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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Nitropress® [sodium nitroprusside] (SNP) injection in pediatric patients.

The currently marketed Nitropress® injection was first approved in 1988 and is indicated for the 1) immediate reduction of blood pressure of adult and pediatric patients in hypertensive crises, 2) producing controlled hypotension in order to reduce bleeding during surgery, and 3) treatment of acute congestive heart failure.

Drug utilization patterns were assessed in order to capture pediatric use of Nitropress® and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database for Nitropress®. From November 2013 through July 2016, a total of approximately 262,000 patients had a hospital discharge billing for Nitropress® from U.S. non-federal hospitals; of which, the pediatric population aged 0-16 years accounted for 5.6% (14,800 patients).

A search of the FAERS database identified twenty-six pediatric reports received by FDA between August 1, 1988 and October 24, 2016. After removing duplicate reports, we identified twenty serious pediatric cases associated with SNP, which included eight deaths and twelve non-fatal post-marketing cases.

The eight deaths reported cyanide toxicity and poisoning (n= 3), cardiovascular disorders (n= 2), lack of effect (n= 2), and carboxyhemoglobinemia (n= 1). In seven cases, determination of the cause of death was confounded by underlying cardiac disease or complications of surgery. In the other case, death was associated with cyanide poisoning due to an overdose of SNP. The twelve non-fatal cases included reports of carboxyhemoglobinemia (n= 4), cyanide toxicity and poisoning (n= 3), cardiovascular disorders (n= 2), lack of effect (n= 2), and eye disorders (n= 1). Three cases reported cyanide toxicity and poisoning - events that are well described in the SNP labeling. Two cases contained inadequate information for assessment. One case was confounded by underlying disease and concomitant drugs. Another case was confounded by the intermittent administration of SNP. Five cases reported a possible association between SNP and carboxyhemoglobinemia (n= 4) and visual impairment (n= 1).

DPV identified a safety signal for carboxyhemoglobinemia in association with SNP. Five cases reported a rise in carboxyhemoglobin following nitroprusside administration. Four cases originated from a foreign publication where one patient died and three recovered with no sequelae following SNP discontinuation. The fifth case reported a temporal relationship to SNP administration with limited clinical details. All cases documented a positive dechallenge upon SNP withdrawal. A plausible biologic mechanism exists for the rise in carboxyhemoglobin level based on induction of heme oxygenase-1 (HO-1) by SNP. A FAERS search did not identify additional cases of carboxyhemoglobinemia in the adult population.

One case of visual impairment reported a temporal relationship and positive dechallenge upon discontinuation of SNP. A FAERS search was performed to identify additional cases of visual impairment in adult and pediatric patients. One foreign adult case reporting blindness was identified, which contained minimal information for assessment. Based on the limited evidence of an association between visual impairment and SNP, DPV will continue to monitor adverse events of visual impairment reported with SNP.

Based on the identification of carboxyhemoglobinemia associated with SNP, DPV recommends the addition of carboxyhemoglobinemia to the Adverse Reactions section of labeling. DPV will continue to monitor adverse events associated with SNP use.

1 INTRODUCTION

In accordance with the Best Pharmaceuticals for Children Act (BPCA), the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of Nitropress (sodium nitroprusside) injection in pediatric patients (0-16 years of age). The main focus of this review is pediatric deaths and pediatric reports of serious adverse events with sodium nitroprusside injection.

1.1 PEDIATRIC REGULATORY HISTORY [1, 2]

Nitropress® injection was approved by the FDA on August 1, 1988. It is indicated for the 1) immediate reduction of blood pressure (BP) of adult and pediatric patients in hypertensive crises, 2) producing controlled hypotension in order to reduce bleeding during surgery, and 3) treatment of acute congestive heart failure. Nitropress injection is not suitable for direct injection. The solution must be further diluted in sterile 5% dextrose injection before infusion. Nitropress is available as a 50 mg vial. Each 2 ml vial contains the equivalent of 50 mg sodium nitroprusside dehydrate in sterile water for injection. Nitropress injection has been marketed by several drug manufacturers in the past; however, all products have been discontinued except for the currently marked Nitropress injection that is manufactured by Hospira under ANDA 071961.

Under Section 409I of the Best Pharmaceuticals for Children Act (BPCA) of 2002, the National Institutes of Health (NIH), in consultation with the FDA, was mandated to establish an annual list of drugs for which additional studies are needed in the pediatric population. Under the BPCA of 2007, the NIH mandate was expanded to require publication of a priority list of needs in pediatric therapeutics, including drugs or indications that require study. The intent of Section 409I is to obtain data on the safe and effective use of off-patent drugs that will result in pediatric labeling.

In the Federal Register of January 21, 2003 (68 FR 2789), SNP was identified as a drug that needed further study in the pediatric population. The approved labeling lacked adequate information on dosing, pharmacokinetics (PK), tolerability, and safety in pediatric patients from birth to 18 years of age who receive SNP for controlled reduction of BP. A written request (WR) for pediatric studies of SNP was issued on July 8, 2002 to Abbott Laboratories, holder of the NDA for SNP. FDA did not receive a response to the WR. Accordingly, the NIH issued a request for proposals to conduct the pediatric studies described in the WR in July 2004 and awarded the funds to Duke University and Stanford University in September 2004 to complete the studies described in the WR. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) submitted clinical study reports for SNP. The two studies were NICHD-2003-09-DR-SNP1, a randomized double-blind, parallel group, dose-ranging, effect-controlled, multicenter study of intravenous (IV) infusions of SNP in pediatric patients (birth to 17 years) who require deliberate, controlled relative-induced hypotension for at least two hours and NICHD-2003-09-LT-SNP2, a multicenter, randomized, double-blind, placebo-controlled, parallel group study to determine the pharmacodynamics of SNP during prolonged infusion in pediatric subjects. This study was a withdrawal to placebo study.

A report of the completed pediatric studies of SNP was submitted to the NIH and FDA. Public docket FDA-2012-N-0284 was opened on August 31, 2012. The docket was open for public comment from October 3, 2102 until November 2, 2012. No comments were received. The data submitted to the docket were submitted in accordance with section 409I of the PHS (Public Health Service) Act and were the same data submitted to investigational new drug (IND) application 71979. The key findings of this submission were:

- The BP lowering effect of SNP was demonstrated in both of the trials.

- A higher proportion of patients in the high-dose group achieved target mean arterial pressure (MAP) compared to the lowest dose of 0.3 microgram/kilogram/minute (µg/kg/min). The time-to-target MAP was also shorter for the high-dose groups.
- With a starting dose of 0.3 µg/kg/min, 25% of patients achieved target MAP in five minutes. Maintaining on a stable dose of 0.3 µg/kg/min for ten minutes resulted in 50% of patients reaching target MAP.
- The proportion of patients with MAP reductions greater than 20% below target increased in a dose-dependent manner.
- The safety profile of SNP in both the trials was consistent with the expected events as a result of the underlying disease and pre-operative setting. BP reduction events were drug-and dose-related.

Efficacy in the pediatric population was established based on adult trials and supported by a dose-ranging trial and an open label trial that achieved adequate MAP control in the pediatric population. Pediatric labeling was approved on November 22, 2013.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES [3]

NITROPRESS® (Sodium Nitroprusside Injection) is not suitable for direct injection. The solution must be further diluted in sterile 5% dextrose injection before infusion.

NITROPRESS can cause precipitous decreases in blood pressure (see *DOSAGE AND ADMINISTRATION*). In patients not properly monitored, these decreases can lead to irreversible ischemic injuries or death. Sodium nitroprusside should be used only when available equipment and personnel allow blood pressure to be continuously monitored.

Except when used briefly or at low (< 2 mcg/kg/min) infusion rates, sodium nitroprusside gives rise to important quantities of cyanide ion, which can reach toxic, potentially lethal levels (see *WARNINGS*). The usual dose rate is 0.5-10 mcg/kg/min, but infusion at the maximum dose rate should never last more than 10 minutes. If blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of sodium nitroprusside should be terminated immediately.

Although acid-base balance and venous oxygen concentration should be monitored and may indicate cyanide toxicity, these laboratory tests provide imperfect guidance.

WARNINGS

Excessive Hypotension: Small transient excesses in the infusion rate of sodium nitroprusside can result in excessive hypotension, sometimes to levels so low as to compromise the perfusion of vital organs. These hemodynamic changes may lead to a variety of associated symptoms. Nitroprusside-induced hypotension will be self-limited within 1-10 minutes after discontinuation of the nitroprusside infusion; during these few minutes, it may be helpful to put the patient into a head-down (Trendelenburg) position to maximize venous return. If hypotension persists more than a few minutes after discontinuation of the infusion of NITROPRESS, NITROPRESS is not the cause, and the true cause must be sought.

Cyanide Toxicity: Sodium nitroprusside infusions at rates above 2 mcg/kg/min generate cyanide ion

(CN^-) faster than the body can normally dispose of it. Methemoglobin normally present in the body can buffer a certain amount of CN^-, but the capacity of this system is exhausted by the CN^- produced from about 500 mcg/kg of sodium nitroprusside. This amount of sodium nitroprusside is administered in less than an hour when the drug is administered at 10 mcg/kg/min (the maximum recommended rate). Thereafter, the toxic effects of CN^- may be rapid, serious, and even lethal.

The true rates of clinically important cyanide toxicity cannot be assessed from spontaneous reports or published data. Most patients reported to have experienced such toxicity have received relatively prolonged infusions, and the only patients whose deaths have been unequivocally attributed to nitroprusside-induced cyanide toxicity have been patients who had received nitroprusside infusions at rates (30-120 mcg/kg/min) much greater than those now recommended. Elevated cyanide levels, metabolic acidosis, and marked clinical deterioration, however, have occasionally been reported in patients who received infusions at recommended rates for only a few hours and even, in one case, for only 35 minutes. In some of these cases, infusion of sodium thiosulfate caused dramatic clinical improvement, supporting the diagnosis of cyanide toxicity.

Cyanide toxicity may manifest itself as venous hyperoxemia (with bright red venous blood, as cells become unable to extract oxygen), metabolic (lactic) acidosis, air hunger, confusion, and death. Cyanide toxicity due to causes other than nitroprusside has been associated with angina pectoris and myocardial infarction, ataxia, seizures, stroke, and other diffuse ischemic damage.

Hypertensive patients, and patients concomitantly receiving other antihypertensive medications, may be more sensitive to the effects of sodium nitroprusside than normal subjects.

PRECAUTIONS

Laboratory Tests: The cyanide-level assay is technically difficult, and cyanide levels in body fluids other than packed red blood cells are difficult to interpret. Cyanide toxicity will lead to lactic acidosis and venous hyperoxemia, but these findings may not be present until an hour or more after the cyanide capacity of the body's red-cell mass has been exhausted.

Pediatric Use: Efficacy in the pediatric population was established based on adult trials and supported by the dose-ranging trial (Study 1) and an open label trial of at least 12 hour infusion at a rate that achieved adequate MAP control (Study 2) with pediatric patients on sodium nitroprusside. No novel safety issues were seen in these studies in pediatric patients.

ADVERSE REACTIONS

Methemoglobinemia: Sodium nitroprusside infusions can cause sequestration of hemoglobin as methemoglobin. The back-conversion process is normally rapid, and clinically significant methemoglobinemia (>10%) is seen only rarely in patients receiving NITROPRESS. Even patients congenitally incapable of back-converting methemoglobin should demonstrate 10% methemoglobinemia only after they have received about 10 mg/kg of sodium nitroprusside, and a patient receiving sodium nitroprusside at the maximum recommended rate (10 mcg/kg/min) would take over 16 hours to reach this total accumulated dose.

Methemoglobin levels can be measured by most clinical laboratories. The diagnosis should be suspected in patients who have received >10 mg/kg of sodium nitroprusside and who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2 . Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is 1-2 mg/kg of methylene blue, administered intravenously over several minutes. In patients likely to have substantial amounts of

cyanide bound to methemoglobin as cyanmethemoglobin, treatment of methemoglobinemia with methylene blue must be undertaken with extreme caution.

Thiocyanate Toxicity: Most of the cyanide produced during metabolism of sodium nitroprusside is eliminated in the form of thiocyanate. When cyanide elimination is accelerated by the co-infusion of thiosulfate, thiocyanate production is increased. Thiocyanate is mildly neurotoxic (tinnitus, miosis, hyperreflexia) at serum levels of 1 mmol/L (60 mg/L). Thiocyanate toxicity is life-threatening when levels are 3 or 4 times higher (200 mg/L). The steady-state thiocyanate level after prolonged infusions of sodium nitroprusside is increased with increased infusion rate, and the half-time of accumulation is 3-4 days. To keep the steady-state thiocyanate level below 1 mmol/L, a prolonged infusion of sodium nitroprusside should not be more rapid than 3 mcg/kg/min; in anuric patients, the corresponding limit is just 1 mcg/kg/min. When prolonged infusions are more rapid than these, thiocyanate levels should be measured daily. Physiologic maneuvers (e.g., those that alter the pH of the urine) are not known to increase the elimination of thiocyanate. Thiocyanate clearance rates during dialysis, on the other hand, can approach the blood flow rate of the dialyzer. Thiocyanate interferes with iodine uptake by the thyroid. Abdominal pain, apprehension, diaphoresis, "dizziness," headache, muscle twitching, nausea, palpitations, restlessness, retching, and retrosternal discomfort have been noted when the blood pressure was too rapidly reduced. These symptoms quickly disappeared when the infusion was slowed or discontinued, and they did not reappear with a continued (or resumed) slower infusion.

See Appendix A for additional relevant pediatric labeling.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the FDA to conduct this analysis. ***Appendix B (Section 8.2)*** includes detailed descriptions and limitations of the databases.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the various settings of care where Nitropress® (sodium nitroprusside) is distributed by the manufacturer. Sales data from November 2013 through July 2016 showed that approximately 98.6% of Nitropress® packages/vials were sold to U.S. non-retail settings (primarily non-federal hospitals), 1% to outpatient retail pharmacy settings and less than <0.5% to mail order/specialty pharmacy settings.[1] Based on these results, we examined the drug utilization data for only the U.S. non-federal hospitals. Data from mail-order/specialty and outpatient retail pharmacy settings were not included in this analysis.

2.1.2 Data Sources Used

The IMS Health Inpatient Healthcare Utilization System (IHCarUS) database was used to obtain the nationally estimated number of patients with a hospital discharge billing for Nitropress® (sodium nitroprusside) from inpatient and outpatient settings of U.S. non-federal hospitals, stratified by patient age groups (0-1 year, 2-11 years, 12-16 years , and 17 years and older) from November 2013 through July 2016, aggregated.

[1] IMS Health, IMS National Sales Perspectives™. November 2013 – July 2016. Extracted October 2016. File: NSP 2016-1586 Nitropress by Sup Ch, 10-21-2016.xlsx.

2.2 DRUG UTILIZATION DATA RESULTS

2.2.1 Number of Patients

Table 2.2.1: Nationally estimated number of patients with an inpatient or outpatient hospital discharge billing for Nitropress® (sodium nitroprusside) from U.S. non-federal hospitals†, stratified by patient age*, November 2013 to July 2016, aggregated

	November 2013 - July 2016	
	Patient Count‡ N	Share %
Nitropress Total Patients	**262,243**	***100.0%***
0-16 years	**14,808**	***5.6%***
0-1 year	**8,621**	***58.2%***
2-11 years	**4,119**	***27.8%***
12-16 years	**2,106**	***14.2%***
17 years and older	**247,435**	***94.4%***

Source: IMS Health, Inpatient HealthCare Utilization System. November 2013 - July 2016. Data extracted October 2016. File: IHCarUS 2016-1586 Nitroprusside by age, 10-21-2016

†Data from standalone pediatric and other specialty hospitals are not available.

***Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).**

‡Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix C for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	October 24, 2016
Time Period of Search	August 1, 1988* to October 24, 2016
Search Type	FBIS Quick Query
Product Names	Product name: Nitropress Product active ingredient: sodium nitroprusside, nitroprusside
Search Parameters	Age 0 to 16.99 years

* *US Approval date*

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* from August 1, 1988 to October 24, 2016 with Nitropress injection

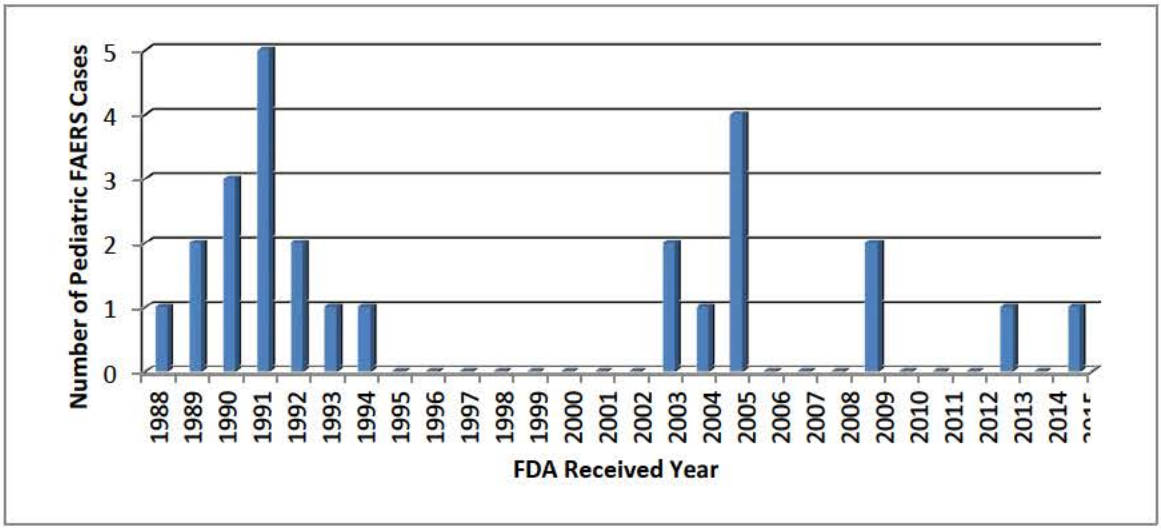
	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	116 (96)	80 (60)	16 (14)
Pediatrics (0 - <17 years)	26 (17)	26‡ (17)	12 (10)

* *May include duplicates and transplacental exposures, and have not been assessed for causality*

† *For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.*

‡ *See Figure 3.2.2*

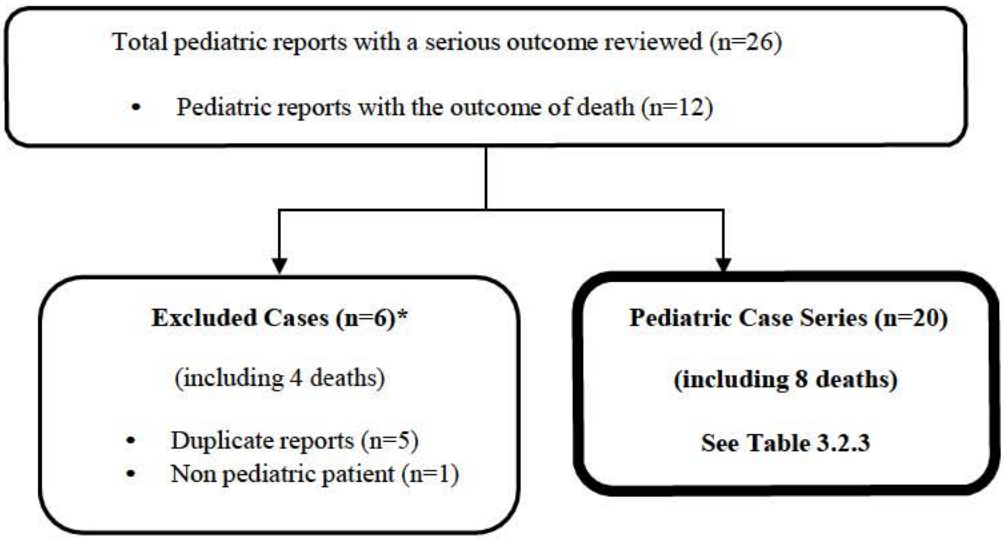
Figure 3.2.1 Serious Pediatric Reports for Nitropress injection, by year of FDA receipt August 1, 1988 to October 24, 2016 (n=26)



3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 26 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Nitropress injection



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

3.2.3 Characteristics of Pediatric Case Series

Appendix D lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Nitropress injection (n=20)

Age	0 - < 1 month	1
	1 month - <2 years	8
	2- < 6 years	7
	6- <12 years	1
	12- < 17 years	3
Sex (n=19)	Male	13
	Female	4
	Unknown	2
Country	United States	11
	Foreign	9
Dose rate µg/kg/min (n=12)	Median	7
	Range	2.2 to 16
Duration of therapy (n=6)	Median	2 days
	Range	36 hours to 4 days
Indication (n=15)	Hypertension (HTN)	7
	Postoperative HTN	5
	Congestive cardiomyopathy	2
	Adjunct to cardiac surgery	1
Serious outcome*	Death	8
	Life-threatening	2
	Hospitalized	2
	Disability	1
	Required intervention	4
	Other serious	3

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=8)

Eight cases reported an outcome of death with use of SNP. The median age was 17 months, ranging from 14 days to 5 years. Gender was specified in seven cases including males (5) and females (2). There were domestic (6) and (2) foreign reports. The median duration of therapy was two days. The median dose rate for SNP was 10 µg/kg per minute (range 8 to 16 µg/kg per minute). The eight fatal cases are described below and categorized by relevant events including cyanide toxicity and poisoning (3), cardiovascular disorders (2), lack of effect (2), and carboxyhemoglobinemia (1).

3.3.1 CYANIDE TOXICITY AND POISONING (N=3)

Three cases with an outcome of death reported cyanide toxicity or poisoning. All patients received surgery to correct coarctation of the aorta. The median age was 4 years, ranging from 3 months to 5

years. The patient was male in all cases. All cases were of a domestic origin. The median dose rate for SNP was 9 µg/ kg per minute (range 5 to 10 µg /kg per minute). Duration of therapy in all cases was unknown.

- **FDA 4794454, Mfr # BRV010002, US, Expedited, FDA Received 05/03/91***
  FDA 4807907, Mfr # H70478AO, US, Expedited, FDA Received 05/20/91 *
  A 5-year old male received SNP 8 µg/kg per minute following surgical correction of a congenital hypoplastic aortic arch. He developed a cyanide level of 8.7 mg/l and thiocyanate level of 25 mg/l twenty-four hours after esmolol 50 to 100 µg/kg per minute was added to the regimen (baseline values unavailable). Esmolol was discontinued. Thirty-six hours later, the cyanide and thiocyanate levels were 5.2 mg/l and 40 mg/l, respectively. Because of the high levels of cyanide and thiocyanate, SNP was discontinued. The following morning, arteriovenous oxygen difference (AVDO2) was 2.1 (normal >3). This was interpreted as cyanide toxicity and sodium nitrite and thiosulfate were administered. AVDO2 rose to normal, but dropped again so both drugs were re-administered. The next morning, the patient's cyanide and thiocyanate levels decreased to 0.21 mg/l and 21 mg/l, respectively. At this time, the patient had been off SNP for two full days but was brain dead. The next day the ventilator was removed and the patient died. The cause of death was determined by autopsy to be anoxic encephalopathy related to surgical manipulation.

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*Case 4794454 and 4807907 refer to the same patient.

- **FDA 4728840, Mfr # 890200573001, US, Non-Expedited, FDA Received 06/26/90**
  A 4-year old male had surgical repair of a coarctation of the aorta. At 1730, SNP was started post-operatively at 5-10 µg/kg per minute for BP control. The following morning at 0825, he developed lip smacking and fixed and dilated pupils followed by unresponsiveness to pain. At 1100, the electroencephalogram (EEG) was isoelectric and flat. SNP was discontinued in the afternoon after blood toxicology showed "toxic" levels of cyanide. The next morning at 0820 blood cyanide level was 1.1 mg/L (toxic >7.5) and thiocyanate level was 11.7 (normal 5-20). These levels were originally reported by the consumer to be "toxic." At 1504 the patient died. The cause of death was reported as cyanide poisoning. No anatomic cause of death was found on autopsy.

- **FDA 4607160, Mfr # 830200178001, US, Expedited, FDA Received 08/08/88**
  A 3-month old male underwent surgery to correct coarctation of the aorta. Three weeks later, he underwent corrective surgery where he remained hypoxic for an extended period of time. For the next three days, he received SNP and experienced cyanide poisoning. The patient developed restlessness, anxiety, agitation, increased salivation, cardiac arrhythmia, metabolic acidosis, muscle twitching, convulsions, eye deviation, and lack of efficacy to the drug. As a consequence, the patient suffered from severe mental retardation, seizure disorder, loss of peripheral vision and poor motor coordination. The patient subsequently died.

The first case reported toxic cyanide and thiocyanate levels due to a suspected drug interaction with SNP. The patient developed a blood cyanide and thiocyanate level of 8.7 mg/l and 25 mg/l, respectively 24 hours after esmolol 50-100 µg/kg per minute was added to SNP 8 µg/kg per minute. Cyanide levels decreased after esmolol withdrawal followed by a further decrease after SNP withdrawal. Of note, baseline cyanide levels were not reported prior to the addition of esmolol to SNP. At present, no known mechanism of a drug interaction between SNP and esmolol exists. The cause of death may be associated with cyanide-induced toxicity secondary to a drug interaction; however, assessment is confounded by complications of surgery.

In the second case, the patient received SNP at a dosage of 5-10 µg/kg per minute over a 12 hour period. The product labeling for SNP contains a Boxed Warning which states "Except when used briefly or at low (< 2 µg/kg per minute) infusion rates, SNP gives rise to important quantities of cyanide ion, which can reach toxic, potentially lethal levels. The usual dose rate is 0.5 to 10 µg/kg per minute, but infusion at the maximum dose rate should never last more than 10 minutes. If the blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of SNP should be terminated immediately." Although "toxic" cyanide levels were not reported in this patient, his clinical symptoms were consistent with cyanide poisoning. Due to temporal relationship and biologic plausibility, death was likely due to cyanide poisoning secondary to an overdose of SNP.

In the third case the relationship of death to SNP is unclear; however, death was likely attributable to the patient's underlying medical conditions.

The terms cyanide toxicity and cyanide poisoning are labeled as cyanide toxicity in the Boxed Warning, Warnings, Precautions, Adverse Reactions, and Overdosage section of SNP labeling.

3.3.2 CARDIOVASCULAR DISORDERS (N=2)

Two cases with an outcome of death reported cardiovascular adverse events including acquired ventricular septal defect, hypotension, and cardiac arrest.

- **FDA 4759821, Mfr # H39650AO, US, Expedited, FDA Received 12/03/90**
  A 10-month old female decompensated and died during surgical repair of a ventricular septal defect. The patient decompensated following SNP and dobutamine administration and improved after both drugs were withdrawn. Other medications were initiated but the patient deteriorated and died. Autopsy showed diffuse acute ischemic event of both ventricles before surgery, focal fibrosis and pericardial/myocardial hemorrhage of both ventricles.

- **FDA 4792370, Mfr # H70451AO, US, Expedited, FDA Received 05/02/91**
  A 2-year old child (gender unknown) with fetal alcohol syndrome experienced 30 seconds of hypotension after a bolus of contrast dye was mistakenly injected in a line infusing SNP. BP normalized within 60 seconds after the infusion was stopped. The incident occurred while the patient was in the CT scanner. The next day the patient died following a series of three cardiac arrests. The day prior a crib fell on the child and the child sustained a cardiac arrest requiring hospitalization for cardiac surgery. A CT scan was ordered as part of the work up in preparation for surgery.

The cause of death in both cases was associated with underlying disease. The term hypotension is labeled as decrease in BP in the Boxed Warning and hypotension under the Warnings, Precautions, Adverse Reactions and Overdosage section of SNP labeling. The unlabeled term acquired ventricular septal defect was confounded by underlying disease and concomitant drugs. Cardiac arrest was unlikely associated with SNP.

3.3.3 LACK OF EFFECT (N=2)

Two cases reported lack of effect with SNP use.

- **FDA 9166125, Mfr # PHHY2013BR025029, Brazil, Expedited, FDA Received 03/15/13**
  A 6-month old male developed severe intestinal involvement as initial manifestation of polyarteritis nodosa.[4] He experienced recurrent post prandial cramping and irritability. At the

age of 7 months, he was hospitalized due to severe arterial HTN, livedo reticularis, and acute ischemic stroke in the left hemisphere. He received hydralazine and SNP for the treatment of arterial HTN with no improvement. Despite treatment with pulse steroids, IV cyclophosphamide, IV immunoglobulin, and methotrexate, the patient died due to "acute orchitis and complication of acute abdominal with severe and diffuse intestinal necrosis and multiple intestinal perforations evidenced in laparotomy."

- **FDA 3942533, Mfr # WAES0305USA00849, US, Expedited, FDA Received 06/11/03**
  A 1-day-old male with congenital diaphragmatic hernia (CDH) developed a sustained elevation in BP following a change of extracorporeal membrane oxygenation (ECMO) tubing and infusion of IV dexamethasone.[5] After initiation with IV hydralazine, therapy was discontinued due to tachycardia and replaced with IV nicardipine. The BP was lowered within 24 hours. Following a second circuit change, nicardipine was discontinued due to bradycardia and SNP was started. Treatment with SNP failed to lower the BP therefore a triple combination of IV hydralazine, transdermal clonidine and SNP was started. BP was stable with the continued combination of hydralazine and clonidine. The patient eventually died due to an infection at the site of CDH repair.

The cause of death in both cases was associated with underlying disease. The unlabeled term drug ineffective was potentially confounded by ECMO placement and underlying disease.

3.3.4 CARBOXYHEMOGLOBINEMIA (N=1)

One case with an outcome of death reported carboxyhemoglobinemia due to a calculation error of SNP. This case was a foreign literature article from Spain.[6] Of note, three additional non-fatal cases of carboxyhemoglobinemia in this article are described under Section 3.4.

- **FDA 5936824, Mfr # 05H-144-0303691-00, Spain, Expedited, FDA Received 11/25/05**
  A 4-year old female developed carboxyhemoglobinemia associated with high doses of SNP after cardiac transplant. The patient was in cardiogenic shock due to dilated cardiomyopathy and received treatment with SNP 2 µg/kg per minute for eight days with a normal carboxyhemoglobin level. Heart transplant was performed and the patient was admitted to the pediatric intensive care unit (PICU) with ECMO and SNP at 2 µg/kg per minute without nitric oxide (NO). On arrival at the unit, the patient was in a coma with anisocoria and sedative drugs were withdrawn. Carboxyhemoglobin level was 1.9% (normal 0-2.3%).[7] NP was increased to 8 µg/kg per minute. However due to a calculation error, the patient received 16 µg/kg per minute for 12 hours, leading to an increase of carboxyhemoglobin level to 6.4%. SNP was withdrawn, but brain death occurred 16 hours after the operation. Care was withdrawn and the patient died.

In this case, the cause of death may be associated with carboxyhemoglobinemia secondary to a medication error; however, assessment is confounded by alternative etiologies including underlying disease or potential complications of surgery. An alternate etiology could be due to cyanide poisoning. Carboxyhemoglobinemia is an unlabeled term and appears to be associated with SNP based on temporal relationship and biologic plausibility. The most probable mechanism causing a rise in carboxyhemoglobin level is the induction of the HO-1enzyme by SNP.[6]

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=12)

Twelve non-fatal cases reported serious outcomes including hospitalization (2), life-threatening (2), disability (1), required intervention (4) and important medical event (3). The median age was two years

ranging from 1 month to 15 years. Gender was specified in ten cases including male (7) and female (3). There were foreign (7) and domestic (5) reports. The median duration of therapy was 58 hours. The median dose rate was 6.5 µg/kg per minute (range 2.2 to 8 µg/kg per minute).

3.4.1 CARBOXYHEMOGLOBINEMIA (N=4)

Four non-fatal cases reported carboxyhemoglobinemia with SNP use. The median age was 2 years ranging from 6 months to 14 years. Gender was specified including male (3) and female (1). There were foreign (3) and domestic (1) reports. Three cases originated from the literature article previously described under the summary of fatal pediatric adverse event cases (Section 3.3.4).[6]

- **FDA 5936786, Mfr # 05H-144-0303684-00, Spain, Expedited, FDA Received 11/25/05**
  A 6-month old male with dilated cardiomyopathy developed HTN 24 hours after heart transplantation and was treated with SNP. At the beginning of the treatment the patient received NO treatment at 10 parts per million (ppm) and carboxyhemoglobin levels were 1.2%. Over the following six days, the SNP dose was increased to 8 µg/kg per minute, which led to a rise in carboxyhemoglobin level to 5.5%. There were no signs of systemic toxicity or hemolysis. SNP was withdrawn and replaced by urapidil and diltiazem which led to a rapid drop in carboxyhemoglobin level. NO was maintained at the same concentration. At the time SNP was discontinued the carboxyhemoglobin level was 2%. Blood cyanide results were cyanide 0.2 µg/ml (normal <0.25 µg/ml) and thiocyanate 5.8 µg/ml (normal < 9 µg/ml). The carboxyhemoglobin level was 0.3% 24 hours following SNP withdrawal. The patient recovered with no sequelae.

- **FDA 5936796, Mfr # 05H-144-0303690-00, Spain, Expedited, FDA Received 11/25/05**
  A 2-year old male developed HTN and low cardiac output 24 hours after heart transplant and was treated with SNP doses up to 7 µg/kg per minute. After five days of treatment, an elevated carboxyhemoglobin level of 7.7% was detected (baseline values unavailable). There were no signs of hemolysis or systemic toxicity. The dose of SNP was reduced and replaced by urapidil, labetalol, and diltiazem which led to a drop in carboxyhemoglobin level. Treatment with NO was maintained at the same dose (6 ppm). When SNP was withdrawn cyanide levels were 0.5 µg/ml, thiocyanate 6.8 µg/ml, pH 7.44, PaO2 97, PaCO2 41.5, hemoglobin saturation 98%, oxyhemoglobin 97%, carboxyhemoglobin 2.4% and lactate 0.6 µmol/l with FIO2 of 0.65 and NO at 5 ppm. The carboxyhemoglobin level was 0% 24 hours after withdrawal of SNP.

- **FDA 5936779, Mfr # 05H-144-0303693-00, Spain, Expedited, FDA Received 11/25/05**
  A 2-year old male with dilated cardiomyopathy received SNP at 3 µg/kg per minute for twelve days. The pre-transplantation carboxyhemoglobin level was 1.2%. After heart transplant, SNP treatment was resumed at 6.5 µg/kg per minute and NO was administered at 10 ppm. An increase in carboxyhemoglobin to 3.7% was observed at 24 hours. Despite this rise, SNP was maintained at the same dose. There was a subsequent increase in carboxyhemoglobin level to 5.3% 24 hours later. However, there were no signs of systemic toxicity or hemolysis. The SNP was replaced by diltiazem while maintaining NO treatment at the same concentration. This led to a progressive reduction in carboxyhemoglobin level. The carboxyhemoglobin concentration was 0% 24 hours after withdrawal of the SNP. The patient recovered with no sequelae.

- **FDA 5164938, Mfr # H4003504AO, US, Non-Expedited*, FDA Received 09/13/94**
  A 14-year old female developed carboxyhemoglobinemia an unknown time after starting SNP (duration of therapy four days). Carboxyhemoglobinemia abated after stopping the drug. The

dose of SNP was "relatively high." Relevant labs included carboxyhemoglobin 16%, methemoglobin 0.9%, and thiocyanate 11 mg/ml. Her medical history was significant for renal failure. She received "numerous" concomitant medications.

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*Case 5164938 erroneously coded as a non-expedited report

Carboxyhemoglobinemia is an unlabeled term. The temporal relationship between SNP and carboxyhemoglobinemia, followed by complete recovery after SNP withdrawal is consistent with a drug-related effect.

3.4.2. CYANIDE TOXICITY AND POISONING (N=3)

Three cases reported events related to cyanide toxicity or cyanide poisoning. Age ranged from 1 month to 14 years with a median of 1.5 months. Gender was specified in two cases including male (1) and female (1). Two cases were foreign and in the published literature.[8,9] The third case reported cyanide poisoning due to an accidental overdose of SNP. The details of the overdose were unclear as the case was partially illegible.

- **FDA 4039011, Mfr # 03H-144-0241228-00, Spain, Expedited, FDA Received 11/21/03**
  A 1.5 month old infant (gender unknown) received SNP 1 µg/kg per minute for HTN following surgical correction of an atrioventricular canal and restricted aorta.[8] The dose was increased to 5.5 µg/kg per minute following an increase in BP. During this time, the patient experienced drowsiness (attributed to concurrent morphine infusion) and self- limiting arrhythmia. The infusion was maintained for 36 hours. Six hours after SNP withdrawal, the patient experienced seizures and cardiorespiratory arrest requiring resuscitation. Hemodynamic deterioration occurred requiring dopamine and noradrenaline administration. The patient developed symptoms consistent with hypoxic-ischemic encephalopathy. Cyanide toxicity was suspected and hydroxocobalamin was given which improved neurologic symptoms. Upon discharge, the patient presented minimal residual paresis in the upper right member with slight axial hypotonia. In retrospect, cyanide levels were paradoxically normal (they were taken eight hours after discontinuation of SNP but the half-life of cyanide is 18 to 60 hours) although an increase of methemoglobinemia to 3.8% was observed (normal < 2%).

- **FDA 6877079, Mfr # 2008PL000290, Ireland, Expedited, FDA Received 01/02/09**
  A 14-year old female developed cyanide poisoning following treatment with SNP for HTN after renal transplantation.[9] Four hours post-transplantation the patient's BP rose to 160/100. Treatment with furosemide was successful, however within six hours BP had risen to 210/130 and IV administration of labetalol was started. The dose of labetalol was increased to a maximum dose of 3 mg/kg without response. Thirty-four hours after transplantation when her BP was 161/111 labetalol was replaced with SNP 0.2 µg/kg per minute. At 53 hours after transplantation, her BP was 145/92 and SNP was being administered at 0.4 µg/kg per minute. A blood sample was obtained to evaluate cyanide levels. The patient experienced delayed graft function and acute tubular necrosis. Hemodialysis was initiated and the patient was maintained on SNP. Despite the addition of atenolol and 4-hourly boluses of furosemide, the patient required doses of 2.2 µg/kg per minute of SNP to maintain a BP of 150/100. A total dose of 200 mg (4.8 mg/kg) of SNP was administered in 56 hours following transplantation. On day four the cyanide level was 1.9 µg/ml. SNP was discontinued and FIO2 was increased to 100%. The cyanide level prior to SNP discontinuation was 3.1 µg/ml and treatment for cyanide toxicity was begun. Sodium nitrite was administered with sodium thiosulfate. Hemodialysis would remove thiocyanate from the bloodstream avoiding thiocyanate toxicity and facilitate

rapid clearance of cyanide. Within twelve hours cyanide levels dropped to 0.4 µg/ml; the patient improved clinically and was normotensive.

- **FDA 4796449, US, Direct, FDA Received 05/20/91**
  A 1-month-old male patient accidentally received a bolus of SNP solution after the infusion was shut off. The reporter stated the patient developed metabolic acidosis and decreased AVDO2 which was indicative of cyanide toxicity. The patient received SNP 0.5 µg/kg per minute for four days before discontinuation. The blood cyanide concentration was "468 mg/ml", while the thiocyanate level was normal. Upon administration of sodium nitrite and sodium thiosulfate, the problem resolved within four hours. Concomitant medications included ampicillin, gentamicin, and enalapril.

In the first case neurological and hemodynamic deterioration occurred after SNP withdrawal; however, due to the long half-life of cyanide a causal association between SNP and cyanide toxicity cannot be excluded. Moreover, an increase in methemoglobin was observed following SNP withdrawal. Neurologic symptoms improved following antidotal treatment with hydroxocobalamin. Manifestations of tissue hypoxia including hypoxic-ischemic encephalopathy are suggestive of cyanide poisoning.

In the second case, cessation of SNP and infusion of sodium thiosulfate together with sodium nitrite caused clinical improvement supporting the diagnosis of cyanide toxicity.

Due to the limited legibility of the third case, it is unclear how the patient was exposed to SNP after the infusion was shut off; however, signs and symptoms including metabolic acidosis and decrease in AVDO2 plus resolution of symptoms following treatment with sodium nitrite and sodium thiosulfate are consistent with cyanide poisoning due to an accidental overdose.

As described above, cyanide toxicity and cyanide poisoning are labeled in the Boxed Warning and under the Warnings, Precautions, Adverse Reactions, and Overdosage section of SNP labeling.

3.4.3 CARDIOVASCULAR DISORDERS (N=2)

Two cases reported cardiovascular adverse events including increase in BP, cardiac arrest, vasodilatation, and ventricular tachycardia. There was one domestic and one foreign report. One case is described in the published literature.[10]

- **FDA 4171313, Mfr # 04H-163-0254369-00, US, Expedited, FDA Received 04/20/04**
  A 4-month old male underwent repair of a patent ductus arteriosus and received SNP (1-4 µg/kg per minute intermittently) towards the end of surgery for BP control. His medical history was significant for Tetralogy of Fallot. Concomitant medications included fentanyl and sevoflurane. The patient's BP was 50/30 when the infusion was started. His BP increased to 80/35 and the infusion was stopped. While transferring the patient to the PICU, the BP increased to 108/63. SNP was restarted and the BP began increasing further from 109/63 to 156/78. The patient was treated with esmolol and the BP decreased to 134/73 and then to 90/54 after one hour of esmolol. When SNP was weaned the BP stabilized and the patient recovered.

- **FDA 7065834, Mfr # 2009 EK001895, Thailand, Expedited, FDA Received 07/20/09**
  A 4- month old patient (gender unknown) with underlying heart disease received an unknown dose of IV nicardipine and nitroprusside.[10] The patient experienced cardiac arrest requiring resuscitation while undergoing a patent ductus arteriosus (PDA) ligation and coarctectomy. The initial rhythm at the time of resuscitation was ventricular tachycardia. The authors

believed that the cause of the cardiac arrest was medication related and possibly attributed to vasodilatation due to the combined use of nicardipine and nitroprusside. The patient recovered.

The terms cardiac arrest, vasodilatation, and ventricular tachycardia are unlabeled terms and the cases reporting those terms were confounded by concomitant drugs and underlying disease. Increase in blood pressure is an unlabeled term. Although temporal relationship and positive dechallenge suggest a causal relationship, the case reporting the increased BP is potentially confounded by intermittent, rather than continuous, administration of SNP.

3.4.4 LACK OF EFFECT (N=2)

Two cases reported a lack of effect with SNP use.

- **FDA 4876795, Mfr # 920200679001, US, Expedited, FDA Received 05/14/92**
  A 15-year old male underwent surgery for repair of a coarctation of the aorta. SNP was used for post-operative BP control. The BP reached an apex of 235 systolic. SNP "did not work" and other unknown drugs were used. The patient suffered a breakdown of the aorta and became a paraplegic.

- **FDA 4822553, Mfr # 891021002F, US, Non-expedited*, FDA Received 10/01/91**
  An 8-year old male did not experience a therapeutic response to the administration of SNP at a rate of 7 µg/kg per minute for HTN.

*Case 4822553 erroneously coded as a non-expedited report

Drug ineffective is an unlabeled term. Both cases do not provide enough information for causality assessment.

3.4.5 EYE DISORDERS (N=1)

One foreign publication reported the occurrence of visual impairment and transient blindness following SNP administration. The authors attribute transient blindness to an overdose of SNP.[11]

- **FDA 5014443, Mfr # 930201300001, Turkey, Expedited, FDA Received 07/27/93**
  A 4-year-old female experienced temporary blindness due to SNP intoxication in the postoperative period after correction of coarctation of the aorta.[11] On post-operative day 1, the patient's BP was 180/90 and SNP was started. Propranolol 1 mg/kg was added on the second day. Because BP could not be controlled, SNP was continued to keep systolic BP under 160. During the 60th hour of SNP infusion, blindness was observed while the BP was 100/70. The patient's ophthalmological and neurological examinations were within normal limits except for pupillary dilatation and blindness. Serum creatinine (SCr), electrolyte, blood gases, and CT scans were within normal limits. It was found that the patient received 234 mg of SNP in 60 hours "(5.4 µm/kg per minute)" by mistake. The drug was stopped immediately. After four hours, improvement in her vision was noted and after eight hours total vision was regained. SNP was not readministered and the patient's BP was controlled with 1 mg/kg of propranolol. The patient was discharged on postoperative day 10.

In this case, the onset of temporary blindness occurred after 60 hours of infusion with SNP. The event resolved following SNP withdrawal; however, it was unclear whether blindness was due to cyanide

poisoning or an alternative mechanism. The patient's SCr, electrolyte, blood gases and CT scans were normal. No cyanide levels or co-oximetry parameters were reported. Additionally, the dose rate of SNP in the report was unclear. Although the mechanism of ocular toxicity was unknown, the presence of a temporal relationship and positive dechallenge support a possible causal relationship between SNP and visual impairment. Visual impairment and transient blindness are unlabeled terms.

4 DISCUSSION

An analysis of drug utilization data showed that pediatric patients aged 0-16 years old accounted for 5.6% (14,800 patients) of total patients with a hospital discharge billing for Nitropress® from U.S. non-federal hospitals from November 2013 through July 2016. Of the Nitropress® use among pediatric patients 16 years or younger, the largest proportion of use was seen among children younger than one year old. Although there appears to be use of Nitropress® in pediatric patients, the data cannot be validated due to the lack of access to patient medical records. Of note, our analyses focused on only the inpatient and outpatient emergency department (ED) non-federal hospital settings where the largest proportion of Nitropress® sales was distributed. Our analyses do not include data from federal hospitals (including VA facilities) and other specialty hospitals (including children's hospitals and other standalone specialty hospitals). Therefore, the overall use of Nitropress® in pediatric patients in our hospital data may be underestimated as we suspect that some pediatric patients using Nitropress® are treated in standalone pediatric and specialty hospitals.

A search of the FAERS database identified twenty pediatric cases received by the FDA from August 1, 1988 to October 24, 2016. Notably, no domestic or foreign cases have been received since pediatric labeling approval on November 22, 2013. In addition, no domestic pediatric reports for SNP have been received in the FAERS database since 2004. Of the twenty cases, eight deaths were reported. The eight deaths included cyanide toxicity and poisoning (3), cardiovascular adverse events (2), lack of effect (2), and carboxyhemoglobinemia (1). In seven cases death was confounded by underlying disease or complications of surgery. In the other case death was associated with cyanide poisoning due to an overdose of SNP.

The twelve non-fatal pediatric cases included carboxyhemoglobinemia (4), cyanide toxicity and poisoning (3), cardiovascular disorders (2), lack of effect (2), and eye disorders (1). Three cases reported cyanide toxicity and poisoning, events that were well described in labeling. Two cases contained insufficient information to assess drug causality. One case was confounded by underlying disease and concomitant drugs. Another case was confounded by the intermittent administration of SNP. Five cases reported a possible association between SNP and carboxyhemoglobinemia (4) and visual impairment (1) which are described in further detail below.

Five cases reported elevated carboxyhemoglobin levels in association with SNP. The median age was 2 years (range 6 months to 14 years). Gender was specified in five cases including males (3) and females (2). There were foreign (4) and domestic (1) reports. The median dose rate was 7.5 µg/kg per minute (range 6.5 to 16 µg/kg per minute). One case reported a duration of therapy of four days. The median carboxyhemoglobin level prior to SNP administration was 1.2 % (range 1.2 to 1.9%). The median carboxyhemoglobin level during SNP treatment was 6% (range 5.3 to 7.7%). The median time to onset was 3.5 days (range 12 hours to 6 days). All cases reported a positive dechallenge upon SNP withdrawal. Four of five cases originated from a foreign publication that reported carboxyhemoglobinemia related to high doses of SNP after cardiac transplant in pediatric patients. One of these cases was associated with a fatal outcome. A female patient experienced elevated carboxyhemoglobin after receiving a double dose (16 versus 8 µg/kg per minute) of SNP following cardiac transplantation. Nitroprusside was withdrawn, however, brain death was confirmed several hours later. It was unclear if carboxyhemoglobinemia contributed to the fatal outcome or if the event was a coincidental finding, however, assessment was

confounded by underlying disease and complications of surgery. The fifth case reported carboxyhemoglobinemia during nitroprusside therapy which abated following drug cessation, but contained limited clinical details. The close temporal relationship and positive dechallenge reported in all cases support a causal relationship between SNP and carboxyhemoglobinemia. Moreover, the authors provide evidence to support a plausible mechanism for carboxyhemoglobinemia. HO is the initial enzyme in heme metabolism. It opens the heme ring (on the hemoglobin molecule) releasing equimolar quantities of biliverdin, iron and carbon monoxide. The inducible isoform of HO, termed HO-1 is induced by its own substrate, heme, and by a variety of stress-associated agents including heavy metals, hyperthermia, hyperoxia and nitric oxide, producing carbon monoxide.[6] Several experimental studies have demonstrated that NO donors, such as SNP can induce HO-1 and produce carbon monoxide by break down of heme molecules.[12, 13, 14] Three cases reported concurrent use of NO gas during SNP therapy, however the increase in carboxyhemoglobin resolved after SNP withdrawal, despite maintaining NO treatment at the same concentration. Carbon monoxide poisoning symptoms tend to correlate well with the patient's peak blood carboxyhemoglobin levels.[15] The clinical findings of carbon monoxide poisoning are highly variable and largely nonspecific. Moderately or mildly carbon monoxide-intoxicated patients present with constitutional symptoms including headache, malaise, nausea, dizziness and loss of consciousness. Severe carbon monoxide toxicity can produce neurologic symptoms such as seizures, syncope, or coma and also cardiovascular and metabolic manifestations such as myocardial ischemia, ventricular arrhythmias, pulmonary edema and profound lactic acidosis.[16] None of the patients in our series exhibited signs of systemic toxicity or hemolysis. Notably no additional cases reporting carboxyhemoglobinemia in pediatric or adult patients were identified in FAERS or the literature.

DPV identified another possible signal for visual impairment in association with SNP. One case reported temporary blindness in a 4-year old female after receiving a nitroprusside infusion for 60 hours. The effect resolved after discontinuation of the nitroprusside. The authors postulate that transient blindness was due to the toxic effect of the drug because the dose given to the patient was higher than the recommended maximum; however, the documented infusion rate of nitroprusside in the report was unclear. The patient's SCr, electrolytes, blood gases, and CT scans were within normal limits. Other laboratory parameters including red blood cell cyanide concentrations were unavailable. Although the mechanism of ocular toxicity was unclear, the presence of a temporal relationship and positive dechallenge with discontinuation of nitroprusside, suggest a possible association between SNP and visual impairment (blindness). A search in the FAERS database for additional adult or pediatric cases yielded one case reporting blindness in a 24-year old female after receiving a nitroprusside infusion for one day. The patient recovered. No additional information was provided. This report, originating from Iceland, was first received by the drug manufacturer in 1978 then submitted to the FDA in 1995. Based on limited evidence of an association between visual impairment and SNP in the FAERS database, DPV will continue to monitor adverse events related to visual impairment reported with SNP.

5 CONCLUSION

We reviewed twenty pediatric cases reported with SNP use including eight deaths and twelve non-fatal post marketing cases. Seven deaths were confounded by alternative etiologies, not directly attributable to SNP including underlying disease or complications of surgery. One death was associated with cyanide poisoning due to an overdose of SNP. Of the twelve non-fatal serious outcome cases, DPV identified a safety signal for carboxyhemoglobinemia in association with SNP.

6 RECOMMENDATIONS

Based on the identification of elevated carboxyhemoglobin associated with SNP, DPV recommends the addition of carboxyhemoglobinemia to the Adverse Reactions section of labeling.

DPV will continue to monitor adverse events associated with SNP.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. PEDIATRIC PRODUCT LABELING

CLINICAL PHARMACOLOGY

Pediatric: The effects of sodium nitroprusside to induce hypotension were evaluated in two trials in pediatric patients less than 17 years of age. In both trials, at least 50% of the patients were pre-pubertal, and about 50% of these pre-pubertal patients were less than 2 years of age, including 4 neonates. The primary efficacy variable was the mean arterial pressure (MAP).

There were 203 pediatric patients in a parallel, dose-ranging study (Study 1). During the 30 minute blinded phase, patients were randomized 1:1:1:1 to receive sodium nitroprusside 0.3, 1, 2, or 3 µg/kg/min. The infusion rate was increased step-wise to the target dose rate (i.e., 1/3 of the full rate for the first 5 minutes, 2/3 of the full rate for the next 5 minutes, and the full dose rate for the last 20 minutes). If the investigator believed that an increase to the next higher dose rate would be unsafe, the infusion remained at the current rate for the remainder of the blinded infusion. Since there was no placebo group, the change from baseline likely overestimates the true magnitude of blood pressure effect. Nevertheless, MAP decreased 11 to 20 mmHg from baseline across the four doses (Table 1).

There were 63 pediatric patients in a long-term infusion trial (Study 2). During an open-label phase (12 to 24 hours), sodium nitroprusside was started at ≤0.3 µg/kg/min and titrated according to the BP response.

Patients were then randomized to placebo or to continuing the same dose of sodium nitroprusside. The average MAP was greater in the control group than in the sodium nitroprusside group for every time point during the blinded withdrawal phase, demonstrating that sodium nitroprusside is effective for at least 12 hours.

In both studies, similar effects on MAP were seen in all age groups.

Table 1: Change from Baseline in MAP (mmHg) After 30 Minutes Double-Blind Infusion (Study 1)

	Treatment			
Endpoint	0.3 µg/kg/min (N = 50)	1 µg/kg/min (N = 49)	2 µg/kg/min (N = 53)	3 µg/kg/min (N = 51)
Baseline	76 ± 11	77 ± 15	74 ± 12	76 ± 12
30 Min	65 ± 13	60 ± 15	54 ± 12	60 ± 18
Change from Baseline	-11 ± 16 (-15, -6.5)	-17 ± 13 (-21, -13)	-20 ± 16 (-24, -16)	-17 ± 19 (-22, -11)
Mean ± SD (95% CI)				

DOSAGE AND ADMINISTRATION

Avoidance of excessive hypotension: While the average effective rate in adult and pediatric patients is about 3 mcg/kg/min, some patients will become dangerously hypotensive when they receive NITROPRESS at this rate. Infusion of sodium nitroprusside should therefore be started at a very low rate (0.3 mcg/kg/min), with upward titration every few minutes until the desired effect is achieved or the maximum recommended infusion rate (10 mcg/kg/min) has been reached.

Because sodium nitroprusside's hypotensive effect is very rapid in onset and in dissipation, small variations in infusion rate can lead to wide, undesirable variations in blood pressure. Since there is inherent variation in blood pressure measurement, confirm the drug effect at any infusion rate after an additional 5 minutes before titrating to a higher dose to achieve the desired blood pressure. Sodium nitroprusside side should not be infused through ordinary I.V. apparatus, regulated only by gravity and mechanical clamps . Only an infusion pump, preferably a volumetric pump, should be used.

Because sodium nitroprusside can induce essentially unlimited blood-pressure reduction, the blood pressure of a patient receiving this drug must be continuously monitored, using either a continually reinflated sphygmomanometer or (preferably) an intra-arterial pressure sensor. Special caution should be used in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

When sodium nitroprusside is used in the treatment of acute congestive heart failure, titration of the infusion rate must be guided by the results of invasive hemodynamic monitoring with simultaneous monitoring of urine output. Sodium nitroprusside can be titrated by increasing the infusion rate until:

- measured cardiac output is no longer increasing,
- systemic blood pressure cannot be further reduced without compromising the perfusion of vital organs, or
- the maximum recommended infusion rate has been reached, whichever comes earliest. Specific hemodynamic goals must be tailored to the clinical situation, but improvements in cardiac output and left ventricular filling pressure must not be purchased at the price of undue hypotension and consequent hypoperfusion.

Table 2 below shows the infusion rates corresponding to the recommended initial and maximal doses (0.3 mcg/kg/min and 10 mcg/kg/min, respectively) for both adult and pediatric patients of various weights. This infusion rate may be lower than indicated in the table for patients less than 10 kg. Note that when the concentration used in a given patient is changed, the tubing is still filled with a solution at the previous concentration.

Table 2: Infusion Rates (mL/hour) to Achieve Initial (0.3 mcg/kg/min) and Maximal (10 mcg/kg/min) Dosing of NITROPRESS

Volume		250 mL		500 mL		1000 mL	
NITROPRESS concentration		50 mg 200 mcg/mL		50 mg 100 mcg/mL		50 mg 50 mcg/mL	
pt weight							
kg	**lbs**	**init**	**max**	**init**	**max**	**init**	**max**
10	22	1	30	2	60	4	120
20	44	2	60	4	120	7	240
30	66	3	90	5	180	11	360
40	88	4	120	7	240	14	480
50	110	5	150	9	300	18	600
60	132	5	180	11	360	22	720
70	154	6	210	13	420	25	840
80	176	7	240	14	480	29	960
90	198	8	270	16	540	32	1080
100	220	9	300	18	600	36	1200

Avoidance of cyanide toxicity: As described in CLINICAL PHARMACOLOGY above, when more than 500 mcg/kg of sodium nitroprusside is administered faster than 2 mcg/kg/min, cyanide is generated faster than the unaided patient can eliminate it. Administration of sodium thiosulfate has been shown to increase the rate of cyanide processing, reducing the hazard of cyanide toxicity. Although toxic reactions to sodium thiosulfate have not been reported, the co-infusion regimen has not been extensively studied, and it cannot be recommended without reservation. In one study, sodium thiosulfate appeared to potentiate the hypotensive effects of sodium nitroprusside.

Co-infusions of sodium thiosulfate have been administered at rates of 5-10 times that of sodium nitroprusside. Care must be taken to avoid the indiscriminate use of prolonged or high doses of sodium nitroprusside with sodium thiosulfate as this may result in thiocyanate toxicity and hypovolemia. Incautious administration of sodium nitroprusside must still be avoided, and all of the precautions concerning sodium nitroprusside administration must still be observed.

Consideration of methemoglobinemia and thiocyanate toxicity: Rare patients receiving more than 10 mg/kg of sodium nitroprusside will develop methemoglobinemia; other patients, especially those with impaired renal function, will predictably develop thiocyanate toxicity after prolonged, rapid infusions. In accordance with the descriptions in ADVERSE REACTIONS above, patients with suggestive findings should be tested for these toxicities

8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Inpatient HealthCare Utilization System (IHCarUS)

The Inpatient HealthCare Utilization System (IHCarUS) provides hospital inpatient and outpatient encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from 2002, is collected weekly and monthly and is available 25-30 days after the end of each monthly period. This robust data set includes >700 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include over 13 million patients and 60 million visits per year projected to approximately 37 million inpatient visits and 560 million outpatient (including Emergency Department) visits per year, representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. IMS' datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

The IMS Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

8.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS

FAERS CASE NUMBER	FAERS VERSION NUMBER	MANUFACTURER CONTROL NUMBER
4794454*	1	BRV010002
4807907*	1	H70478AO
4728840	1	890200573001
4607160	1	830200178001
4759821	1	H39650AO
4792370	1	H70451AO
9166125	1	PHHY2013BR025029
3942533	2	WAES 0305USA00849
5936824	1	05H-144-0303691-00
4039011	1	03H-144-0241228-00
4171313	1	04H-163-0254369-00
4796449	1	
4822553	1	891021002F
4876795	1	920200679001
5014443	1	930201300001
5164938	1	H4003504AO
5936779	1	05H-144-0303693-00
5936786	1	05H-144-0303684-00
5936796	1	05H-144-0303690-00
6877079	1	2008PL000290
7065834	1	2009EK0001895

*Case 4794454 and 4807907 refer to the same patient

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/s/

AMY I CHEN
01/10/2017

KUSUM S MISTRY
01/11/2017
The drug use data in this review has been cleared by the database vendors.

MONICA MUNOZ
01/11/2017

JUSTIN A MATHEW
01/11/2017

GRACE CHAI
01/11/2017

CINDY M KORTEPETER
01/11/2017