NDA	21983
SD#	199
Sequence Number	0010
Supplement number	23
Sponsor	MERIDIAN MEDICAL TECHNOLOGIES INC
Drug	DUODOTE® (atropine and pralidoxime chloride injection) Auto-Injector
Proposed Indication	Treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides in adults and children weighing >41 kg.
Material Submitted	Prior Approval Supplement
Correspondence Date	12/7/16
Date Received	12/7/16
Date Review Completed	8/30/17
Reviewer	Steven Dinsmore, DO

1. Introduction

DuoDote was approved on 9/28/06 for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides. The approval letter established postmarketing requirement (PMR) 1300-1 under the Pediatric Research Equity Act (PREA) with a deferred submission of pediatric studies until 9/30/09.

1300-1: *Deferred pediatric study under PREA for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides in pediatric patients ages birth to less than 17 years.*

A "Prior Approval" labeling supplemental new drug application, supplement 09, was submitted on 10/14/09 to provide for conversion to the physician's labeling rule (PLR) format. A CR (complete response) letter was issued in response to supplement 09 on 12/11/13. Meridian Medical Technologies, Inc. (the sponsor) has submitted a Prior Approval Supplement 023 to NDA 021983 DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector. This supplement contains package insert (PI) labeling in PLR format in follow up to the CR letter and proposes the use of the currently approved auto-injector in pediatric patients weighing >41 kg to fulfill, in part, the original pediatric postmarketing requirement (1300-1) for this product. The sponsor proposes (b) (4)

The sponsor references the following New Drug Applications (NDAs) in support of the efficacy and safety of proposed atropine and pralidoxime chloride doses for the DuoDote Auto-Injector for use in children >41 kg:

- MMT's pediatric AtroPen® NDA 017106/S028
- Baxter's PROTOPAM NDA 14134/ (b) (4)

In the General Advice/Deferral Extension Granted letter of July 9, 2013 the FDA advised that pediatric dosing information for both atropine and pralidoxime for use in DuoDote Auto-Injector labeling "is already available for the labeling of the dosage of both products…", i.e., from MMT's AtroPen® and Baxter's PROTOPAM labeling. These two referenced NDAs, in conjunction with FDA's pediatric intramuscular (IM) pralidoxime dosing analysis of July 9, 2013, provide support of efficacy for the DuoDote Auto-Injector for use in the >41 kg pediatric subpopulation.

The following review will document the pediatric development of supporting products AtroPen and Protopam.

2. Review Strategy

Atropine and pralidoxime are the components of DuoDote. These are the active ingredients of the referenced drugs AtroPen and Protopam. Both of these products are labeled for the pediatric age group >41kg. The proposed pediatric labeling in the supplement is supported by this labeling. The review will document the supporting pediatric development of AtroPen and Protopam. In addition, an updated safety review relevant to the pediatric age range for DuoDote and the atropine and pralidoxime components will be performed.

3. Pediatric Development History
    a. AtroPen Autoinjector (NDA 17106)

The AtroPen autoinjector was approved on 5/15/1973 for the management of patients who have suffered a toxic exposure to organophosphorus or carbamate insecticides[1]. It is uncertain when the expanded indication to include organophosphorus nerve agents was added. DARRTS and PharmaPendium[2] have a gap in available package inserts from supplement 05 in 1986 to supplement 028 on December 27, 2002. The Division Acknowledgement of supplement 028 states that "*The supplemental application provides information and labeling to support use of AtroPen® autoinjectors in both pediatric and adult civilian populations. Additionally, it provides data to support the manufacture of 0.5 and 1 mg AtroPen® autoinjectors for younger pediatric populations*." The CMC filing review for supplement 028 confirms this supplement acknowledgement with a statement that "*Meridian Medical Technologies (MMT) has manufactured* (b) (4) Thus supplement 28 expands the treatment population to the pediatric age range and adds the 0.5 and 1.0 mg atropine autoinjector dose. Supplement 28 was approved on Jun 19, 2003. See Appendix 1, AtroPen Pediatric Dosing and Administration. At some point between these two supplements the indication for AtroPen was expanded from "organophosphorus or carbamate insecticides" to "treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides"[4] although examination of the available databases do not reveal accessible written content for the interval between supplements 06 and supplement 027.

[1] Copy of original 1973 package insert is included in Supplement 05 from 7/16/1986.
[2] Commercial, publically available database by ELSEVIER, Copyright © 2017 RELX Intellectual Properties SA. All rights reserved
[3] W. Janusz Rzeszotarski, Ph.D. Chemistry Review, supplement 28, 3/17/03.
[4] Kevin Prohaska, DO, Labeling Review, supplement 28, 4/17/03.

b. Protopam (NDA 14134)

The NDA was approved in 1964 for the use of 2-PAM in adults and children. The review of the sponsor's response to approvable letter issued for supplement 22, on 5/2/01 provides a brief history of pediatric labeling for this product as follows: "*The original product label included an indication in children however this was removed in 1995 at the request of the Agency (FDA letter dated December 21, 1994). At issue was the statement "safety and effectiveness in children has not been established" which was added to the label in 1991 by the sponsor in order to comply with updated Content and Format Guidelines. It was felt by the Agency that the statement was contradictory to the advice on dosage for children found in the Dosage and Administration Section of the original label*."[5]

The above statement identifies the beginning the complex path of pediatric labeling for Protopam. As noted, the original product approval in 1964 contained language for the use of Protopam in adults and children. In the Division Director action memo for approval of supplement 22 on August 29, 2010 it is noted that "*The original application contained dosing recommendations in both adult and pediatric patients that did not derive from adequate and well-controlled clinical trials, as they would have been essentially impossible to conduct. Presumably, these dosing recommendations came, in part, from the results of animal studies*." Subsequent to the 1964 approval there were labeling format changes introduced that resulted in a 1991 addition to the label of the phrase "Safety *and effectiveness in children have not been established*". The resulting label which concurrently provided dosing recommendations for pediatric patients with the statement "*Safety and effectiveness in children have not been established*" was internally inconsistent.

After development of the above noted label that had internally contradictory properties, the Agency received several reports of significant adverse events in pediatric patients, including a case of methemoglobinemia and a case of laryngospasm in a 14 month old girl that appeared to recur on rechallenge. The methemoglobinemia resolved with continued treatment with 2-PAM while the outcome in the report of laryngospasm resolved with supplemental oxygen. In response, on December 21, 1994 the Agency issued a letter to the sponsor requesting removal of the pediatric dosing recommendations. The sponsor submitted the requested supplement on 9/13/95, and it was approved on 12/11/95. On November 17, 1995, the sponsor submitted supplement 022 to reintroduce pediatric dosing recommendations into the labeling for Protopam.

The Division Director Action memo states that in the interval from 1995 until 2010 supplement 22 was "*reviewed by numerous reviewers, including reviewers in the Division of Neuropharmacological Drug Products (now the Division of Neurology Products), the Office of Counter-terrorism and Pediatric Drug Development, the Pediatric and Maternal Health Staff, and the Office of Clinical Pharmacology*." As a result of this work the Division determined acceptable pediatric dosing recommendations for Protopam. These were incorporated into labeling at the approval of supplement 022. See pediatric dosing; Appendix 2, Protopam Pediatric Dosing and Administration.

c. DuoDote

[5] Kevin Prohaska, DO, Clinical Review of Supplement 22 "sponsors response to an Approvable Letter dated May 2, 2001."

On September 17, 2009 the sponsor [redacted] The Division responded on November 21, 2012 with a request for resubmission of arguments with the following verbatim entry "*if you resubmit your arguments with the Protopam approval in mind and more fully explain the challenges behind developing a pediatric drug delivery device*."

The statement concerning Protopam is in reference to the approval on September 8, 2010 of pediatric labeling for Protopam. This Protopam labeling includes recommendations for pediatric intramuscular dosing in patient ≥ 40kg. In response to the Division's 11/21/2012 request, on December 20, 2012 Meridian submitted a request for deferral extension based on the fact that no further action to develop pediatric dosages was taken while awaiting a decision from FDA regarding the September 17, 2009 [redacted]. On April 5, 2013 the sponsor submitted a proposal for [redacted]. On July 9, 2013 the Division responded by granting the deferral extension for PMR 1300-1 "*because you have made good faith efforts to conduct the required pediatric studies*." The new, deferred, final report submission date was March 30, 2015.

On December 22, 2014 the sponsor submitted [redacted] This plan included use of the adult DuoDote product for children over 10 years of age (>41kg) [redacted] The plan did include submission of information supporting the use of the approved DuoDote product in Children >41kg by March 30, 2015. [redacted]

On December 7, 2016 the sponsor submitted this sNDA supplement proposing the use of the currently approved auto-injector for pediatric patients weighing >41 kg. The proposed labeling will support the expanded patient population of adults and children >41 kg.

4. Clinical Pharmacology Review Conclusion on Dosing

The Clinical Pharmacology review team has examined the sponsor's support for pediatric dosing of patient's with weight > 41kg for atropine and pralidoxime. The Office of Clinical Pharmacolgy finds the application acceptable and recommends approval of the proposed dosing regimen for DuoDote in >41kg pediatric population.

5. Safety

<u>Overview</u>

As discussed in the previous sections both AtroPen and Protopam have labeling to support treatment of children with a weight >41 Kg. In the case of pralidoxime this labeling was supported with extensive examination of the two reports that identified the potential for serious risk of laryngospasm and methemoglobinemia. In his action memo for the use of Protopam in pediatric patients Dr. Katz states the following: "*Further, even if the case of laryngospasm could unequivocally be attributed to treatment with 2-PAM (and this is highly questionable), given the (often) life-threatening nature of organophosphate poisoning, this risk is acceptable. In this regard, two points are worth making. The doses recommended here have been routinely given to many pediatric patients and have been very well tolerated (I am aware of no other cases of laryngospasm). Further, many of these patients will be observed in a hospital setting where laryngospasm, should it occur, could be rapidly assessed and treated.*"[6]

a. Injection volume

The total injection volume delivered by a dose of DuoDote is 2.7ml. The sponsor has not identify literature that indicates definitive age based limits to injection volume, however, two FDA approved drugs are identified for use in pediatrics with injections volumes greater than 2.7ml.

- Maxipime (cefipime) United States Package Insert (USPI) recommends a 1g IM dose (3.6 mL after reconstitution for IM injection) for mild/moderate uncomplicated urinary tract infections in a 40 kg pediatric patient. This dose is to be given twice a day for 7-10 days.

- Ivanz (ertapenem) USPI recommends a 1g IM dose (3.2 mL after reconstitution for IM administration) for a variety of indicated infections in a 13-year-old adolescent. This dose is to be given twice a day for a variable number of days, depending on the infection. The normal weight range for a 13-year-old female (10th to 90th percentile) is 37 kg to 61 kg (Centers for Disease Control and Prevention; NOV 2000) and thus includes 41 kg.

These examples of currently labeled drugs that require repeated injections of >3 ml volume in the relevant pediatric cohort over a period of several days provides support for the safety of the DuoDote 2.7ml injection volume as labeled for three injections.

b. Safety Update

AtroPen

FAERS

Atropine has a wide spectrum of uses in several serious circumstances of medical intervention including premedication for anesthetic procedure, advanced cardiac life support procedures, bradyarrymthia, AV nodal heart block, intraoperative treatment of excess vagal stimulation, congenital hypertrophic pyloric stenosis in addition to a more extensive list of less serious circumstances. Atropine is also commonly administered with other medications, often multiple medications. This background profile of conditions where atropine is employed tends to confound the ability to determine causality of adverse events that are identified in the FAERS database.

[6] Russel Katz MD, Action Memo for NDA 14-134/S-022, for the use of Protopam Chloride (pralidoxime chloride) in pediatric patients with organophosphate poisoning. August 29, 2010.

Empirica Signal is used to capture adverse event reports from patients <17 years of age from the entire atropine FAERS database. The search scheme used "generic(S)" for the "run name" with generic name = "Atropine". MedDRA hierarchy level is PT with a blank field to capture all preferred terms. This search strategy yielded 486 reports.. From among these reports were 354 individual preferred terms, 209 high level terms (HLT) and 113 high level group terms (HLGT). The maximum frequency from among the group of 486 reports for the PT's was 0.8%, HLT's 2.5% and HLGT's 5.4% where the terms anesthetic complication, breathing abnormalities and Cardiac arrhythmias were the most frequently identified terms for each MedDRA grouping respectively. The system organ class (SOC) terms are also examined. This examination reveals 24 SOC terms are present with investigations seen to be the most frequent at 11.1%.

The profile of HLGT's with a frequency >2% is shown in Table 3. Overall, this array of terms is consistent both with the circumstances and medical conditions where atropine is involved in treatment (see Table 4) as well as the known physiologic effects of atropine.

An examination of the more recent body of FAERS adverse event reports from the year 2010 to present is examined using the MERCADO quick search Drug Safety Analytics. Search Fields are Initial FDA Received date "01/01/2010 – 8/29/2017", Product Name "atropine", Drug Role "suspect", Patient age Group <1 year to <17 years. This search strategy yields 89 reports. From among these reports 79 are of foreign origin and 10 from the US. The most common reason for use was "not reported". All terms "reason for use" are shown in Table 4. These terms reveal the frequency of atropine use for surgical and anesthetic procedures, eye examination, and treatment of strabismus, amblyopia, and cardiovascular events.

The preferred terms identified from among the <17 age cohort is shown in Figure 1. This profile of terms again is largely difficult to differentiate from the medical conditions where atropine is employed for treatment. An exception to this concept is the preferred term "drug reaction with eosinophilia and systemic symptoms (DRESS)" seen as the most frequent entry in Figure 1. The FAERS preferred term search identified 12 reports of DRESS. Examination of each of the 12 reports reveals they are duplicates of a single report. Review of the index report reveals there were multiple suspect drugs including phenobarbital, ceftriaxone, famotidine and spironolactone. Atropine is not included in the final follow up narrative as a suspect drug.

Medical Literature

A Medical Literature Review is performed using Web of Science. The search parameters entered are "atropine" in the topic field and years 2010 to 2017 in the "timespan" field. This search yielded 2825 returns. This search was further filtered to restrict the citations to "pediatrics" category. Following this restriction there were 97 returns. All titles were examined for clinical topics. From among the 97 citations in the pediatrics category there were 14 with clinical relevance. Abstracts were examined for these 14 citations. The content of these references included use of atropine in cardiac arrhythmias, newborn intubation pre-medication, use in conduction disturbances, adverse events in NICU intubation. None of the references revealed a new safety signal.

Protopam

FAERS

The FAERS database is searched using MERCADO quick search Drug Safety Analytics. Search Fields are Initial FDA Received date "01/01/2010 – 8/29/2017", Product Name "pralidoxime chloride", Drug Role "suspect", Patient age Group <1 year to <17 years. The search yields 1 report, Case # 9631063. This 14 yo female suffered an interval of psychosis during treatment for a case of accidental OPC (organophosphate insecticide) poisoning. The patient had a protracted hospital stay due to an interval of psychosis. Causality is confounded by the background intensive care unit setting and treatment with multiple psychoactive medications. The patient recovered completely.

Medical Literature

Medical Literature Review is performed using Web of Science. The search parameters entered are "pralidoxime" in the topic field and years 2010 to 2017 in the "timespan" field. This search yielded 253 citations. The titles of all citations were examined for relevance to clinical pediatric safety events. From among these 253 citations there were eight (8) titles identified with content on direct patient care utilizing pralidoxime in organophosphate poisoning. The abstracts of these eight titles were further examined for pediatric safety data. None of these eight citations contained pediatric safety data.

One citation was an adult safety report. This reference was entitled "Respiratory arrest caused by accidental rapid pralidoxime infusion". In this report a 41 yo male suffered an organophosphorus (OPP) insecticide poisoning. The patient was treated with continuous infusion of pralidoxime, apparently successfully, for 3 days. Upon preparation for discharge the pralidoxime infusion bag was accidently fully opened such that the patient received 4 to 5 grams of pralidoxime over 10 to 20 minutes. This is nearly 4 times the recommended dose at 1.5 times the maximum recommended rate of the initial pralidoxime loading infusion. The patient subsequently complained of blurred vision, developed rigid extremities and had lateral gaze palsy. The patient was intubated and received mechanical ventilation with sedation. The next day the patient was extubated and was discharged from the hospital after an additional uneventful hospital day (on day 5 ,2 days after the accidental pralidoxime overdose).

DuoDote

FAERS

The FAERS database is searched using MERCADO quick search Drug Safety Analytics. Search Fields are Initial FDA Received date "01/01/2010 – 8/29/2017", Product Name "atropine/pralidoxime chloride", Drug Role "suspect". The search yields 0 reports. The search is repeated with Product Name "duodote", again the search yields 0 reports.

Medical literature

Medical Literature Review is performed using Web of Science. The search parameter entered is "atropine and pralidoxime" in the topic field for years 1900 to 2017 in the "timespan" field. This search yields 67 citations. This cohort of citations is further filtered to capture only "pediatric" relevant citations. Using this filter there are 5 citations from among the initial 67. The abstracts of these reports are examined for relevant pediatric safety issues. From among these discussion there is no new safety signal identified related to the use of DuoDote in pediatric treatment.

6. Conclusion

In the General Advice/Deferral Extension Granted letter of July 9, 2013 for pediatric PMR 1300-1 in response to question 3, the FDA advised that "*information is already available for the labeling of the dosage of both products"* (atropine [AtroPen] and pralidoxime [Protopam]). In this sNDA the sponsor supports labeling for pediatric patients weighing >41kg with reference to the AtroPen and Protopam labels. No new clinical studies are performed and use of the adult DuoDote autoinjector device is proposed.

An examination of the pediatric development of both AtroPen and Protopam is performed. Protopam development reveals an event of laryngospasm in a 14 month old patient in the 1993. The Division concluded that the evidence in this report did not provide evidence for causal certainty and the risk benefit analysis remained in favor of a benefit for treatment of organophosphate and nerve agent toxicity.

An updated examination of the FAERS database and the medical literature for atropine, pralidoxime and DuoDote respectively do not reveal a new safety signal for use of these agents in pediatric treatment of organophosphate insecticide or nerve agent toxicity.

The sponsor adequately supports safety of the proposed injection volume of 2.7mg. The clinical pharmacology review discipline finds the application acceptable and recommends approval.

7. Recommendation

Approval of the expanded DuoDote indication for children weighing >41 kg is recommended based on the absence of evidence for a new safety signal and acceptability of dosing for this pediatric weight range by the Office of Clinical Pharmacology review.

8. Appendix 1, AtroPen Pediatric Dosing and Administration

Table 1 AtroPen, Pediatric Dosing and Administration

Different dose strengths of the AtroPen ☐ are		
Adults and children weighing over 90 lbs (41 kg) (generally over 10 years of age)	AtroPen® 2 mg	(green)
Children weighing 40 lbs to 90 lbs (18 – 41 kg) (generally 4 to 10 years of age)	AtroPen® 1 mg	(dark red)
Children weighing 15 lbs to 40 lbs (7 – 18 kg) (generally 6 months to 4 years of age)	AtroPen® 0.5 mg	(blue)
Infants weighing less than 15 lbs (7 kg) (generally less than 6 months of age)	AtroPen® 0.25 mg	(yellow)

9. Appendix 2, Protopam Pediatric Dosing and Administration

Table 2 Protopam, Pediatric Intramuscular Dosing Recommendations1

Weight in kg	Dose Per Injection[2]	Total Dose per Three-Injection Course[3]
< 40kg	15 mg/kg	45 mg/kg
≥ 40 kg[4]	Use Adult Dosing Recommendations[5]	Use Adult Dosing Recommendations

[1]Dosing is based on an approximate 300 mg/mL solution.

[2]During the treatment for mild symptoms, if at any time after the first dose, the patient develops severe symptoms, administer two additional weight- appropriate intramuscular doses of PROTOPAM in rapid succession.

[3]Additional courses of PROTOPAM may be administered beginning one hour after the last injection. A single course consists of three separate, weight-appropriate injections, administered either with 15 minute inter-injection observation periods for patients with mild symptoms, or all in rapid succession for patients with severe symptoms.

[4]Weight of 40 kg corresponds to approximately the 50th percentile for a 12 year old child per the weight-for-age percentile growth charts published by the Centers for Disease Control and Prevention in 2000.

[5]Adult Dose Per Injection is 600 mg; Total Adult Dose per Three-Injection Course is 1800 mg.

10. Appendix 3 Evaluation of atropine related FAERS reports

Table 3 High Level Group Terms from FAERS with 2 or more reports present, patients <17 years, from approval. Empirica Signal

HLGT	# Reports	% of Total		HLGT	# Reports	% of Total
Cardiac arrhythmias	26	5.4		Seizures (incl subtypes)	4	0.8
Respiratory disorders NEC	23	4.7		White blood cell disorders	4	0.8
Neurological disorders NEC	22	4.5		Acid-base disorders	3	0.6
General system disorders NEC	19	3.9		Administration site reactions	3	0.6
Medication errors and other product use errors and issues	19	3.9		Anxiety disorders and symptoms	3	0.6
Epidermal and dermal conditions	15	3.1		Cardiac disorder signs and symptoms	3	0.6
Infections - pathogen unspecified	14	2.9		Changes in physical activity	3	0.6
Cardiac and vascular investigations (excl enzyme tests)	11	2.3		Disturbances in thinking and perception	3	0.6
Therapeutic and nontherapeutic effects (excl toxicity)	11	2.3		Gastrointestinal haemorrhages NEC	3	0.6
Procedural related injuries and complications NEC	10	2.1		Heart failures	3	0.6
Gastrointestinal signs and symptoms	9	1.9		Hepatic and hepatobiliary disorders	3	0.6
Lower respiratory tract disorders (excl obstruction and infection)	9	1.9		Mood disorders and disturbances NEC	3	0.6
Metabolic, nutritional and blood gas investigations	9	1.9		Neurological, special senses and psychiatric investigations	3	0.6
Ocular neuromuscular disorders	9	1.9		Psychiatric and behavioural symptoms NEC	3	0.6
Allergic conditions	8	1.6		Salivary gland conditions	3	0.6
Body temperature conditions	8	1.6		Sleep disorders and disturbances	3	0.6
Haematology investigations (incl blood groups)	8	1.6		Toxicology and therapeutic drug monitoring	3	0.6
Ocular infections, irritations and inflammations	8	1.6		Vascular hypertensive disorders	3	0.6
Urinary tract signs and symptoms	7	1.4		Vision disorders	3	0.6
Vascular disorders NEC	7	1.4		Central nervous system vascular disorders	2	0.4
Bronchial disorders (excl neoplasms)	6	1.2		Enzyme investigations NEC	2	0.4
Decreased and nonspecific blood pressure disorders and shock	6	1.2		Gastrointestinal inflammatory conditions	2	0.4
Deliria (incl confusion)	6	1.2		Gastrointestinal stenosis and obstruction	2	0.4
Eye disorders NEC	6	1.2		Glaucoma and ocular hypertension	2	0.4
Hepatobiliary investigations	6	1.2		Injuries NEC	2	0.4
Movement disorders (incl parkinsonism)	6	1.2		Mental impairment disorders	2	0.4
Neuromuscular disorders	6	1.2		Muscle disorders	2	0.4
Respiratory tract signs and symptoms	6	1.2		Nephropathies	2	0.4
Upper respiratory tract disorders (excl infections)	6	1.2		Ocular sensory symptoms NEC	2	0.4
Anterior eye structural change, deposit and degeneration	5	1		Ocular structural change, deposit and degeneration NEC	2	0.4
Exposures, chemical injuries and poisoning	5	1		Oral soft tissue conditions	2	0.4
Gastrointestinal motility and defaecation conditions	5	1		Personality disorders and disturbances in behaviour	2	0.4
Overdoses and underdoses NEC	5	1		Pigmentation disorders	2	0.4
Water, electrolyte and mineral investigations	5	1		Product quality, supply, distribution, manufacturing and quality system issues	2	0.4
Electrolyte and fluid balance conditions	4	0.8		Psychiatric disorders NEC	2	0.4
Fatal outcomes	4	0.8		Renal and urinary tract investigations and urinalyses	2	0.4
Musculoskeletal and connective tissue disorders congenital	4	0.8		Schizophrenia and other psychotic disorders	2	0.4
Physical examination and organ system status topics	4	0.8		Skin vascular abnormalities	2	0.4
Renal disorders (excl nephropathies)	4	0.8		Viral infectious disorders	2	0.4

Table 4 Reason for Atropine Use (MERCADO quick search Drug Safety Analytics)*

Reported Reason For Use	Total Cases	% of Cases
Not Reported	27	30.3%
PRODUCT USED FOR UNKNOWN INDICATION	8	9.0%
Ophthalmological examination	6	6.7%
Product used for unknown indication	5	5.6%
Sedation	4	4.5%
Drug use for unknown indication	3	3.4%
Mydriasis	3	3.4%
Extrasystoles	2	2.2%
GENERAL ANAESTHESIA	2	2.2%
Heart rate decreased	2	2.2%
Hypotension	2	2.2%
ILL-DEFINED DISORDER	2	2.2%
NEUROMUSCULAR BLOCKADE REVERSAL	2	2.2%
Respiratory rate decreased	2	2.2%
Strabismus	2	2.2%
ANESTHESIA	1	1.1%
Amblyopia	1	1.1%
Anaesthesia	1	1.1%
Anesthesia procedure	1	1.1%
Biopsy bone marrow	1	1.1%
Cycloplegia	1	1.1%
DRUG USE FOR UNKNOWN INDICATION	1	1.1%
ENDOTRACHEAL INTUBATION	1	1.1%
Fundoscopy	1	1.1%
General anesthesia	1	1.1%
INDUCTION OF ANAESTHESIA	1	1.1%
Iridocyclitis	1	1.1%
MYDRIASIS	1	1.1%
MYOPIA	1	1.1%
NEUROMUSCULAR BLOCKADE	1	1.1%
OPHTHALMOLOGICAL EXAMINATION	1	1.1%
PREMEDICATION	1	1.1%
Poisoning	1	1.1%
Preoperative care	1	1.1%
RETINOPATHY OF PREMATURITY	1	1.1%
Torticollis	1	1.1%
Toxicity to various agents	1	1.1%
ULCERATIVE KERATITIS	1	1.1%
VENTRICULAR FIBRILLATION	1	1.1%
Total	89	100.0%
* patients <17 years from year 2010 to present		

Figure 1 Preferred terms from FAERS reports in patients <17 years from year 2010 to present (MERCADO quick search Drug Safety Analytics)

Preferred Term	Total Cases	% of Cases	Preferred Term	Total Cases	% of Cases	Preferred Term	Total Cases	% of Cases
Drug reaction with eosinophilia and systemic symptoms	12	13.5%	Psychotic disorder	2	2.2%	Hypovolaemic shock	1	1.1%
Tachycardia	12	13.5%	Pulmonary haemorrhage	2	2.2%	Incorrect dose administered	1	1.1%
Cardiac failure	9	10.1%	Rhabdomyolysis	2	2.2%	Increased bronchial secretion	1	1.1%
Agitation	8	9.0%	Seizure	2	2.2%	Intraocular pressure increased	1	1.1%
Acute pulmonary oedema	7	7.9%	Suicide attempt	2	2.2%	Irritability	1	1.1%
Bradycardia	7	7.9%	Supraventricular extrasystoles	2	2.2%	Laryngospasm	1	1.1%
Respiratory failure	7	7.9%	Tonsillar hypertrophy	2	2.2%	Left ventricular dysfunction	1	1.1%
Condition aggravated	6	6.7%	Tonsillolith	2	2.2%	Left ventricular failure	1	1.1%
Hyperthermia	5	5.6%	Ulcerative keratitis	2	2.2%	Leukocytosis	1	1.1%
Hypotension	5	5.6%	Vasoplegia syndrome	2	2.2%	Lip oedema	1	1.1%
Opsoclonus myoclonus	5	5.6%	Ventricular fibrillation	2	2.2%	Long QT syndrome	1	1.1%
Bronchospasm	4	4.5%	Accidental exposure to product by child	1	1.1%	Lung disorder	1	1.1%
Flushing	4	4.5%	Accidental overdose	1	1.1%	Lung infiltration	1	1.1%
Pleural effusion	4	4.5%	Acute kidney injury	1	1.1%	Medication error	1	1.1%
Pyrexia	4	4.5%	Aggression	1	1.1%	Mental disorder due to a general medical condition	1	1.1%
Drug ineffective	3	3.4%	Agitation postoperative	1	1.1%	Metabolic acidosis	1	1.1%
Erythema	3	3.4%	Alveolitis	1	1.1%	Miosis	1	1.1%
Generalised erythema	3	3.4%	Anaphylactic reaction	1	1.1%	Mouth ulceration	1	1.1%
Hallucination	3	3.4%	Angle closure glaucoma	1	1.1%	Nephrotic syndrome	1	1.1%
Hypertension	3	3.4%	Apnoea	1	1.1%	Neuroleptic malignant syndrome	1	1.1%
Lymphocyte stimulation test positive	3	3.4%	Arrhythmia	1	1.1%	Ocular hyperaemia	1	1.1%
Mydriasis	3	3.4%	Asthenia	1	1.1%	Oedema	1	1.1%
Oxygen saturation decreased	3	3.4%	Autoimmune hepatitis	1	1.1%	Off label use	1	1.1%
Pallor	3	3.4%	Balance disorder	1	1.1%	Oliguria	1	1.1%
Rash	3	3.4%	Blood creatinine increased	1	1.1%	Oxygen therapy	1	1.1%
Respiratory distress	3	3.4%	Blood potassium decreased	1	1.1%	Photophobia	1	1.1%
Splenomegaly	3	3.4%	Brain injury	1	1.1%	Pneumonia	1	1.1%
Tachypnoea	3	3.4%	Bronchial disorder	1	1.1%	Pneumonia aspiration	1	1.1%
Toxicity to various agents	3	3.4%	Cardio-respiratory arrest	1	1.1%	Product label confusion	1	1.1%
Abasia	2	2.2%	Cataract subcapsular	1	1.1%	Productive cough	1	1.1%
Anticholinergic syndrome	2	2.2%	Catatonia	1	1.1%	Pulmonary alveolar haemorrhage	1	1.1%
Blood pressure increased	2	2.2%	Clonus	1	1.1%	Pulmonary oedema	1	1.1%
Cardiac arrest	2	2.2%	Confusional state	1	1.1%	Purpura	1	1.1%
Corneal oedema	2	2.2%	Conjunctival hyperaemia	1	1.1%	Rash erythematous	1	1.1%
Corneal perforation	2	2.2%	Constipation	1	1.1%	Renal failure	1	1.1%
Crepitations	2	2.2%	Corneal dystrophy	1	1.1%	Renal tubular disorder	1	1.1%
Drug dispensing error	2	2.2%	Counterfeit drug administered	1	1.1%	Respiratory dyskinesia	1	1.1%
Dyspnoea	2	2.2%	Dark circles under eyes	1	1.1%	Restlessness	1	1.1%
Electrocardiogram QT prolonged	2	2.2%	Delirium	1	1.1%	Schizophreniform disorder	1	1.1%
Extrasystoles	2	2.2%	Delirium febrile	1	1.1%	Screaming	1	1.1%
Eye infection	2	2.2%	Depressed level of consciousness	1	1.1%	Skin warm	1	1.1%
Eye pain	2	2.2%	Drug administration error	1	1.1%	Speech disorder	1	1.1%
Gastrointestinal haemorrhage	2	2.2%	Drug effect delayed	1	1.1%	Staring	1	1.1%
Haemodynamic instability	2	2.2%	Drug effect prolonged	1	1.1%	Streptococcal infection	1	1.1%
Haemoglobin decreased	2	2.2%	Drug use disorder	1	1.1%	Sudden infant death syndrome	1	1.1%
Heart rate decreased	2	2.2%	Ejection fraction decreased	1	1.1%	Syncope	1	1.1%
Heart rate increased	2	2.2%	Electrocardiogram QRS complex prolonged	1	1.1%	Tachyarrhythmia	1	1.1%
Hypokalaemia	2	2.2%	Encephalopathy	1	1.1%	Tremor	1	1.1%
Hypopyon	2	2.2%	Extrapyramidal disorder	1	1.1%	Urinary hesitation	1	1.1%
Hypoxia	2	2.2%	Eye discharge	1	1.1%	Urticaria	1	1.1%
Infection	2	2.2%	Eyelid pain	1	1.1%	Ventricular extrasystoles	1	1.1%
Iris adhesions	2	2.2%	Fatigue	1	1.1%	Viral upper respiratory tract infection	1	1.1%
Iritis	2	2.2%	Fever neonatal	1	1.1%	Vocal cord disorder	1	1.1%
Malaise	2	2.2%	Gait disturbance	1	1.1%	Vocal cord dysfunction	1	1.1%
Necrotising colitis	2	2.2%	Haemorrhage	1	1.1%	Vomiting	1	1.1%
Pain	2	2.2%	Hyperhidrosis	1	1.1%	Weaning failure	1	1.1%
Pneumomediastinum	2	2.2%	Hyperthermia malignant	1	1.1%	Wrong drug administered	1	1.1%
Product quality issue	2	2.2%	Hypertonia	1	1.1%	**Total**	**89**	**100.0%**
Product use issue	2	2.2%	Hyponatraemia	1	1.1%			
			Hypotonia	1	1.1%			

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/s/

STEVEN T DINSMORE
09/05/2017

TERESA J BURACCHIO
10/04/2017