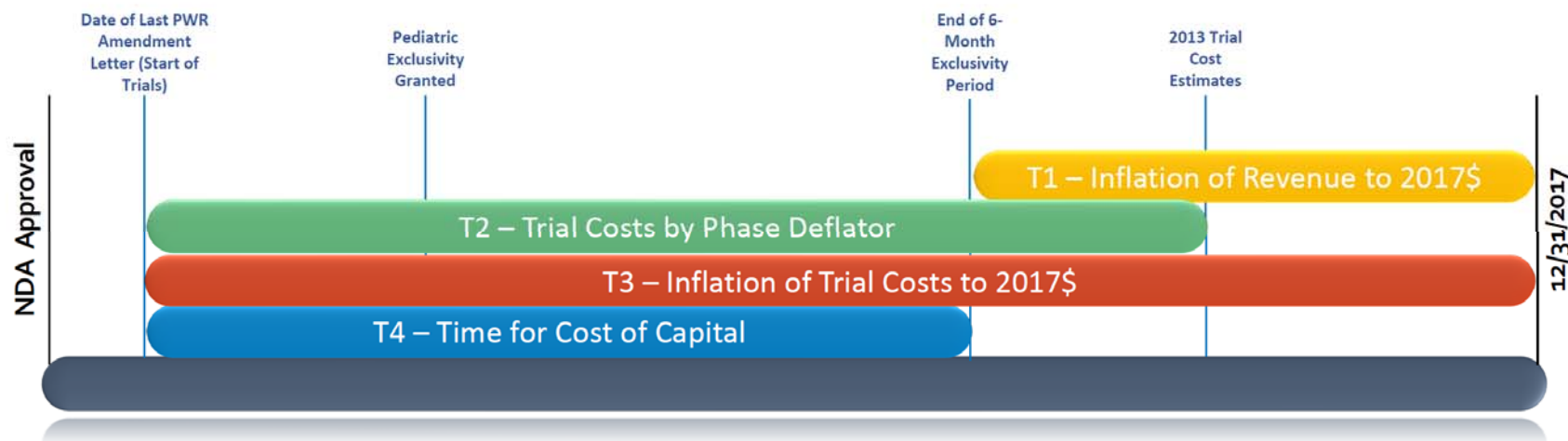
EUR: alfuzosin [Uroxatral], clopidogrel [Plavix], docetaxel [Taxotere], levetiracetam [Keppra], levocetirizine [Xyzal]

JPY: eszopiclone [Lunesta], lansoprazole [Prevacid]

eFigure 1: Annual Number of Pediatric Exclusivity Awards, 1998 – 2016



eFigure 2. Time periods used when calculating net economic return.



Legend: Of note, time period T1 varies and may begin before or after the 2013 estimate of clinical trial costs. Where the pediatric exclusivity period ends after 12/31/2017, T1 = 0 and T4 will extend to 12/31/2017.

eTable 1: Consumer Price Index, All Urban Consumers, 2003-2017 (Source: <https://www.bls.gov/cpi/data.htm>)

CPI-All Urban Consumers (Current Series)

Series Id: CUUR0000SA0
 Not Seasonally Adjusted
Series Title: All items in U.S. city average, all urban consumers, not seasonally adjusted
Area: U.S. city average
Item: All items
Base Period: 1982-84=100

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Annual	HALF1	HALF2
2007	202.416	203.499	205.352	206.686	207.949	208.352	208.299	207.917	208.490	208.936	210.177	210.036	207.342	205.709	208.976
2008	211.080	211.693	213.528	214.823	216.632	218.815	219.964	219.086	218.783	216.573	212.425	210.228	215.303	214.429	216.177
2009	211.143	212.193	212.709	213.240	213.856	215.693	215.351	215.834	215.969	216.177	216.330	215.949	214.537	213.139	215.935
2010	216.687	216.741	217.631	218.009	218.178	217.965	218.011	218.312	218.439	218.711	218.803	219.179	218.056	217.535	218.576
2011	220.223	221.309	223.467	224.906	225.964	225.722	225.922	226.545	226.889	226.421	226.230	225.672	224.939	223.598	226.280
2012	226.665	227.663	229.392	230.085	229.815	229.478	229.104	230.379	231.407	231.317	230.221	229.601	229.594	228.850	230.338
2013	230.280	232.166	232.773	232.531	232.945	233.504	233.596	233.877	234.149	233.546	233.069	233.049	232.957	232.366	233.548
2014	233.916	234.781	236.293	237.072	237.900	238.343	238.250	237.852	238.031	237.433	236.151	234.812	236.736	236.384	237.088
2015	233.707	234.722	236.119	236.599	237.805	238.638	238.654	238.316	237.945	237.838	237.336	236.525	237.017	236.265	237.769
2016	236.916	237.111	238.132	239.261	240.229	241.018	240.628	240.849	241.428	241.729	241.353	241.432	240.007	238.778	241.237
2017	242.839	243.603	243.801	244.524	244.733	244.955	244.786	245.519	246.819	246.663	246.669	246.524	245.120	244.076	246.163

Inflation Rate for Conversion to 2017 Dollars

An average annual inflation rate “i” from 2007 to 2017 was calculated as follows:

$$(2017 \text{ average annual CPI}) = (2007 \text{ average annual CPI}) \times (1 + i)^{10}; i = 0.0169.$$

eTable 2: Estimated Locally-Based Per Patient Costs by Selected Disease Areas and Phase

Disease Area	Phase 0*	Phase I	Phase II	Phase III	Phase IV	Avg. All Phases
Cardiovascular/Circulatory	\$9,500	\$21,500	\$25,000	\$26,000	\$9,500	\$20,500
Central Nervous System/Brain/Pain	\$15,000	\$34,000	\$39,500	\$40,500	\$15,000	\$36,000
Diabetes/Metabolic/Nutrition	\$7,000	\$16,000	\$18,500	\$19,000	\$7,000	\$17,500
Hematology	\$11,500	\$26,000	\$30,000	\$31,000	\$11,500	\$26,000
Infectious	\$6,500	\$15,000	\$17,500	\$18,000	\$6,500	\$16,500
Oncology	\$25,500	\$57,500	\$67,500	\$69,000	\$25,500	\$59,500
Respiratory	\$11,500	\$26,000	\$30,500	\$31,000	\$11,500	\$30,000
Other	\$13,000	\$29,500	\$34,500	\$35,000	\$13,000	\$30,500
Avg. All Diseases	\$16,500	\$38,500	\$40,000	\$42,000	\$16,500	\$36,500

Source: <http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf>

eTable 3: Average annual growth rates of clinical trial costs: alternative models and periods, 1989-2011 (in percent)

Model and phase	Pooled 1989–2011			1989–1999	2000–2011
	1989–2011	1989–1999	2000–2011		
Base model					
U.S. only	7.01	5.80	8.01	5.70	7.38
Rest of world	8.70	6.66	10.39	6.54	12.36
With SWE and LPATIENTS by phase					
U.S. only					
Phase I	6.78	5.72	7.66	5.07	8.58
Phase II	6.00	7.77	4.52	7.61	4.32
Phase IIIa	3.78	4.33	3.32	3.68	2.93
Phase IIIb	3.48	3.92	3.11	4.24	3.34
Phase IV	6.43	8.02	5.11	7.80	4.03
Rest of world					
Phase I	15.51	11.69	18.70	10.62	23.96
Phase II	7.64	8.48	6.95	8.65	9.52
Phase IIIa	6.29	6.87	5.81	6.30	7.87
Phase IIIb	12.29	15.54	9.59	13.72	11.55

Source: <https://www.bls.gov/opub/mlr/2014/article/price-indexes-for-clinical-trial-research-a-feasibility-study.htm>

eTable 4: Components of Total Trials Conducted for Each Drug in Conjunction with each Written Request for Pediatric Studies

Drug	# Trials (Total)	# Patients (Total)	# Phase I Trials	# Patients in Phase I	# Phase II Trials	# Patients in Phase II	# Phase III Trials	# Patients in Phase III	# Phase IV Trials	# Patients in Phase IV
Eplerenone	4	576	2	38			2	538		
Aripiprazole	4	915	1	21			3	894		
Anastrozole	4	174	2	66	1	28	1	80		
Divalproex	3	522					3	522		
Zoledronic acid	2	166	1	11			1	155		
Technetium Tc99m sestamibi	3	956			1	78	2	878		
Ezetimibe	2	266	1	18			1	248		
Valacyclovir	3	112	1	57			2	55		
Lopinavir/ Ritonavir	2	57			2	57				
Tipranavir	1	110			1	110				
Rocuronium	2	356					2	356		
Caspofungin	5	197	3	66	2	131				
Levetiracetam	3	469			1	98	2	371		
Lansoprazole	1	162					1	162		
Topiramate	5	568	3	135			2	433		
Valganciclovir	4	133	3	109	1	24				
Albuterol	3	250					3	250		
Bicalutamide	1	14			1	14				
Almotriptan	3	1176	1	36			2	1140		
Quetiapine	4	1070	1	28			3	1042		
Pantoprazole	8	567			3	122	5	445		
Colesevelam	1	194							1	194
Risedronate	2	175	1	28			1	147		
Esomeprazole	3	217	2	119			1	98		
Gatifloxacin	1	171					1	171		

Bivalirudin	2	126			2	126				
Rosuvastatin	2	194	1	18			1	176		
Candesartan	5	598	2	32			3	566		
Olopatadine	2	1320			1	132	1	1188		
Levocetirizine	2	242					2	242		
Tamsulosin	2	250			1	88	1	162		
Famciclovir	3	69	1	18			2	51		
Olmesartan	3	412	2	50			1	362		
Docetaxel	4	343	2	90	2	253				
Alfuzosin	3	226	1	29			2	197		
Saquinavir	3	90			1	18	1	22	1	50
Nitric Oxide	2	1387					2	1387		
Pemetrexed	2	105	1	33	1	72				
Loteprednol/Tobramycin	1	137							1	137
Paliperidone	3	508	1	25			2	483		
Clopidogrel	2	998			1	92	1	906		
Fulvestrant	1	30			1	30				
Ixabepilone	2	82	1	21	1	61				
Darunavir	1	27			1	27				
Tenofovir	2	129	1	32			1	97		
Rizatriptan	3	1173	1	30			2	1143		
Fosamprenavir	2	163			2	163				
Sildenafil	1	235					1	235		
Temsirolimus	2	71	1	19	1	52				
Bendamustine	2	43	1	11	1	32				
Eszopiclone	4	674	2	85			2	589		
Duloxetine	3	872			1	72	2	800		
Everolimus	1	28			1	28				
Rabeprazole	2	135	1	24	1	111				
TOTALS	141	20 240	41	1249	32	2019	65	16591	3	381

eTable 5: Pediatric Exclusivity grants, Food and Drug Administration, September 27, 2007 – December 31, 2012

Drug	Brand Name	NDA Approval Date	Date Pediatric Exclusivity Granted	Pediatric Studies Mandated Under PREA?	Pediatric Trials Sponsor	Indications Tested in Pediatric Populations	New or Extended Indication in Children?	Disease Category	Estimated Date of Generic Entry
Eplerenone	Inspira	9/27/2002	10/24/2007	Yes	Pfizer	Hypertension	No	Cardiovascular / Circulatory	6/8/2020
Anastrozole	Arimidex	12/27/1995	11/14/2007	No	AstraZeneca	Male pubertal patients with gynecomastia, female pediatric patients with McCune-Albright syndrome with progressive precocious puberty.	No	Oncology	6/27/2010
Aripiprazole	Abilify	11/15/2002	11/14/2007	Yes	Otsuka (& Bristol-Myers Squibb)	Schizophrenia in adolescents; Bipolar mania in children and adolescents	Yes	Central Nervous System / Brain / Pain	4/20/2015
Divalproex	Depakote ER	9/12/1989	12/14/2007	Yes	Abbott	Migraine, Bipolar disorder, Epilepsy	Yes for partial seizures, no for mania/bipolar	Central Nervous System / Brain / Pain	7/29/2008
Zoledronic acid	Zometa	3/7/2003	12/21/2007	No	Novartis	Severe osteogenesis imperfecta	No	Diabetes / Metabolic / Nutrition	3/2/2013
Technetium Tc99m sestamibi	Cardiolite	12/21/1990	1/11/2008	No	Bristol-Myers Squibb	Kawasaki's disease	No	Other	7/29/2008
Ezetimibe	Zetia	10/25/2002	2/14/2008	Yes	MSP Singapore	Heterozygous familial hypercholesterolemia	Yes	Diabetes / Metabolic / Nutrition	4/25/2017
Valacyclovir	Valtrex	6/23/1995	2/28/2008	Yes	GlaxoSmithKline	Herpes simplex virus infection	Yes	Infectious	12/23/2009
Lopinavir/Ritonavir	Kaletra	9/15/2000	3/7/2008	Yes	Abbott	HIV	Yes	Infectious	12/26/2016
Tipranavir	Aptivus	6/22/2005	3/7/2008	Yes	Boehringer Ingelheim	HIV	Yes	Infectious	4/29/2020
Rocuronium	Zemuron	3/17/1994	4/3/2008	Yes	Organon	Anesthesia	Yes	Other	2/28/2012

Caspofungin	Cancidas	1/26/2001	4/15/2008	Yes	Merck & Co	Fungal Infections	Yes	Infectious	9/28/2017
Levetiracetam	Keppra	7/15/2003	6/3/2008	Yes	UCB Inc.	Partial seizures	Yes	Central Nervous System / Brain / Pain	7/14/2009
Lansoprazole	Prevacid	5/10/1995	7/15/2008	Yes	Tap Pharmaceutical Products, Inc.	Treatment of GERD in infants	Yes	Other	11/10/2009
Topiramate	Topamax	12/24/1996	7/24/2008	No	Ortho-McNeil-Janssen Pharmaceuticals, Inc.	- Mono- and adjunctive therapy for partial onset or primary generalized tonic-clonic seizures (epilepsy) - Adjunctive therapy for seizures associated w/ Lennox-Gastaut syndrome	No	Central Nervous System / Brain / Pain	3/26/2009
Valganciclovir	Valcyte	3/29/2001	7/24/2008	Yes	Hoffman-La Roche Inc.	Treatment & prevention of Cytomegalovirus (CMV) Disease	Yes	Infectious	9/29/2015
Albuterol	Ventolin HFA	4/19/2001	8/27/2008	No	GlaxoSmithKline	Treatment and prevention of bronchospasm in children from birth to <4 years of age with obstructive airway disease	No	Respiratory	8/26/2026
Bicalutamide	Casodex	10/4/1995	9/19/2008	No	AstraZeneca	Treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis	No	Oncology	4/1/2009
Almotriptan	Axert	5/7/2001	1/13/2009	No	Johnson & Johnson	Acute treatment of migraine headache in adolescents, ages 12 to 17 years	Yes (no for migraine-associated symptoms)	Central Nervous System / Brain / Pain	11/7/2015

Quetiapine	Seroquel	9/26/1997	1/23/2009	Yes	AstraZeneca	Treatment of schizophrenia and bipolar mania in pediatric patients	Yes (schizophrenia 13-17, bipolar 10-17)	Central Nervous System / Brain / Pain	6/2/2013
Colesevelam	Welchol	5/26/2000	2/17/2009	Yes	Daiichi Sankyo	Treatment of patients diagnosed with heterozygous familial hypercholesterolemia (heFH)	Yes	Diabetes/Metabolic/Nutrition	10/17/2022
Pantoprazole	Protonix	2/2/2000	2/17/2009	Yes	Wyeth	Short-term treatment of Symptomatic GERD in pediatric patients	Yes	Other	1/19/2011
Risedronate	Actonel	3/27/1998	4/24/2009	No	Procter & Gamble	Prevent vertebral and non-vertebral fractures in children with moderate-to-severe osteogenesis imperfecta (OI)	No	Diabetes / Metabolic / Nutrition	6/10/2014
Esomeprazole	Nexium	2/20/2001	5/1/2009	Yes	AstraZeneca	Treatment of gastroesophageal reflux disease (GERD)	No	Other	8/3/2015
Gatifloxacin	Zymar	3/28/2003	5/19/2009	No	Allergan	Treatment of bacterial conjunctivitis in infants 0 - 1 month of age	Yes	Infectious	10/3/2013
Bivalirudin	Angiomax	12/15/2000	6/17/2009	No	The Medicines Company	Use as an anticoagulant in children during percutaneous intravascular procedures for the management of congenital heart disease	No	Hematology	6/15/2015
Rosuvastatin	Crestor	8/12/2003	7/7/2009	Yes	AstraZeneca	Adjunct to diet to reduce cholesterol and ApoB levels in children 10-17 years of age	Yes	Diabetes / Metabolic / Nutrition	5/2/2016
Candesartan	Atacand	6/4/1998	7/20/2009	No	AstraZeneca	Reduce blood pressure	Yes	Cardiovascular / Circulatory	12/4/2012

Olopatadine	Patanol	12/18/1996	8/12/2009	Yes	Alcon	Allergic rhinitis	Yes	Other	12/6/2015
Levocetirizine	Xyzal	5/25/2007	8/25/2009	Yes	UCB Inc.	Treatment of allergic rhinitis and urticaria in children 6 months to < 6 years of age	Yes	Other	11/25/2010
Tamsulosin	Flomax	4/15/1997	9/17/2009	No	Boehringer Ingelheim	Treatment of 2 – 16 year olds w/ elevated detrusor leak point pressure associated w/ a known neurological disorder (e.g., spina bifida)	No	Other	4/27/2010
Famciclovir	Famvir	6/29/1994	9/21/2009	Yes	Novartis	Treatment of children 1 month – 12 years of age w/ herpes simplex (HSV) & 1 – 12 years w/ varicella zoster (VSV)	No	Infectious	3/21/2011
Olmesartan	Benicar	4/25/2002	10/7/2009	Yes	Daiichi Sankyo	Treatment of hypertension in pediatric patients 1 – 16 years of age	Yes	Cardiovascular / Circulatory	10/25/2016
Docetaxel	Taxotere	5/14/1996	3/17/2010	No	Sanofi Aventis	Solid Tumors	No	Oncology	3/28/2011
Alfuzosin	Uroxatral	6/12/2003	9/7/2010	No	Sanofi Aventis	Treatment of patients 2 - 16 yrs with elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida)	No	Other	7/8/2011
Saquinavir	Fortovase	11/7/1997	10/26/2010	Yes	Hoffman-La Roche Inc.	Treatment of HIV infection in pediatric patients in combination with other antiretroviral agents	Yes	Infectious	5/16/2020

Nitric Oxide	INOmax	12/23/1999	11/2/2010	No	INO Therapeutics	Provide ventilatory assistance to preterm neonates with respiratory distress and reduce the risk of chronic lung disease (CLD) in preterm neonates at high risk of developing CLD	No	Respiratory	7/6/2031
Pemetrexed	Alimta	2/4/2004	12/3/2010	No	Eli Lilly	Treatment of pediatric patients with refractory and recurrent solid tumors, including osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, and neuroblastoma	No	Oncology	1/24/2017
Loteprednol /Tobramycin	Zylet	12/14/2004	12/28/2010	Yes	Bausch & Lomb	Treatment of superficial bacterial ocular infection	No	Infectious	9/9/2012
Paliperidone	Invega	12/19/2006	1/5/2011	Yes	Ortho-McNeil-Janssen	Treatment of adolescent schizophrenia	Yes	Central Nervous System / Brain / Pain	9/25/2015
Clopidogrel	Plavix	11/17/1997	1/20/2011	No	Sanofi-Aventis	Reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease	No	Hematology	5/17/2012
Fulvestrant	Faslodex	4/25/2002	2/1/2011	No	AstraZeneca	Treatment of progressive precocious puberty in girls with McCune-Albright Syndrome	No	Other	7/9/2021
Ixabepilone	Ixempra	10/16/2007	4/5/2011	No	Bristol-Myers Squibb	Solid tumors	No	Oncology	2/21/2025

Darunavir	Prezista	6/23/2006	6/7/2011	Yes	Tibotec	HIV	Yes	Infectious	8/16/2024
Tenofovir	Viread	10/26/2001	9/6/2011	Yes	Gilead	HIV	Yes	Infectious	1/25/2018
Rizatriptan	Maxalt	6/29/1998	9/20/2011	No	Merck	Migraine headaches	Yes	Central Nervous System / Brain / Pain	12/29/2012
Fosamprenavir	Lexiva	10/20/2003	1/10/2012	Yes	ViiV	HIV	Yes	Infectious	10/27/2015
Sildenafil	Viagra	3/27/1998	2/9/2012	Yes	Pfizer	Treatment of pulmonary arterial hypertension (PAH)	No	Cardiovascular / Circulatory	12/11/2017
Temsirolimus	Torisel	5/30/2007	2/28/2012	No	Pfizer	Treatment of relapsed/refractory solid tumors	No	Oncology	11/10/2032
Bendamustine	Treanda	3/20/2008	5/24/2012	No	Cephalon	Relapsed or refractory acute leukemia	No	Oncology	4/26/2031
Eszopiclone	Lunesta	12/15/2004	6/29/2012	Yes	Sunovion	Insomnia in children with ADHD	No	Central Nervous System / Brain / Pain	8/14/2014
Duloxetine	Cymbalta	8/3/2004	7/2/2012	Yes	Eli Lilly	Major depressive disorder (MDD)	No	Central Nervous System / Brain / Pain	12/11/2013
Everolimus	Afinitor	3/30/2009	7/10/2012	No	Novartis	Treatment of patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA)	Yes	Oncology	3/9/2020
Rabeprazole	Aciphex	8/12/2005	12/4/2012	Yes	Eisai	Healing & maintenance of healing of GERD & improvement of GERD symptoms in children 1 to 11 years of age	Yes	Other	11/8/2013

eTable 6: Estimated Cost to Consumers (Net Return) and Ratio of Net Return to Cost of Investment for 48 Pediatric Exclusivity Extensions with Revenue Data (Listed in Order of Pediatric Exclusivity Grant Date)

Drug	Pediatric Exclusivity Grant Date	Cost of Investment (\$ millions)*	Cost to Consumers (Net Return) (\$ millions)*	Ratio of Net Return to Cost of Investment (%)**
Eplerenone	10/24/2007	161.8	-85.1	-50%
Anastrozole	11/14/2007	45.6	277.1	610%
Aripiprazole	11/14/2007	325.9	189.1	60%
Divalproex	12/14/2007	78.1	491.0	630%
Zoledronic acid	12/21/2007	16.8	208.8	1250%
Technetium Tc99m sestamibi	1/11/2008	109.1	44.7	40%
Ezetimibe	2/14/2008	44.2	496.4	1120%
Valacyclovir	2/28/2008	7.9	498.2	6320%
Lopinavir/ Ritonavir	3/7/2008	6.9	47.7	690%
Tipranavir	3/7/2008	17.6	-	-
Rocuronium	4/3/2008	55.5	-	-
Caspofungin	4/15/2008	22.3	159.2	710%
Levetiracetam	6/3/2008	75.2	343.2	460%
Lansoprazole	7/15/2008	24.5	1199.3	4900%
Topiramate	7/24/2008	81.7	762.7	930%
Valganciclovir	7/24/2008	10.0	132.0	1320%
Albuterol	8/27/2008	162.4	38.7	20%
Bicalutamide	9/19/2008	2.9	108.9	3720%
Almotriptan	1/13/2009	375.9	-366.1	-100%
Quetiapine	1/23/2009	318.0	1124.5	350%
Colesevelam	2/17/2009	16.8	121.6	730%
Pantoprazole	2/17/2009	82.2	168.9	210%
Risedronate	4/24/2009	23.3	155.2	670%
Esomeprazole	5/1/2009	35.7	597.2	1670%
Gatifloxacin	5/19/2009	16.6	5.1	30%
Bivalirudin	6/17/2009	22.6	183.2	810%
Rosuvastatin	7/7/2009	27.2	920.4	3390%
Candesartan	7/20/2009	78.5	-14.3	-20%
Olopatadine	8/12/2009	303.6	-224.8	-70%
Levocetirizine	8/25/2009	30.7	14.5	50%
Tamsulosin	9/17/2009	33.5	766.1	2280%
Famciclovir	9/21/2009	4.8	67.1	1400%
Olmesartan	10/7/2009	63.9	266.6	420%
Docetaxel	3/17/2010	83.7	318.1	380%

Alfuzosin	9/7/2010	29.7	50.5	170%
Saquinavir	10/26/2010	8.4	-	-
Nitric Oxide	11/2/2010	1006.4	-850.1	-80%
Pemetrexed	12/3/2010	36.8	325.5	880%
Loteprednol /Tobramycin	12/28/2010	3.5	-	-
Paliperidone	1/5/2011	106.2	15.0	10%
Clopidogrel	1/20/2011	143.7	2217.0	1540%
Fulvestrant	2/1/2011	12.6	131.8	1050%
Ixabepilone	4/5/2011	61.9	-	-
Darunavir	6/7/2011	6.7	368.9	5550%
Tenofovir	9/6/2011	13.6	377.1	2770%
Rizatriptan	9/20/2011	193.4	-20.4	-10%
Fosamprenavir	1/10/2012	13.7	11.3	80%
Sildenafil	2/9/2012	35.9	353.2	980%
Temsirolimus	2/28/2012	109.4	-	-
Bendamustine	5/24/2012	56.1	161.6	290%
Eszopiclone	6/29/2012	123.5	184.9	150%
Duloxetine	7/2/2012	160.3	1198.3	750%
Everolimus	7/10/2012	14.6	484.9	3320%
Rabeprazole	12/4/2012	16.1	113.1	700%
	Median	36.4	176.0	680%
	Mean	91.1	294.5	1110%

* In 2017 dollars, rounded to nearest hundred thousand

** Rounded to the nearest 10%