Published in final edited form as:

Pediatr Cardiol. 2013 October ; 34(7): 1628–1636. doi:10.1007/s00246-013-0688-2.

Food and Drug Administration (FDA) Postmarket Reported Side Effects and Adverse Events Associated with Pulmonary Hypertension Therapy in Pediatric Patients

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Abstract

Because most medications for pediatric pulmonary hypertension (PH) are used off label and based on adult trials, little information is available on pediatric-specific adverse events (AEs). Although drug manufacturers are required to submit postmarket AE reports to the Food and Drug Administration (FDA), this information is rarely transmitted to practitioners. In the setting of a recent FDA warning for sildenafil, the authors sought to give a better description of the AEs associated with current therapies in pediatric PH. In January 2010, a written request was made to the Food and Drug Administration for AE records of commonly used PH medications. Reports were screened for pediatric patients, analyzed in terms of AEs, and compared with the medical literature. Arbitrarily, AEs that could be attributed to concomitant medications were not attributed to the PH medication in question. Adverse events occurring in more than 5 % of events for each drug were assumed to be associated with the targeted PH medication. Between November 1997 and December 2009, 588 pediatric AE reports (death in 257 cases) were reported for the three most commonly used therapies: bosentan, epoprostenol, and sildenafil. Many of the AEs were similar to those reported previously. However, 27 AEs not previously reported in the literature (e.g., pulmonary hemorrhage, hemoptysis, and pneumonia) were found. The FDA postmarket records for PH medications in pediatric patients show a significant number of AEs. The discovery of AEs not previously reported will better inform those caring for these complex and critically ill children, and the large number of deaths suggest they may be underreported in current literature.

Keywords

Adverse drug events; Pediatrics; Pulmonary; hypertension

The Food and Drug Administration (FDA) mandates that adverse events be reported as part of pivotal trials leading to drug approval. After approval, drug manufacturers are required to continue submitting these reports. Consumers and health care professionals also are encouraged to report adverse events via the FDA's MedWatch program. If at any point the FDA determines that a drug's risks outweigh its benefits, regulatory action is taken to restrict the drug or remove it from the market.

Over the past 10–15 years, several drugs have been found to cause significant adverse events after their release and approval by the FDA. One of the most well-known examples involving pulmonary hypertension therapies included two drugs used in combination: fenfluramine and phentermine (fen-phen). Although each drug had been FDA approved as single agents for years, the “off-label” use of combining these two drugs was widely prescribed and believed to be a safe and effective regimen for weight-loss management. However, the use of these drugs was associated with an increased risk of pulmonary hypertension and valvular heart disease. Both fenfluramine and dexfenfluramine were withdrawn from the market soon afterward.

More recently, the FDA issued a warning recommending against the use of Revatio [7] for children with pulmonary hypertension ages 1–17 years. Although providers may disagree with this recommendation, it underscores the need for ongoing review of adverse events with FDA-“approved” therapies.

Pulmonary arterial hypertension is a progressive disease characterized by increased pressure in the pulmonary arteries. Without therapy, the high pulmonary vascular resistance contributes to progressive right ventricular failure, low cardiac output, and eventually death [1]. Multiple therapies are available for use in treating patients with pulmonary hypertension, and their use has become more commonplace although a cure remains elusive.

In 1995, the FDA approved epoprostenol for the treatment of pulmonary arterial hypertension in adults. Subsequently, the endothelin receptor antagonists bosentan and ambrisentan were approved in 2001 and 2007, respectively [8]. The prostacyclin analogues treprostinil and iloprost were approved respectively in 2002 and 2004, and the oral phosphodiesterase type 5 inhibitors sildenafil and tadalafil were approved respectively in 2005 and 2009 [3, 10].

None of the aforementioned drugs are approved for the treatment of pediatric pulmonary hypertension, but they all are commonly used off-label. Because few long-term data exist with respect to the therapeutic benefits of these drugs in a pediatric population, it becomes even more critical to understand the potential side effects and safety issues. Gaining this knowledge would help clinicians understand the long-term risks of these pharmacologic treatments, if any, and make more informed decisions when prescribing these medications.

The majority (90 %) of adverse event reports received by the FDA come from drug manufacturers, whereas the remaining 10 % come from MedWatch reports voluntarily sent by consumers and health care professionals. These reporting schemes are acknowledged to be imperfect because both underreporting and determination of causal relationships are problematic. In one case, a government audit team found that Actelion Pharmaceuticals Inc. failed to report more than 3,500 patient deaths associated with bosentan or iloprost to the FDA [6].

Our study examined adverse events among pediatric patients receiving therapy for pulmonary hypertension reported to the FDA and compared them with adverse events reported in pivotal trials to determine whether health care providers could have, based on the literature and FDA reporting, a full understanding of common side effects and adverse events in this population.

Materials and Methods

Beginning in 1997, the FDA has maintained an electronic information database, the Adverse Events Reporting System, to assist its postmarketing safety surveillance program for all approved drugs and therapeutic biologic products. For this study, individual safety reports (ISRs) for common pulmonary hypertension medications were acquired through the FDA via the Freedom of Information Act. Specifically, a written request for adverse events records of all FDA-approved pulmonary hypertension medications was made to the Center for Drug Evaluation and Research, a division of the FDA.

Data for each medication were received on compact discs for the period November 1997 through December 2009. Pediatric records were extracted for date of adverse event, patient's age and gender, outcome, reported reaction, report source, and concomitant drugs (Table 1). A sample record is shown in "Appendix 1". Many records did not contain all the critical pieces of information, for example and most commonly, dose and duration.

A substantial number of entries for bosentan, epoprostenol, and sildenafil were available for analysis. No pediatric adverse events were reported for ambrisentan or tadalafil, likely because of their short time on the market and their limited pediatric use during this time. Similarly, iloprost and treprostinil had only a small number of reports and are not included in this report.

Records were first analyzed in terms of adverse event. For each record, reported adverse events were compared with established adverse events for the pulmonary hypertension medication and concomitant medications. Established events were gathered from package insert listings, pivotal trials, and reports from the literature. Certainly, other events may be known to clinicians with significant experience, but this study sought to evaluate what was available to the "general" health care provider. Reported adverse events related to the disease itself or known to be associated with concomitant medications were not considered in the analysis. An example of cross referenced concomitant medications is shown in "Appendix 2". Clearly, adverse events attributed to another medication could be related to the pulmonary hypertension medication. However, further analysis of these types of events is difficult given the small overall number of events and lack of clarifying data. The remaining events were assumed to be associated with the pulmonary hypertension medication.

Adverse events that had not been previously associated with either the pulmonary hypertension medication or concomitant medications were noted. Adverse events present in more than 5 % of records, particularly those concerning other significant events, were noted as well. Investigators considered 5 % to be clinically relevant.

The records then were grouped in terms of outcome. The deaths for each medication were aggregated and analyzed in terms of medication regimen at the time of death. No comprehensive statistical analysis was performed because the total number of pediatric pulmonary hypertension patients experiencing adverse events is unknown. Instead, results were analyzed in terms of simple distribution percentages.

Results

A total of 9,329 adverse event records were available for bosentan, epoprostenol, and sildenafil. Of these, 588 records (6.30 %) were for children ages 0–18 years and included 468 distinct event types. After elimination of adverse events “attributable” to concomitant medications, 554 records were suitable for analysis (Table 2).

Patients receiving monotherapy accounted for 74 % of all adverse events records. However, records containing multidrug therapy technically could occur only after the year 2001 and approval of bosentan, the second therapy for pulmonary hypertension. Since 2001, patients receiving monotherapy have accounted for 69 % of all adverse events records (Fig. 1a).

Bosentan

A total of 342 adverse events were reported for 326 patients receiving bosentan. Six adverse events were present in more than 5 % of the records, one of which, thrombocytopenia, had not been described previously in the pediatric literature (Table 3). Death was reported for 121 patients and clinical worsening for 68 patients. It is not possible to discern whether these reported events were related to bosentan or the disease process. As such, no further analysis was performed on this subset of adverse events for any of the therapies.

One may be tempted to argue that clinical worsening or cardiac failure must be related to the disease process. This, however, is untrue because some therapies, whether due to fluid retention or increasing cardiac output in the setting of left ventricular dysfunction, may lead to clinical worsening. This concept is not unique to any particular agent. There were 207 patients on bosentan monotherapy reporting 146 unique adverse events and 258 total adverse events. A summary is shown in Table 3.

Epoprostenol

A total of 157 adverse events were reported for 175 patients receiving epoprostenol. This number of adverse events reflects different events such as pulmonary hemorrhage and cardiac failure. Of these, 108 reports listed death as the outcome. As reported, 12 adverse events were present in more than 5 % of the records, 10 of which, including pulmonary hemorrhage and cardiac failure, had not been previously described in the pediatric literature (Table 3). Clinical worsening was noted in 21 patients. A total of 132 patients receiving epoprostenol monotherapy reported 78 unique adverse events and 140 total adverse events.

Sildenafil

A total of 105 adverse events were reported for 89 patients receiving sildenafil. The reports describe 40 deaths. Of the 15 adverse events present in more than 5 % of the records, 12 had not been previously described in the pediatric literature, including hypotension and hemoptysis (Table 3). Clinical worsening was noted in 13 patients. There were 62 patients on sildenafil monotherapy reporting 62 unique adverse events and 105 total adverse events.

Subgroup Analysis: Deaths

Of the 257 deaths reported, 28 involved patients receiving a combination of an oral medication and an intravenous medication, specifically sildenafil ($n = 18$) or bosentan ($n = 10$) and epoprostenol. There were 18 deaths associated with combination therapy consisting of sildenafil and bosentan and 17 deaths associated with the concomitant use of sildenafil, bosentan, and epoprostenol.

The examination of deaths among patients receiving monotherapy alone ($n = 177$) showed that 18 % of the deaths involved patients receiving epoprostenol, 60 % involved patients receiving bosentan, and 22 % involved patients receiving sildenafil (Fig. 1b).

Discussion

In this retrospective review of pediatric adverse events reported to the FDA for pulmonary hypertension therapies, we describe adverse events for the three most commonly used pulmonary artery hypertension therapies: bosentan, sildenafil, and epoprostenol. In this descriptive report, conclusions are based on a potentially incomplete data set. Furthermore, the medications and adverse events have not been verified as having a cause-and-effect relationship.

In the analysis of these records, a wide range of adverse events appeared that were not previously described in pivotal trials or in postmarketing literature. For epoprostenol, 25 cases of pulmonary hemorrhage were reported out of 175 total reports. In the pivotal trial for epoprostenol, none were reported [9]. In fact, for epoprostenol, bosentan, and sildenafil, the majority of adverse events reported were not described in pivotal trials (Table 3). For example, one of the most common adverse events reported in the sildenafil records was hypotension. Although hypotension routinely occurs in adults, it is not routinely observed in pediatric patients. The adverse events reports did not define hypotension, and it is unclear to what extent it occurred.

Findings such as these suggest that any of these medications used long term may result in consequences not previously described or may be specific to pediatrics. In the examination of all the deaths reported while patients were receiving these three medications, it becomes clear that the majority of deaths (62 %) occurred for patients being treated with a single pulmonary hypertension medication. The STARTS-2 [4] extension of the STARTS-1 trial found that treatment-naïve children treated with higher-dose sildenafil monotherapy had an increased risk of death. By trial design, patients were withdrawn from the study if additional pulmonary hypertension therapy was added. The children who died were more likely to have had idiopathic pulmonary hypertension as well as increased pulmonary artery pressure and pulmonary vascular resistance. A cause-and-effect relationship has not been determined [5].

Patients receiving multiple therapies, however, accounted for only one fourth of all the deaths reported. Of course, patients may have been receiving a single medication for a number of reasons such as lack of availability of multiple therapies, lack of evidence to support multidrug regimens, clinician preference, or clinician inexperience with pulmonary hypertension or available therapies. Although concerning but not surprising, deaths associated with sildenafil were reported even before it was FDA approved in 2005 for use to treat pulmonary hypertension (Fig. 1b).

This study reports the largest number of deaths to date in the pediatric population receiving therapy for pulmonary hypertension. Strikingly, however, this number most likely underestimates the total number of deaths because physicians are unlikely to submit voluntary reports for all cases. In addition, an adverse event is by definition associated with the use of a medical product. Deaths not attributed to a medication (i.e., due to disease progression) therefore go unreported.

Although based on a potentially incomplete data set (see limitations), the large number of deaths among patients receiving monotherapy does illuminate the need for systematic examination of long-term outcomes for patients receiving monotherapy and for those receiving combination therapy through controlled clinical trials in an effort to optimize outcomes.

This study had several limitations, and it is critical to understand that our conclusions are speculative. First, pulmonary hypertension is a progressive disease that leads to worsening and death despite therapy. Although we appreciate that many of the side effects described in this report may simply represent clinical worsening, given the lack of understanding concerning the full effects of the drugs on the disease process, simply disregarding the possibility of drug-related adverse events is in neither the patients' nor the field's best interest. For example, although pulmonary hypertension is associated with hemoptysis and pulmonary hemorrhage, it would not be unreasonable to consider that the antiplatelet effects and thrombocytopenia associated with epoprostenol may lead to more frequent pulmonary hemorrhage. Similarly because bosentan has been shown to worsen outcomes in left heart failure patients due to fluid retention, similar effects could be possible in patients with pulmonary hypertension.

Second, the information in the adverse events reports has not been verified as describing a cause-and-effect relationship and cannot be used to estimate the incidence of adverse drug reactions [2]. In the absence of detailed information about patient characteristics, any or all of the adverse events could be related to the underlying disease. Therefore, the list of adverse events cannot be used to make conclusions about timeliness or appropriateness of treatment.

Third, our report that among patients receiving monotherapy 18 % of deaths occurred for patients administered epoprostenol, 60 % for patients administered bosentan, and 22 % for patients administered sildenafil cannot and should not for many reasons be interpreted to mean that epoprostenol is better than bosentan or sildenafil.

Fourth, although adverse events may be underreported to the FDA, those reported are undoubtedly biased toward severity without necessarily a clear relation to causality. This may account for the high number of deaths.

Finally, the data set is most likely incomplete in terms of the number and types of events reported. Apart from mandatory drug company reporting, the FDA relies on health care professionals to report any adverse events or effects, but because such reports are not required of them, health care professionals are likely to underreport less severe events such as nausea or vomiting and may not report them at all. Moreover, the FDA asks for reports concerning adverse events as associated with medications, not diseases. Therefore, some deaths go unreported, whereas other consequences of the disease (falsely identified as adverse events) are incorrectly associated with treatment.

One salient finding from our study was the large number of pediatric deaths reported. The literature may be underestimating deaths in pediatric pulmonary hypertension cases. Therefore, our finding may potentially indicate the lack of adequate education regarding consensus recommendations for the diagnosis and treatment of pediatric pulmonary hypertension. However, these data warrant further investigation.

In conclusion, we report the largest series of pediatric adverse events related to pulmonary hypertension therapies, including a number of adverse events not previously described in pivotal trials or in postmarketing literature, and the largest number of deaths in this patient population. We also characterize therapies prescribed to pediatric patients with pulmonary hypertension at the time of death.

Our work underscores the need for ongoing reporting and assessment of therapies. It is not possible to draw clear correlations between these medications and deaths. However, the issues raised in this report give urgency for further investigation. In the case of fen-phen, postmarketing surveillance brought attention to serious potential side effects and altered

prescribing practices. Our findings underscore the need to make adverse event and severe adverse event statistics more easily accessible, especially for the pediatric population and for rare diseases.

Acknowledgments

We thank Raymond R. Balise, PhD, for his assistance in the statistical analysis.

Appendix 1

Example of MEDWATCH form

Individual Safety Report		Actelion Pharmaceuticals US, Inc.		Relays International, Inc., FDA Facsimile Approval: 20-APR-2007
6021818-8-00-01		Use by user-facilities, distributors and manufacturers (MANDATORY reporting)		MR Report # A-NJ2008-20657 UFI/Reporter Report # FDA Use Only	
Page 1 of 2					
A. PATIENT INFORMATION					
1. Patient Identifier	2. Age at Time of Event: 11 Years	3. Sex: ☒ Male	4. Weight: UNK lbs		
In confidence	Date of Birth: [REDACTED]		UNK kgs		
B. ADVERSE EVENT OR PRODUCT PROBLEM					
1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/mafunctions)					
2. Outcomes Attributed to Adverse Event (Check all that apply)					
☒ Death (mm/dd/yyyy) ☐ Disability or Permanent Damage ☐ Life-threatening (mm/dd/yyyy) ☐ Congenital Anomaly/Birth Defect ☒ Hospitalization - initial or prolonged ☒ Other Serious (Important Medical Events) ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)					
3. Date of Event (mm/dd/yyyy) UNK			4. Date of This Report (mm/dd/yyyy) 12/22/2008		
5. Describe Event or Problem Event Verbatim (PREFERRED TERM) (Related symptoms if any separated by commas) ARDS[Acute respiratory distress syndrome] Multi System Failure[Multi-organ failure] Elevated LFTs[Liver function test abnormal]					
Case Description: Initial reception date 21May08 and additional information received on 22May08: This solicited report from the prescribing physician concerned an 11-year-old male patient with pulmonary hypertension secondary to unspecified lung disease (off-label use), who was hospitalized due to acute respiratory distress syndrome (ARDS), developed elevated liver function tests (LFTs), and subsequently expired on [REDACTED] due to ARDS and multi-system failure during the use of Tracleer (bosentan). Medical history and concomitant medications were not provided. The start date of Tracleer was unknown and Tracleer was discontinued three weeks prior to the patient's death. continued in additional info section...					
6. Relevant Tests/Laboratory Data, Including Dates #1 Liver function test Elevated, "in the thousands"					
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) #1 Indication, Pulmonary hypertension (continued) #2 UNK Current Condition, (continued) #3 UNK Historical Condition, (continued) #4 UNK Historical Condition, (continued) #5 UNK Current Condition, (continued)					
C. SUSPECT PRODUCT(S)					
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)					
#1. Tracleer(Bosentan Tablet Unknown US mg) (continued)					
#2.					
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration from/to (or best estimate))			
#1. 31.25 mg, bid, Oral		#1. 06/~/2005 to 03/26/2008			
#2.		#2.			
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?			
#1. Pulmonary hypertension		#1. ☐ Yes ☐ No ☒ Doesn't Apply			
#2.		#2. ☐ Yes ☐ No ☐ Doesn't Apply			
6. Lot #		7. Exp. Date		8. Event Reappeared After Reintroduction?	
#1. UNK		#1. UNK		#1. ☐ Yes ☐ No ☒ Doesn't Apply	
#2.		#2.		#2. ☐ Yes ☐ No ☐ Doesn't Apply	
9. NDC# or Unique ID					
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) Sildenafil (SILDENAFIL) Tablet UNK to UNK					
G. ALL MANUFACTURERS					
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Actelion Pharmaceuticals US, Inc. 5000 Shoreline Court, Suite 200 South San Francisco, CA 94080 UNITED STATES				2. Phone Number +1 6506246900	
4. Date Received by Manufacturer(mm/dd/yyyy) 12/12/2008				5. (A)NDA # US-NDA 21-290	
6. If IND, Give Protocol #				IND #	
7. Type of Report (Check all that apply)				STN #	
☐ 5-day ☐ 30-day				PMA/ 510(k) #	
☐ 7-day ☐ Periodic				Combination Product ☐ Yes	
☐ 10-day ☐ Initial				Pre-1938 ☐ Yes	
☒ 15-day ☒ Follow-up #1				OTC Product ☐ Yes	
9. Manufacturer Report Number A-NJ2008-20657				8. Adverse Event Term(s) Acute respiratory distress syndrome, Multi-organ failure, Liver function test abnormal	
E. INITIAL REPORTER					
1. Name and Address [REDACTED] MD [REDACTED] [REDACTED] UNITED STATES				Phone # [REDACTED]	
2. Health Professional? ☒ Yes ☐ No				3. Occupation Physician	
4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☒ Unk					

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

DSS

MEDWATCH
3500A Facsimile (Back) (continued)

Actelion Pharmaceuticals US, Inc.

Adi Report #	A-NJ2008-20657
UFI/Importer Report #	
FDA Use Only	

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ADDITIONAL INFORMATION

B5. EVENT DESCRIPTION (cont.)

The physician reported that the patient was hospitalized with ARDS five weeks prior to his death. Tracleer was discontinued due to elevation of LFTs that "were in the thousands" (exact values were unavailable). The LFTs had decreased somewhat prior to the patient's death but had not resolved due to the multi-system failure. The physician assessed the death due to ARDs and multi-system failure as not related to Tracleer and the event of elevated LFTs as related to Tracleer.

Follow-up reception date 12Dec08: The prescribing physician confirmed that pulmonary arterial hypertension secondary to interstitial lung disease (off-label use) was the indication for Tracleer. Medical history included a severe neurologic degenerative disease of unknown etiology and graft versus host disease due to a prior bone marrow transplant for an unspecified reason that may have contributed to the severe interstitial lung disease. Concomitant medications at the time of the elevated LFTs included sildenafil and unspecified seizure medications, nebulizers for bronchodilation, and high dose steroids for lung disease. Tracleer started at 31.25 mg daily in Apr05, was up-titrated to 31.25 mg twice daily in Jun05 and was discontinued on 26Mar08 (days prior to the patient's death).

The patient had been taking Tracleer for approximately three years when the event of elevated LFTs occurred. The physician confirmed that the elevated LFTs did not occur prior to the multi-system failure. The physician could provide no further details regarding the elevated LFTs. There was no change in the causality of the events. As previously reported, the physician assessed the death due to ARDS and multi-system failure as not related to the use of Tracleer and the event of elevated LFTs as related to the use of Tracleer.

The global drug safety physician assessed the elevated LFTs as medically significant.

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	UNK	Indication Pulmonary hypertension	Secondary to interstitial lung disease (off-label use)
2	UNK	Current Condition Interstitial lung disease	
3	UNK	Historical Condition Graft versus host disease	
4	UNK	Historical Condition Bone marrow transplant	
5	UNK	Current Condition Neurodegenerative disorder	

C1. Name (cont.)

Suspect Medication #1: Tracleer(BOSENTAN) Tablet

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Tracleer Regimen # 2	31.25 mg, qd, Oral	04/-/2005, duration UNK	UNK	UNK

DSS

Appendix 2

Example of cross-referenced concomitant medications

Record #	ISR #	Date	Age	Gender	Preferred Term (PT)	Outcome	Report Source	Product	Role
12	4066579-7	7/5/2003	18	F	Anxiety	Death	Foreign Health Professional	Sildenafil	PS

Record #	ISR #	Date	Age	Gender	Preferred Term (PT)	Outcome	Report Source	Product	Role
					Chest Pain			Ranitidine	C
					Dyspepsia			Bosentan	C
					Hemoptysis			Digoxin	C
					Headache			Epoprostenol	C
					Insomnia			Furosemide	C
					Muscle Tightness			Spironolactone	C

In this example, dyspepsia, headache, and insomnia have been associated with sildenafil, anxiety with epoprostenol, and chest pain with bosentan. The remaining events of hemoptysis and muscle tightness are thus assumed to be associated with the targeted pulmonary hypertension medication

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Fig. 1.

a Number of adverse events reported per medication by year. The spike in adverse events associated with bosentan in 2004 is unclear. **b** Total reported pediatric deaths associated with PAH medications by year. Deaths associated with sildenafil were reported before 2005, the date of FDA approval

Table 1

Data available from the Freedom of Information (FOI) Report

Data type	Description
Date	Date the report was received by the Food and Drug Administration (FDA)
Individual Safety Report (ISR) no.	Unique number for identifying an Adverse Event Reporting System (AERS) report
Report type	The type of ISR received. <i>Expedited</i> (15 day) and <i>periodic</i> reports are from manufacturers; <i>direct</i> reports are voluntarily submitted to the FDA by nonmanufacturers
Company report no.	Manufacturer's unique report identifier
Age	Numeric value of patient's age at event
Gender	The gender of the patient (male, female, unknown, or not specified)
I/FU	Inpatient or follow-up visit
Outcome	The results of the adverse event (death, life-threatening, hospitalization—initial or prolonged, disability, congenital anomaly, required intervention to prevent permanent/impairment/damage, other)
Preferred term (PT)	The reported reaction, in medical terminology, describing the event. This is coded using the <i>Medical Dictionary for Regulatory Activities</i>
Report source	Identifies the initial source of the report (foreign health professional, health professional, consumer)
Product	Name of drug
Role	Suspected role of drug (suspect, concomitant, primary suspect, secondary suspect)
Manufacturer	The company that manufactures the drug
Route	Route administration of the drug (oral, intravenous)
Dose	Quantity of drug administered in a 24-h period
Duration	No. of days the drug was used

Table 2

Demographic information for bosentan, epoprostenol, and sildenafil from FDA Adverse Event Records

Variable	Bosentan	Epoprostenol	Sildenafil	Total
Records available				
Pediatric	324	175	89	588
Total	6,646	1,903	780	9,329
Sex				
Male	127	63	39	229
Female	180	110	38	328
Not reported	17	2	12	31
Age (years)				
0–1	47	62	28	137
2–3	6	24	9	39
4–9	41	86	22	149
10	81	152	30	263

FDA Food and Drug Administration

Table 3

Adverse events (> 5 % of reports)

Event	No. of events (%)
Bosentan (<i>n</i> = 326)	
Liver function test abnormalities	202 (62)
Cardiac failure	37 (11)
Syncope	28 (8.6)
Blood bilirubin Increased	24 (7.4)
Thrombocytopenia	17 (5.5)
Epoprostenol (<i>n</i> = 175)	
Pulmonary hemorrhage	23 (13.1)
Cardiac failure	17 (9.7)
Hemoptysis	14 (8)
Right ventricular failure	14 (8)
Cardiac arrest	13 (7.4)
Dyspnea	11 (6.3)
Cyanosis	9 (5)
Hypoxia	9 (5)
Oxygen saturation decreased	9 (5)
Pneumonia	9 (5)
Sildenafil (<i>n</i> = 89)	
Cardiac failure	11 (12.4)
Hypotension	10 (11.2)
Dyspnea	9 (10.1)
Hemoptysis	8 (9)
Pneumonia	8 (9)
Cardiac arrest	7 (7.9)
Cough	6 (6.7)
Pleural effusion	6 (6.7)
Convulsion	5 (5.6)
Coronary artery disease	5 (5.6)
Disease recurrence	5 (5.6)
Exercise tolerance decreased	5 (5.6)
Hypoxia	5 (5.6)
Oxygen saturation decreased	5 (5.6)
Pulmonary hemorrhage	5 (5.6)
Respiratory failure	5 (5.6)
Stridor	5 (5.6)

n no. of patients

Events in bold have not been previously reported in clinical trials