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Neonatal Safety Information Reported to the FDA During Drug Development Studies

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Abstract

Background—Relatively few neonatal drug development studies have been conducted, but an increase is expected with the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA). Understanding the safety of drugs studied in neonates is complicated by the unique nature of the population and the level of illness. The objective of this study was to examine neonatal safety data submitted to the FDA in studies pursuant to the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) between 1998 and 2015.

Methods—FDA databases were searched for BPCA and/or PREA studies that enrolled neonates. Studies that enrolled a minimum of 3 neonates were analyzed for the presence and content of neonatal safety data.

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Declaration of Conflicting Interests

No potential conflicts were declared.

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Results—The analysis identified 40 drugs that were studied in 3 or more neonates. Of the 40 drugs, 36 drugs received a pediatric labeling change as a result of studies between 1998 and 2015, that included information from studies including neonates. Fourteen drugs were approved for use in neonates. Clinical trials for 20 of the drugs reported serious adverse events (SAEs) in neonates. The SAEs primarily involved cardiovascular events such as bradycardia and/or hypotension or laboratory abnormalities such as anemia, neutropenia, and electrolyte disturbances. Deaths were reported during studies of 9 drugs.

Conclusions—Our analysis revealed that SAEs were reported in studies involving 20 of the 40 drugs evaluated in neonates, with deaths identified in 9 of those studies. Patients enrolled in studies were often critically ill, which complicated determination of whether an adverse event was drug-related. We conclude that the traditional means for collecting safety information in drug development trials needs to be adjusted for neonates and will require the collaboration of regulators, industry, and the clinical and research communities to establish appropriate definitions and reporting strategies for the neonatal population.

Keywords

neonates; serious adverse events; drug development; safety; US FDA

Introduction

Neonates requiring admission to neonatal intensive care units (NICUs) are at significant risk for experiencing an adverse event (AE) or adverse drug reaction (ADR).[1,2] A neonate is defined as being less than 28 postnatal days of age per FDA draft guidance: *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*; preterm is defined as a neonate born prior to 37 weeks' gestation.[3] An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug, whether or not it was considered to be caused by the drug.[4] An adverse drug reaction (ADR) is an undesirable effect, reasonably associated with the use of a drug.[5] The number of medications a neonate receives and the fact that the majority of the drugs used to treat NICU patients are used off-label[6–8] contribute to that risk. Because many of the drugs administered in the NICU are not FDA-approved for use in neonates, clinicians may need to make therapeutic decisions based on literature sources that may not contain comprehensive assessments of efficacy, safety, and dosing for neonates.

Off-label use of medications in children may increase the potential for adverse events. In one pharmacovigilance survey, children prescribed a medication off-label were more than 3 times as likely to experience an adverse event as children prescribed the medication according to the approved labeling.[9] In addition, AEs may be difficult to recognize in neonates, because of both comorbidities and dynamic physiology. Adverse events in the NICU may result from the disease states that necessitate intensive care, comorbidities, treatments, or other factors, and causal inference is often problematic.

FDA monitors and reviews safety information about a drug throughout the product's lifecycle. The Food and Drug Administration Safety and Innovation Act (FDASIA)[10] was enacted in 2012 and made permanent the Best Pharmaceuticals for Children Act (BPCA)[11]

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and the Pediatric Research Equity Act (PREA),[12] which had been in place since 1997 and 2003, respectively.

BPCA is a voluntary incentive program that allows sponsors to qualify for an additional 6 months of marketing exclusivity if the sponsor completes and submits pediatric studies as outlined in a Written Request (WR) issued by the FDA. The marketing exclusivity applies to the entire moiety (the molecule responsible for the physiological or pharmacological action of the drug substance).[13] BPCA permits the FDA to request all feasible pediatric studies for a given moiety including studies in neonates when appropriate.

PREA requires all applications or supplements to applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral. Studies may be deferred in certain situations, such as a new drug application that is ready for approval for use in adults before pediatric studies are complete, or when additional safety or effectiveness data need to be collected before studying in the pediatric population. Pediatric studies may be waived in full or in part in certain situations, including when studies are impossible or highly impracticable, when there is evidence to suggest a product is unsafe or ineffective for an age group, when the product does not represent a meaningful benefit over existing therapies and is unlikely to be used, or when reasonable attempts have failed to produce a pediatric formulation for a particular age group (ie, liquid).

BPCA and PREA have substantially increased the study of drugs in pediatric patients, and a large body of pediatric trial data has become available. Pediatric studies have led to a total of 608 pediatric drug labeling changes pursuant to BPCA and/or PREA through December 2015. However, BPCA and PREA have not had as profound an impact on the development of therapies for neonatal conditions.

FDASIA specifically mandates and incentivizes drug development studies for neonates. Given the anticipated increase in studies enrolling neonates, the safety information collected as a result of the earlier legislative initiatives was analyzed. The objective was to describe the publicly-available neonatal safety information resulting from pediatric studies performed as a result of BPCA and/or PREA between 1998 and 2015. The analysis focused on ADRs and SAEs. A serious adverse event (SAE) is defined as any event occurring at any dose of a drug that results in death, a life-threatening adverse drug event, hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or other event requiring intervention.[4]

Patients and Methods

The following publicly accessible FDA websites were searched for studies that enrolled neonates: (1) the FDA New Pediatric Labeling Information Database[14]; (2) Medical, Statistical, and Clinical Pharmacology reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act (the Act) as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA)[15]; (3) Medical, Statistical, and Clinical Pharmacology reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA

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Safety and Innovation Act of 2012 (FDASIA)[10]; (4) summaries of Pediatric Medical and Clinical Pharmacology reviews conducted under BPCA 2002[11]; and (5) FDA-approved drug labeling and reviews posted at Drugs@FDA.[16] A prior review of neonatal drug labeling and use provided an additional source of information.[17]

The search included pediatric studies performed under BPCA and/or PREA with neonatal study data publicly available through December 2015. Drugs with studies that enrolled at least 3 neonates were included in the analysis. The authors chose to include pediatric studies that included at least 3 neonates because reviews of studies that included only 1 or 2 neonates are unlikely to provide sufficient information about any neonatal findings. The information collected included the drug name, indication studied, all safety information, and whether the drug was approved for use in neonates. All safety information was extracted from the FDA Reviews.

Results

The analysis identified 40 drugs with pediatric studies completed between 1998 and 2015 that included data from at least 3 neonates (Table 1). Of the 40 drugs, 36 drugs received a pediatric labeling change, including 32 with information about neonatal studies. Fourteen drugs were approved for use in neonates.

SAEs were reported in neonates for 20 of the 40 drugs with neonatal data (Table 2). Death in neonates was reported during studies of 9 of the 20 drugs that contained SAE information. For example, in the caspofungin studies, there were a total of 12 deaths out of 171 pediatric patients 1 week to 17 years of age. Three deaths occurred in neonates, 1 occurred in an infant 13 months of age, and 8 occurred in children 6 to 13 years of age. None of the deaths were considered related to treatment with caspofungin.

Other studies reported SAEs involving cardiovascular dysfunction such as bradycardia and/or hypotension or comorbidities of premature birth (ie, patent ductus arteriosus, sepsis, or periventricular-intraventricular hemorrhage). Convulsions and hyperbilirubinemia were reported in one study. ADRs described in FDA reviews included hematologic abnormalities such as anemia and neutropenia and electrolyte and liver function disturbances.

In 2 studies, neonates were enrolled with a larger population of pediatric patients, but precise numbers of neonates and neonatal SAEs were not specified. It was determined that safety analyses in FDA reviews have sometimes grouped neonates with the broader pediatric population, making identifying neonate-specific safety information more difficult. In addition, the neonatal population may be ambiguously defined in FDA reviews and labeling, such as in the interchangeable use of the terms “infants” and “neonates.”

Nine of 20 drugs listed in Table 2 had preclinical juvenile animal studies documented in the FDA product reviews or product labeling.

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Discussion

The analysis revealed that serious adverse events were reported in neonates during studies of 20 of the 40 drugs with neonatal data, with deaths identified in 9 studies. The background of severe illness, physiologic immaturity, and use of multiple medications frequently makes neonatal AEs challenging to interpret, with determination of causality difficult. In addition to the clinical variables, drug safety assessment for neonates in pediatric trials may be challenging as a result of (1) small sample size, particularly in studies that were not designed to address a neonatal problem; (2) grouping of neonates in trials and reviews with the broader pediatric population; and (3) ambiguous definitions of the neonatal population, such as the interchangeable use of the terms “infant” and “neonate.”

Ill and immature neonates may be more vulnerable to the long-term impact of ADRs and SAEs than more mature pediatric populations. In addition, premature neonates frequently have multiple comorbid conditions requiring treatment, and the need to treat these conditions may lead to a large medication burden in neonates. In Hsieh’s 2014 study that evaluated medication use in 305 NICUs between 2005 and 2010, on average, hospitalized term neonates were exposed to 4 medications while extremely low birth weight premature infants were exposed to an average of 17 medications.[7] Treatment with multiple medications complicates the pharmacokinetics in neonates because of the potential for drug interactions and has been shown to increase the likelihood of ADRs.[18]

Neonatal comorbidities, polypharmacy, and physiologic immaturity all contribute to the difficulty in adjudicating adverse events. A multipronged approach to safety assessment and surveillance can facilitate the safe use of drugs in neonates. Safety assessments available to detect potential serious adverse events in neonates include, but are not limited to, preclinical toxicology studies, randomized controlled trials, premarketing safety studies as well as postmarketing safety studies, voluntary postmarketing reporting, product- or disease-oriented registries, and large data repositories such as electronic health records.[19]

Decisions to conduct a preclinical juvenile animal study are based on existing data, such as a safety signal already identified in adult studies, or previous knowledge of the drug or chemical class for its potential to impair growth or developmental milestones.[20] The extent and timing of nonclinical safety studies will depend on the available safety information for a particular product. For example, the information needed to support a new pediatric indication for an approved product used in adults may be quite different from the information needed to support pediatric use of a new molecular entity because of the lesser-known safety profile of the novel product.[21]

Most of the studies in our analysis were trials involving small numbers of neonates that were not fully powered to establish effectiveness and safety of the drug specifically for neonates. In the event safety and effectiveness have not been established in the pediatric population or a subpopulation such as neonates, the Code of Federal Regulations 21 CFR 201.57(c)(9)(iv)(F) requires a statement similar to “The safety and effectiveness in pediatric patients less than X have not been established.” Twenty-two of the pediatric studies were safety and efficacy studies; 23 were PK and safety; and 7 were PK/PD and safety. It is important to

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note that, in general, if there is a safety issue identified during studies involving neonates, that information will be added to the labeling.

Well-designed randomized, controlled trials (RCTs) are ideal for assessing safety, efficacy, and dosing of a product in neonates. Large neonatal RCTs, such as the inhaled nitric oxide (iNO) trials, enrolled critically ill neonates. The 3 iNO trials described in Table 2 randomized more than 2000 neonates to either study drug or placebo, and although there were 296 deaths during the trials,[22–24] the group receiving the study treatment did not have an increased mortality rate. Although the neonates were premature and ill, it was possible to enroll enough neonates to detect differences in serious adverse events between control and treatment groups.

Randomized, controlled, clinical trials of the size and quality described above, submitted for regulatory evaluation, historically have been the exception, rather than the rule in neonatal therapeutic trials. Since 1998, there have been more than 1200 pediatric studies submitted to the FDA as a result of BPCA and/or PREA. Fifty-six of those studies (for 40 drugs) included data from neonates. It is important to note that drug studies in neonates may be performed independent of the BPCA and PREA mandates.

After the premarketing stage, voluntary postmarketing adverse event reporting, registries, and observational pharmacoepidemiology studies are additional tools that may deepen the understanding of the safety of a particular drug in any population, including neonates. All these adjunct methods have limitations, but combined, they help to provide a more complete drug safety profile.

Patients, pharmacists, physicians, and nurses are encouraged to submit adverse event and medication error reports to FDA's MedWatch site,[25] and the reports are collected in the FDA's Adverse Event Reporting System (FAERS) database for surveillance. FAERS is a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product. If a potential safety concern is identified in FAERS, further investigation is undertaken. The limitations of this system include the lack of certainty about causality, incomplete reports, underreporting due to the voluntary nature of the reporting, and the minimal requirements to file a report (product name, event that occurred, and reporter name are the only elements required). Because the age of the patient is not always provided by the reporter on the MedWatch form, it is challenging to capture adverse events for neonates in FAERS. The database also cannot provide a "denominator" of how many people receive a drug; therefore, FAERS data alone cannot be used to calculate the incidence of an adverse event or medication error in the US population.

Despite its limitations, there have been numerous safety problems that may not have been recognized swiftly without spontaneous postmarketing adverse event reporting. In 2011, FDA approved changes to the Kaletra (lopinavir/ritonavir) oral solution product label after a postmarketing review revealed 10 cases of life-threatening adverse events in primarily preterm neonates. The review concluded that the toxicities were presumed to be related to lopinavir and/or the excipients, propylene glycol and ethanol. Premature neonates have a decreased ability to eliminate propylene glycol, which may lead to adverse events such as

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serious heart, kidney, or breathing problems.[26] The Kaletra adverse events also highlight the issues of neonatal formulation and excipient safety.[27]

NICU physicians, nurses, pharmacists, and other clinicians responsible for patient care are uniquely positioned to help gather neonatal drug safety information. Quality improvement or prospective studies could be designed to follow patients for adverse drug events in the NICU. Safety concerns should be shared with regulators via MedWatch, so that further evaluation may occur when indicated.

Conclusions

Traditional means for collecting safety information in drug development trials need to be adjusted for the neonatal population through the collaboration of regulators, industry, and the clinical community to establish appropriate definitions and reporting strategies. A multipronged approach across all the phases of product development is required to understand the safety issues associated with therapeutics for neonates. Safety information collection tools should be developed specifically for neonatal studies with input from neonatologists and clinical caregivers in the NICU. Preclinical studies are useful for the identification of unexpected off-target drug effects. Well-designed RCTs are crucial for evaluating the safety and efficacy of a new product. Postmarketing surveillance, registries, and electronic health record data also are important to follow the safety of products used in the real-world setting. Surveillance initiatives, such as MedWatch, should capture the ages of neonates and young infants with more specificity, and clinicians should be encouraged to report age along with the details of suspected SAEs and ADRs to ensure the FDA has as much information as possible when evaluating possible safety signals. This active area of research and collaboration must remain a high priority, with attention paid to developing innovative ways to differentiate true safety signals from confounding disease processes and concomitant medication exposure.[28] There is a paucity of neonatal safety information in drug development trials. This is an opportunity for regulators, industry, and neonatologists to collaborate on methods to address this problem.

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Abbreviations

ADR	adverse drug reaction
AE	adverse event
BPCA	Best Pharmaceuticals for Children Act
FAERS	FDA Adverse Event Reporting System

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FDASIA	Food and Drug Administration Safety and Innovation Act
NICU	neonatal intensive care unit
PREA	Pediatric Research Equity Act
SAE	serious adverse event

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Table 1

Forty Drugs Studied in at Least 3 Neonates Between 1998 and 2015 Under BPCA and PREA.

Antiviral	Anti-infectives	Gastrointestinal	Cardiovascular	Respiratory	Anesthetics/Analgesics	Ophthalmics	Miscellaneous
emtricitabine	caspofungin	rabeprazole sodium	sotalol	nitric oxide	acetaminophen injection	ciprofloxacin[a]	bivalirudin[a]
lamivudine	meropenem[b]	esomeprazole	fenoldopam[b]	levalbuterol	oxycodone	difluprednate[b]	gadobutrol[b]
lopinavir/ritonavir	micafungin sodium	esomeprazole sodium IV	sodium nitroprusside[b]		dexmedetomidine hydrochloride	ocriplasmin	6% Hydroxyethyl Starch 130/0.4 in 0.9% sodium chloride injection[b]
didanosine[b]	linezolid[b]	famotidine[b]	clopidogrel bisulfate		sevoflurane[b]	ofloxacin[a]	
valganciclovir		lansoprazole			remifentanil[b]	moxifloxacin	
nelfinavir		pantoprazole			rocuronium[b]	gatifloxacin[a]	
nevirapine[b]		ranitidine					
stavudine[b]							

Abbreviations: BPCA, Best Pharmaceuticals for Children Act; PREA, Pediatric Research Equity Act.

[a]Drug did not receive a pediatric labeling change as a result of studies.

[b]Approved for use in neonates.

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Table 2

Neonatal Severe Adverse Events and Adverse Drug Reactions Reported in Drug Studies.

Generic Name	Indication Studied	Approved for Neonatal Use	n: Number of Neonates on Study Drug; SAEs from FDA Review (frequency)[a]	ADRs from FDA Review Event (frequency)	Neonatal Labeling Information Resulting from Studies	Preclinical Juvenile Animal Studies Performed?
rabeprazole sodium	GERD	No	n = 69—*Death (1) in a premature infant with multisystem complications of prematurity including lung disease, pseudomonas sepsis, cerebral atrophy, and NEC. Apnea/bradycardia (2); apnea (1) presumed sepsis (1); retinopathy of prematurity (2)*[b]	Anemia (13)	• Studies do not support the use in pediatric patients aged <1 y • Use in neonates is strongly discouraged based on the risk of prolonged acid suppression and lack of demonstrated safety and effectiveness in neonates	Yes
sotalol	Arrhythmia	No	n = 9—Prolonged QTc (1)		• Analysis of 2 trials provided information on PK and PD in children 3 d-12 y; safety and efficacy have not been established	No
caspofungin	Empirical therapy for presumed fungal infections in febrile, neutropenic patients; Candidemia and certain Candida infections; Esophageal candidiasis; Invasive aspergillosis in patients who are refractory to or intolerant of other therapies	No	n = 18—*Death (3)*[b]		• The efficacy and safety have not been adequately studied in neonates and infants aged <3 mo • Although limited PK data were collected in neonates and infants <3 mo old, these data are insufficient to establish a safe and effective dose in the treatment of neonatal candidiasis.	Yes
fenoldopam	Indicated for the in-hospital, short-term reduction in blood pressure	Yes	n = 34[c] (aged <2 y)—Death (1) intracranial hemorrhage in newborn after concomitant use of TPA		• Indicated for the in-hospital, short-term (up to 4 h) reduction in blood pressure in pediatric patients <1 mo (at least 2 kg) to 12 y old	No
difluprednate	Treatment of postoperative inflammation following cataract surgery	Yes	n = 4—*3 neonates experienced an unspecified nonfatal SAE*[b]		• Information on PK, dose, and AE profile • Approved in pediatric patients	No

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Generic Name	Indication Studied	Approved for Neonatal Use	n: Number of Neonates on Study Drug; SAEs from FDA Review (frequency)[a]	ADRs from FDA Review Event (frequency)	Neonatal Labeling Information Resulting from Studies	Preclinical Juvenile Animal Studies Performed?
					• Evaluated in a 3-mo, multicenter, double-masked trial in 79 pediatric patients 0–3 y old	
emtricitabine	HIV-1 infection in combination with other antiretroviral agents	No	n = 21—gastroenteritis and bronchopneumonia (1), bronchiolitis (1)	Grade 3 and 4 events: anemia (1), neutropenia (2), bronchiolitis (1) and hypoglycemia (4). Grade 1 and 2 events: decreases in their hemoglobin and hematocrit (22). All neonates were receiving concomitant ZDV; anemia is a common related AE. Upper respiratory tract infection, oral candidiasis, candidiasis, lymphadenopathy, constipation or diarrhea, hypoglycemia and pyrexia (>3 patients)	• No reference to neonates in labeling • Efficacy in preventing or treating HIV in neonates to 3-mo-olds could not be determined after a PK study in 20 neonates born to HIV-positive mothers	No
lamivudine	HIV	No	n = 36—Death (3) secondary to gastroenteritis with acidosis and convulsions (1), traumatic injury (1), unknown causes (1)	Increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis (unspecified number of neonates); nonfatal gastroenteritis or diarrhea cases were reported (2), including 1 with convulsions; transient renal insufficiency	• Lamivudine clearance substantially reduced in 1-wk-old neonates relative to pediatric patients >3 mo of age; safety and efficacy have not been established	Yes

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Generic Name	Indication Studied	Approved for Neonatal Use	n: Number of Neonates on Study Drug; SAEs from FDA Review (frequency)[a]	ADRs from FDA Review Event (frequency)	Neonatal Labeling Information Resulting from Studies	Preclinical Juvenile Animal Studies Performed?
				associated with dehydration (1)		
nitric oxide	Prevention of bronchopulmonary dysplasia (BPD)	No (previously approved in neonates for a different indication)	INOT27: n = 395—Death (53), 158 SAEs including patent ductus arteriosus (59), intestinal perforation (16), sepsis (32), intracranial hemorrhage (49), pneumothorax (12), pulmonary hemorrhage (12) BALLR1: n = 295—Death (16), 26 SAEs including NEC (6), bacterial sepsis (4), fungal sepsis (2), therapy cessation (2), staphylococcal sepsis, (2) pulmonary pneumatocele (2) hypotension (2), resuscitation (4) INOT 25: n = 398—Death (77), 100 SAEs including neonatal IVH (27), sepsis (21), pneumothorax (10); neonatal necrotizing enterocolitis (10); and pulmonary hemorrhage (8)		• Efficacy and safety for the prevention of BPD in preterm infants were not established in 3 double-blind, placebo-controlled clinical trials in a total of 2149 preterm infants	No
lopinavir/ritonavir	Use in combination with other antiretroviral agents for HIV-1 infection	No	n = 10[c] (14 d–6 wk)—decreased absolute neutrophil (1), neutropenia count (1), decreased hemoglobin (1), anemia (2), hyperkalemia (1), hyponatremia (1), increased ALT (1), abnormal amylase (1), abnormal stools (1), and vomiting (1)		• Approved in 14 d and older neonates. • The safety, efficacy, and PK profiles in pediatric patients <14 d old have not been established • Revised the dosage and administration, warnings and precautions and overdosage sections of the labeling to add information regarding toxicities associated with the use of Kaletra oral solution in preterm infants	No
Meropenem	Complicated intra-abdominal infections	Yes	n = 200, GA ≤40 weeks—*Death (11)*,[b] convulsion (10), hyperbilirubinemia (9)		• Indication extended pediatric to patients <3 mo of age with intra-abdominal infections	Yes

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micafungin sodium	Treatment or prophylaxis of Candida infections	No	n = 13 (including 6 patients <1000 g)—Renal failure (1); subarachnoid haemorrhage (1)	Infusion site phlebitis (1), increased alkaline phosphatase (1) and hypokalemia (1)	• Safety and effectiveness in pediatric patients <4 mo old have not been established	Yes
esomeprazole	Short-term treatment of GERD	No	n = 26—Pertussis (1)		• Effectiveness was not demonstrated in a randomized, placebo-controlled study in neonates to <1-y-old infants	Yes
oxycodone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment	No	n = 12—Obstructive apnea and tachypnea (1)		• Safety and efficacy have been established in pediatric patients 11–16 y old	No
famotidine	Gastroesophageal reflux	Yes	n = 12—*Death (1); congenital anomaly (1); drug malabsorption, overdose (1)*[b]		• Labeling for patients <1 y old including information on dose, PK/PD parameters and, AE profile • Lower dose recommended in patients <3 mo old • Pediatric patients 0–3 months of age had clearance values 2 to 4-fold less than those in older patients and adults	No
clopidogrel bisulfate	Reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease	No	n = 27—*Death in a neonate with bradycardia, hypotension, oxygen desaturation (1)*[b]		• Safety and efficacy have not been established	No
dexmedetomidine	Loading and maintenance infusion for sedation in intubated and mechanically ventilated pediatric patients	No	n = 36—*Death due to cardiac arrest*[b] (1), bradycardia, cardiorespiratory arrest and oxygen saturation decrease, respiratory failure (n=1)		• Safety and efficacy have not been established	Yes
lansoprazole	Short-term treatment of symptomatic GERD and erosive esophagitis	No	n = 24	Anemia (1); flushing (2); transaminases increased (1)	• Safety and effectiveness in pediatric patients <1 year of age have not been established	No

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pantoprazole	Erosive esophagitis associated with GERD	No	n = 59—*Urinary tract infection during the follow-up (1); hematochezia due to colitis (1)*[b]	Elevated liver enzyme (1); contact dermatitis (1)	• Effectiveness for erosive esophagitis has not been demonstrated in patients <1 y old	Yes
Valganciclovir	Congenital cytomegalovirus (CMV) infection	No	CASG112: n = 107—The most common SAEs were reported from the SOC blood and lymphatic system disorders (4) and infections and infestations (5); numbers not specified. CASG 109: n = 24—Anemia, neutropenia (most common), rash, agitation, fever and, emesis.		• Safety and efficacy have not been established in infants with congenital CMV infection.	No
moxifloxacin	Bacterial conjunctivitis	No	n = 107—Pyloric stenosis (n = 1), fever (n = 1)		• Safety and efficacy have not been established	Yes

Abbreviations: AE, adverse event; ALT, alanine transaminase; ECG, electrocardiogram; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; NDA, new drug application; NEC, necrotizing enterocolitis; PD, pharmacodynamics; PK, pharmacokinetics; SAE, severe adverse event; TPA, tissue plasminogen activator.

[a] Italicized events adjudicated as not drug related.

[b] Adjudicated as not drug related in Medical Review or Summary. In drugs without the designation b, the Medical Review or Summary did not assign attribution to drug, or underlying condition for the SAEs.

[c] Denotes a sample including other age groups in addition to neonates and combined safety data.