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Safety Monitoring of Drugs Receiving Pediatric Marketing Exclusivity

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Abstract

Objective—The Food and Drug Administration (FDA) Modernization Act provided for an additional 6-month period of marketing exclusivity to companies that perform pediatric drug trials in response to an FDA-issued written request. Because many safety concerns cannot be detected until after the introduction of a product to a larger and more diverse market, the Best Pharmaceuticals for Children Act required the FDA to report to the Pediatric Advisory Committee (PAC) on adverse events occurring during the 1-year period after granting pediatric exclusivity. We sought to describe the PAC's recommendations made in response to safety reviews informed by data from the FDA's Adverse Event Reporting System in 67 drugs granted exclusivity.

Patients and Methods—PAC meetings and data presented by the FDA for all drugs were reviewed from June 2003 through April 2007. We divided the drugs into 2 groups: those that were returned to routine adverse event monitoring and those that had specific PAC recommendations.

Results—Forty-four (65.7%) drugs were returned to routine monitoring for adverse events. The PAC, sometimes working with other advisory committees, recommended label changes for 12 (17.9%) drugs, continued monitoring for 10 (14.9%), production of MedGuides for 9 (13.4%), and an update on label changes resulting from discussions with the sponsor for 1 (1.5%) drug. Some drugs had more than 1 action. Several of the adverse events revealed during this process were rare and life-threatening.

Conclusions—Safety monitoring during the early post-marketing period is crucial to detect rare, serious, or pediatric-specific adverse events. Fortunately, the majority of drugs given exclusivity had no adverse events of a frequency or severity that prevented a return to routine adverse event monitoring.

Keywords

pediatric drug safety; Pediatric Advisory Committee; adverse event reporting; drug labeling

In response to impediments—real and perceived—to performing drug studies in the pediatric population, Congress passed the Food and Drug Administration Modernization Act (FDAMA) in 1997.^{1,2} FDAMA provides for an additional 6-month period of marketing exclusivity to the innovator drug company that responds to an FDA-issued written request for studies of its drug

in pediatric patients. The exclusivity program has been very successful in stimulating much-needed drug studies in children; as a result of this program, as of April 2007, over 130 labeling changes have been made for drugs used in children.^{2,3} However, most pediatric studies conducted for FDA approval of an individual drug include fewer than 1000 children, and drugs are used after marketing in a population of children more diverse and numerous than that in the controlled studies. Thus, safety concerns may become apparent after the introduction of a product to the market. Because children represent a smaller percentage of the population receiving drugs for which adverse events are reported to the FDA, it is often more difficult to identify pediatric-specific problems as they are “submerged” in the larger number of reports submitted for adults. In addition, voluntary reporting of adverse events (AEs) is a passive process. To address these issues, Congress included in the Best Pharmaceuticals for Children Act (BPCA) of 2002 a requirement for the FDA to report to the Pediatric Advisory Committee (PAC) a review of safety concerns identified in the 1-year period following the granting of exclusivity and to obtain recommendations for action from the PAC.⁴

The PAC consists of 14 voting members including the Chair. Members and the Chair are selected by the FDA Commissioner from authorities knowledgeable in pediatric research, pediatric subspecialties, statistics, and/or biomedical ethics. Some of the duties tasked to the PAC include advising and making recommendations to the FDA Commissioner regarding: (1) pediatric research; (2) the ethics of clinical trials related to pediatric therapeutics; (3) pediatric labeling disputes; and (4) AE reports for drugs granted pediatric exclusivity and any safety issues that may occur.

Safety information for these reports is obtained from the electronic Adverse Event Reporting System (AERS). AERS is a computerized information database designed to support the FDA’s post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The ultimate goal of AERS is to improve public health by providing a mechanism for collecting post-marketing AEs. Safety reports are received by the FDA from manufacturers as required by regulation, as well as from patients and health care professionals. The AEs reported to AERS are evaluated by safety evaluators, medical reviewers, and epidemiologists at the FDA to detect safety signals.

As of March 2007, 67 drugs granted exclusivity have been reviewed by the PAC. The purpose of this study was to describe the PAC recommendations in response to the safety reports provided by the FDA.

PATIENTS AND METHODS

We reviewed PAC recommendations for the 67 drugs reviewed from June 2003 until April 2007.⁵ The unit of observation for this study was the PAC recommendation. Drugs were divided into 2 groups: those that were returned to routine monitoring for AEs and those that had specific recommendations from the PAC. The date exclusivity was granted and the date the report was made to the PAC were noted.

RESULTS

The PAC made specific recommendations for 23 (34.3%) of the drugs reviewed (Table 1) including: labeling changes (n=12), continued monitoring (n=10), MedGuide production (n=9), and update of labeling changes (n=1). Of these 23 drugs, 11 (47.8%) had pediatric-specific findings. Some drugs had more than 1 action. The PAC recommended return to routine AE monitoring for 44 (65.7%) drugs (Table 2). A number of the recommendations are described in detail below. Some of the recommendations were applied to a class of drugs, while others were product-specific.

Labeling Changes

Selective serotonin reuptake inhibitors (SSRIs)—Information on 2 important AEs (suicidality and neonatal toxicity/withdrawal syndrome) was incorporated in the label of all SSRIs. In February 2004, the PAC (then a subcommittee of the Anti-infectives Advisory Committee) and the Psychopharmacologic Drugs Advisory Committee agreed the FDA should proceed with the planned reclassification of AEs and re-analysis of the SSRI pediatric clinical trial data and should report back to the committees upon completion of the analysis. They advised the FDA to issue a warning in the interim to physicians and the public concerning the potential suicidality signal. The PAC also agreed to a future update on neonatal withdrawal syndrome. In June 2004, the PAC endorsed labeling for neonatal toxicity/withdrawal syndrome for this class of drugs.⁶ In this case, the AE data did provide evidence for effects on the fetus from maternal therapy.⁷ In September 2004, the FDA completed and presented a reanalysis of the data from pediatric studies conducted for all antidepressants.⁶ During this meeting, the PAC (now a full committee) and the Psychopharmacologic Products Advisory Committee recommended that all antidepressants receive a Box Warning regarding suicidality in children and adolescents. In October 2004, the FDA directed manufacturers of all antidepressants to add a “black box” warning and to develop a MedGuide.

Fentanyl—Fentanyl transdermal system (Duragesic®) is an opioid analgesic in the form of an adhesive patch used for the treatment of chronic pain and approved for use in children ≥ 2 years of age. In the 12 years prior to the 1-year pediatric review period, only 4 pediatric deaths were reported to AERS. During the 1-year pediatric review period, 5 additional pediatric deaths were reported.⁸ The fentanyl transdermal system was implicated in the deaths of 2 teenagers with histories of polysubstance abuse. An 8-year-old patient with a rhabdomyosarcoma who was switched from the fentanyl transdermal system to intravenous morphine died 2 months after being switched to intravenous morphine (the fentanyl transdermal system did not contribute to the death of this child). A 9-year-old died after the fentanyl transdermal system was applied to control acute postoperative pain. Finally, a 4-year-old female died after having the fentanyl transdermal system applied by her grandmother for pain relief. Outside the 1-year pediatric review period, deaths had been reported after use of the fentanyl patch for sore throat pain and acute migraines. In June 2004, the PAC recommended that a Box Warning indicate that inappropriate use may result in serious AEs including death. The February 2005 label update included a Box Warning which also reinforced the statement that the product should be used only in opioid-tolerant patients. Because of ongoing reports of deaths and serious AEs, in 2007 the FDA required a MedGuide for this product.

Methylphenidate—Methylphenidate (Concerta®) is a stimulant used to treat attention deficit hyperactivity disorder (ADHD) in patients 6–17 years of age. During the pediatric safety review period, 135 AEs were identified and reported to the PAC in June 2005.⁹ Psychiatric events (n=36) were the most commonly reported AE. These reports included 11 cases of suicidal ideation/attempts, 15 cases of behavior disturbances, and 12 cases of hallucinations. Withdrawal of methylphenidate improved or resolved hallucinations in 8/12 (67%) cases. Because of concerns that these AEs would also be seen in other products used to treat ADHD, the PAC deferred a labeling recommendation until a review of AEs for the other stimulants was completed. The subsequent review of dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate (Adderall XR®) in March 2006 resulted in the PAC recommendation that the labeling for psychosis and mania could be further clarified and that the current warnings concerning certain neuropsychiatric events should be enhanced. They also recommended a MedGuide, and in February 2007, the FDA directed ADHD drug manufacturers to notify patients about cardiovascular and psychiatric adverse events.

Oseltamivir—Oseltamivir (Tamiflu®) is a neuraminidase inhibitor indicated for the treatment of influenza in adults and children ≥ 1 year of age and influenza prophylaxis in adults and children ≥ 13 years of age. For the August 2005 PAC meeting, 8 pediatric deaths were reported to AERS in the 1-year pediatric review period, and an additional 4 were deaths were reported outside of this period.¹⁰ All 12 deaths occurred in Japan. The reported causes of death were sudden death (4), cardio-respiratory arrest (4), pneumonia (1), asphyxiation (1), and acute pancreatitis (1). Additionally, 1 report involved the death of a 14-year-old male after a fall from the ninth floor of a building 2 hours after his first dose of oseltamivir. Central nervous system side effects were the most commonly reported AE (n=32; 31 in Japan). Two of these AEs involved patients jumping from upstairs windows, and a third reported a patient running into the street. In November 2006, the label was changed advising patients and prescribers that, though the relationship of the neuropsychiatric events was undetermined, monitoring for such AEs seemed prudent. This product was subsequently reviewed in 2007 and additional wording directed to the association of these symptoms with influenza and the rapidity of their onset were added to the label.

Oxybutynin—Oxybutynin (Ditropan®) is an anticholinergic agent labeled for use in adult patients with neurogenic bladder and bladder irritability. Only 5 cases of pediatric AEs were reported to AERS during the original pediatric review period.⁷ However, 2 of these AEs were visual hallucinations, and a third was an instance of increased aggression. Therefore, the PAC requested a report after further marketing experience. The AERS database revealed 15 additional pediatric AEs from February 2002 to August 2006. Five of these AEs were related to central nervous system excitation (hallucinations, irritability, and insomnia). In April 2007, the PAC requested that the label include reports of hallucinations and agitated behavior in the pediatric population, highlighting the differences in AEs between adult and pediatric patients. Labeling changes, which included statements about central nervous system effects including hallucinations, were made in February of 2008.

Paucity of Data and Continued Monitoring

The PAC recommended additional monitoring for several drugs after the 1-year pediatric review. This was often done because of a paucity of AERS reports during the 1-year pediatric review period or a low frequency of use of the product in pediatric populations. As noted above, oxybutynin required a number of years of follow-up before sufficient cases were noted to warrant labeling changes. Only 2 pediatric AEs were reported to AERS involving benazepril (Lotensin®), 1 involving esmolol (Brevibloc®), and 1 involving sibutramine (Meridia®).^{11–13}

Linezolid (Zyvox®) is an oxazolidinone antibacterial agent indicated for some Gram-positive and Gram-negative infections in adult patients. Of the 15 AEs reported to AERS in the 1-year pediatric review period for linezolid, 6 were previously unlabeled AEs, and all 6 were cardiac AEs.¹⁴ In November 2006, the PAC requested a report pending completion of a review of cardiac events of all age populations by the FDA's Offices of Surveillance and Epidemiology.

MedGuides

In addition to label change recommendations, the PAC has also requested that the FDA produce Patient Medication Guides (MedGuides). MedGuides are FDA-approved patient information necessary for a patient's safe and effective use of prescription drugs that pose a serious public health concern. They are given to patients with each prescription. Budesonide (Pulmicort®/Rhinocort®) is a glucocorticoid used for asthma in adults and children ≥ 1 year of age and has an indication for treatment of nasal allergies in adults and children ≥ 6 years of age. Fluticasone (Cutivate®/Flonase®/Flovent®) is also a glucocorticoid. Cutivate® is approved for patients ≥ 3 months of age for treatment of pruritic dermatoses. Flonase® is approved for patients ≥ 4

years of age for relieving symptoms of allergic rhinitis, and Flovent® is approved for patients ≥ 4 years of age for treatment of asthma. Both budesonide and fluticasone are often administered with a long-acting beta-agonist for asthma. The PAC recommended that a MedGuide be provided to pediatric family caregivers for patients taking these steroids, reflecting the new labeling for fluticasone/salmeterol (Advair®) regarding the association of long-acting beta-agonists with increased risks of death in asthmatic patients. Salmeterol was granted pediatric exclusivity in October 2006 and will come up for review by the PAC in 2008.

The FDA directed manufacturers of all antidepressants to develop MedGuides in addition to the Box Warning regarding suicidality in children and adolescents (Table 1). In addition, the FDA directed ADHD drug manufacturers to develop MedGuides regarding cardiovascular and psychiatric AEs in children and adolescents.

Requests for Labeling Changes Update

Sirolimus (Rapamune®) is an immunosuppressive agent indicated as a prophylactic agent for renal transplant patients ≥ 13 years of age. Two episodes of pericardial effusions were reported during the pediatric review period.^{15,16} Because of these reports, the PAC asked to be informed of ongoing discussions with the sponsor regarding potential labeling changes. This information is now included in the labeling changes approved on 10/17/07.

DISCUSSION

As of March 2007, 136 drugs have been granted pediatric exclusivity; the result of over 300 studies. However, rare and serious AEs may be missed due to the trials' small sample sizes and relatively short durations.¹⁷ Although post-marketing surveillance of AEs in millions of children is difficult, continued surveillance in children is of crucial importance for several reasons including: the variation in metabolism, distribution, and elimination across pediatric age groups leading to potentially higher or unpredictable levels; unique toxicities present in children; drug effects on child growth and development; extensive off-label use of drugs in the pediatric population; the limited number of children involved in the initial studies including dose finding and safety studies; lack of appropriate pediatric formulations; unique exposure of children to drugs through breast milk or *in utero* exposures; and drug–drug interactions unique to children.^{18–21}

AERS is a passive, voluntary reporting system designed by the FDA as a post-marketing safety surveillance program for approved drugs and biologics in all age groups. The system records both US and foreign reports. All AEs are coded with the Medical Dictionary for Regulatory Activities. Although the AERS system has many critics,^{17,22–25} its strengths include its relatively low cost, provision of large-scale surveillance, detection of rare events, and clinician contribution.^{17,24–26} Despite relying on voluntarily submitted reports, the AERS system can be used to infer causality in instances where the AE and drug are temporally related, biologically plausible, and there is a positive de-challenge and/or re-challenge test.²⁷ Occasionally, there is sufficient information to proceed with a labeling recommendation, as seen with the fentanyl transdermal system (Duragesic®). The AERS system may also be analyzed for indications of AEs that are particular to a drug class.²⁷

Physicians should understand that reporting an AE to the FDA does not mean one knows that drug exposure was the cause. Providers should report AEs for which there are temporal or other relationships to the administration of a drug. This approach allows the FDA to develop hypotheses to further investigate these events and their possible relationship to the therapy. As discussed in this paper, post-marketing surveillance is an even more important component of AE identification in the pediatric population. The Health Insurance Portability and Accountability Act (HIPAA) allows for patient and reporter information to be provided, but

this information is protected. The FDA will not release any confidential information, and public AERS data do not contain confidential information (names of patients, healthcare professionals, or hospitals). Reporting to the AERS system can be done electronically at www.fda.gov/medwatch/report.htm or by phone at 1-800-FDA-1088.

Limitations of the AERS system include underreporting because of reliance on passive reporting. It has been estimated that only 1–10% of AEs are reported to AERS.^{28,29} Other limitations include reporting bias, erroneous reporting, inadequate documentation, duplicate reporting, difficulty establishing causality, and inability to estimate the true rate of events or exposure risks.^{23,24} The FDA attempts to correct some of these limitations by contracting to acquire large databases of drug use data which provide a context for the AERS reports.

AERS does function as a useful tool that provides signals which can help direct future investigation, as with SSRIs and ADHD medications. Its importance is demonstrated by the finding of the US General Accounting Office that 51% of serious AEs are detected after approval of the drug.³⁰ Since the adoption of the 1992 Prescription Drug User Fee Act, the time for drug approval has decreased from 27 to 14 months.^{24,31} One might expect the percentage of AEs detected after drug approval to rise as a result. Already the FDA has seen an increase in the number of drug recalls following approval.^{24,31} In addition, historically for pediatrics, industry has undertaken less than 50% of the post-marketing studies promised as a condition of drug approval.³²

Because of the unique challenges involved with drug studies in children, they are often excluded from research.^{20,33,34} This approach results in off-label use of many drugs for which there is inadequate efficacy, dosing, and safety information. Because serious AEs are often rare and pediatric clinical trials are often performed in limited numbers of patients for short periods of time in controlled circumstances, detection during clinical studies may be difficult. Monitoring during the early post-marketing period is crucial to detect signals of these events, and health care providers can play a more active role in this area. The FDA is able to use AERS along with retrospective safety analysis across previously completed trials (SSRIs and ADHD medications) and sponsor-completed phase IV safety studies to detect serious and rare AEs. Many of the products brought before the PAC have phase 4 safety studies underway. The PAC is made aware of these ongoing studies and is unlikely to ask for additional studies when the results of these studies are still pending. However, the PAC may ask for additional follow-up during this time period.

The BPCA required the FDA to report to the PAC on safety concerns identified in AERS in the 1-year period following the granting of exclusivity, but the PAC found this data required more context if the AE reporting was to be useful. The reauthorization of BPCA expands the reporting review to encompass, if necessary, all AEs since the original marketing of the product. This mechanism ensures that these data are reviewed and carefully considered. As a result, the PAC is able to recommend label changes, MedGuide production, or continued close surveillance. In a short period of time, this provision of the BPCA has made important contributions to the safety of drugs used in pediatric populations. It is important for clinicians using these therapies to report when patients experience AEs that are or are not in the labeling for the product. To learn more about the AEs discussed in this paper, one can go to the FDA's Web page, click on "Pediatrics," and then select "Safety Reporting" or check the specific PAC meeting that reviewed the safety reports. The Pediatric Therapeutics web site will also take you to the label changes.

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ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
AE	adverse event
AERS	Adverse Event Reporting System
BPCA	Best Pharmaceuticals for Children Act
FDAMA	Food and Drug Administration Modernization Act
PAC	Pediatric Advisory Committee
SSRI	serotonin reuptake inhibitors

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TABLE 1
Drugs Receiving Specific Recommendation from the PAC

Drug	PAC meeting	Category	Label change	MedGuide	Continued monitoring	Requested labeling change updates
Atorvastatin (Lipitor®)	6/12/2003	M			X	
Benazepril (Lotensin®)	2/14/2005	CR			X	
Budesonide (Pulmicort®/Rhinocort®)	9/15/2004	AP		X		
Citalopram (Celexa®)	2/3/2004	P	X	X		
Dextroamphetamine, amphetamine (Adderall XR®)	3/22/2006	P	X	X		
Esmolol (Brevibloc®)	2/14/2005	CR			X	
Fentanyl (Duragesic®)	6/9/2004	Pa	X			
Fluticasone (Cutivate®/Flonase®/Flovent®)	9/15/2004	AP		X		
Linezolid (Zyvox®)	11/16/2006	AM-T			X	
Methylphenidate (Concerta®)	6/30/2005	P	X	X		
Nefazodone (Serzone®)	10/29/2003	P	X	X		
Octreotide (Sandostatin®)	4/11/2005	GI	X			
Orlistat (Xenical®)	2/14/2005	M			X	
Oseltamivir (Tamiflu®)	11/18/2005	AM-T	X		X	
Oxcarbazepine (Trileptal®)	11/16/2006	N			X	
Oxybutynin (Ditropan®)	6/12/2003	U	X		X	
Paroxetine (Paxil®)	2/3/2004	P	X	X		
Rosiglitazone (Avandia®)	11/16/2006	M	X			
Sertraline (Zoloft®)	6/12/2003	P	X	X		
Sibutramine (Meridia®)	3/22/2006	M			X	
Simvastatin (Zocor®)	6/12/2003	M			X	
Siroliimus (Rapamune®)	11/16/2006	AM-T				X
Venlafaxine (Effexor®)	6/9/2004	P	X	X		

Abbreviations: AM-T = antimicrobial/transplant; AP = allergy/pulmonary; CR = cardiorenal; GI = gastroenterology; M = metabolic; N = neurologic; P = psychiatric; Pa = pain; U = urologic.

TABLE 2

Drugs Returned to Routine Monitoring by the PAC

Drug	PAC meeting	Category
Alendronate (Fosamax®)	9/15/2004	M
Anagrelide (Agrylin®)	11/18/2005	H
Atovaquone/proguanil (Malarone®)	2/14/2005	AM-T
Busulfan (Buslfex®)	10/29/2003	Oc
Carboplatin (Paraplatin®)	11/18/2005	Oc
Cetirizine (Zyrtec®)	10/29/2003	AP
Ciprofloxacin (Ciloxan®)	6/9/2004	AM-T
Ciprofloxacin (Cipro®)	6/30/2005	AM-T
Clofarabine (Clolar®)	3/22/2006	Oc
Desloratadine (Clarinex®)	9/15/2004	AP
Dorzolamide (Trusopt®)	6/30/2005	O
Ertapenem (Invanz®)	11/16/2006	AM-T
Ethinyl estradiol/norgestimate (Ortho-Tri- Cyclin®)	6/30/2005	R
Fexofenadine (Allegra®)	6/9/2004	AP
Fluconazole (Diflucan®)	11/18/2005	AM-T
Fludarabine (Fludara®)	9/15/2004	Oc
Fluvastatin (Lescol®)	4/11/2007	M
Fosinopril (Monopril®)	6/9/2004	CR
Gemcitabine (Gemzar®)	11/16/2006	Oc
Glimepiride (Amaryl®)	11/16/2006	M
Glyburide/metformin (Glucovance®)	2/14/2005	M
Insulin aspart recombinant (Novolog®)	11/16/2006	M
Irbesartan (Avapro®)	3/22/2006	CR
Irinotecan (Camptosar®)	11/18/2005	Oc
Leflunomide (Arava®)	6/30/2005	Rh
Losartan (Cozaar®)	10/29/2003	CR
Meloxicam (Mobic®)	11/16/2006	Pa
Moxifloxacin (Vigamox®)	6/9/2004	AM-T
Nelfinavir (Viracept®)	2/14/2005	AM-T
Ofloxacin (Oculfloxx®)	9/15/2004	AM-T
Ondansetron (Zofran®)	11/16/2006	GI
Paricalcitol (Zemlar®)	6/30/2005	M
Pravastatin (Pravachol®)	2/3/2004	CR
Quinapril (Accupril®)	10/29/2003	CR
Ritonavir (Norvir®)	11/16/2006	AM-T
Rofecoxib (Vioxx®)	11/18/2005	Pa
Sodium ferric gluconate (Ferlecit®)	11/18/2005	M
Sumatriptan (Imitrex®)	11/18/005	N
Tamoxifen (Nolvadex®)	10/29/2003	Oc
Temozolomide (Temodar®)	6/9/2004	Oc
Tolterodine (Detrol®, Detrol LA®)	6/30/2005	U
Topotecan (Hycamtin®)	6/9/2004	Oc
Vinorelbine (Navelbine®)	2/3/2004	Oc
Zolmitriptan (Zomig®)	6/30/2005	N

Abbreviations: AM-T = antimicrobial/transplant; AP = allergy/pulmonary; CR = cardiorenal; GI = gastroenterology; H = hematologic; M = metabolic; N = neurologic; O = ophthalmologic; Pa = pain; Oc = oncologic; R = reproductive; Rh = rheumatologic; U = urologic.