Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	February 6, 2019
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Product Name:	Eucrisa (crisaborole) ointment, 2%
Pediatric Labeling Approval Date:	December 14, 2016
Application Type/Number:	NDA 207695
Applicant/Sponsor:	Pfizer, Inc.
OSE RCM #:	2018-1594

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for crisaborole in pediatric patients through age 17 years. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with crisaborole in pediatric patients.

The FDA approved crisaborole on December 14, 2016 and it is indicated for the topical treatment of mild to moderate atopic dermatitis. The approved pediatric labeling is for mild to moderate atopic dermatitis in ages 2 years and older.

To characterize utilization in the pediatric population and to provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns were assessed. From December 2016 through July 2018, an estimated 314,000 patients received a dispensed prescription for crisaborole from U.S. outpatient retail pharmacies. Pediatric patients less than 18 years accounted for 42% (130,000 patients) of total patients. Approximately 94% of the use in pediatric patients was in patients aged 2 – 17 years. Off-label use of crisaborole in pediatric patients < 2 years of age accounted for approximately 6%-7% of pediatric patients. Dermatologists and physician assistants were the top prescribing providers for all prescribing of crisaborole.

The Division of Pharmacovigilance (DPV) reviewed all serious U.S. FAERS reports with crisaborole in the pediatric population from December 14, 2016 to July 4, 2018. We identified anaphylactic reaction, angioedema, application site exfoliation, and application site burn as adverse events of interest among the three unlabeled, serious cases in our case series. We expanded our FAERS search for these adverse events of interest with related Preferred Terms to include non-serious cases in both the pediatric and adult population. The cases of application site burns appear to be consistent with the crisaborole labeling. The remainder of the cases were generally non-serious and provided limited information for assessment.

OSE did not identify any previously unrecognized pediatric safety concerns for crisaborole. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of crisaborole.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for crisaborole in pediatric patients through age 17 years. The Office of Surveillance and Epidemiology (OSE) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with crisaborole in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Crisaborole is a phosphodiesterase-4 inhibitor indicated for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. The FDA approved crisaborole on December 14, 2016. It is currently available as a 2% ointment. Crisaborole should be applied in a thin layer to the affected areas twice daily.

This PREA review was triggered by the pediatric indication gained during the initial approval of crisaborole. Crisaborole was studied in two multicenter, randomized, double-blind, parallel-group, vehicle-controlled 28-day trials in 1,313 pediatric subjects aged 2 years and older.

1.2 RELEVANT LABELED SAFETY INFORMATION

The current approved labeling for crisaborole provide the following safety information in the Highlights of Prescribing Information, the Warnings and Precautions section, and the Adverse Reactions section:[1]

> **----------CONTRAINDICATIONS----------**
> Known hypersensitivity to crisaborole or any component of the formulation. (4)
> **----------WARNINGS AND PRECAUTIONS----------**
> Hypersensitivity reactions: If signs and symptoms of hypersensitivity occur, discontinue EUCRISA immediately and initiate appropriate therapy. (5.1)
> **----------ADVERSE REACTIONS----------**
> The most common adverse reaction occurring in ≥1% in subjects is application site pain. (6.1)
>
> **WARNINGS AND PRECAUTIONS**
> **5.1 Hypersensitivity Reactions**
> Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with EUCRISA. Hypersensitivity should be suspected in the event of severe pruritus, swelling and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, discontinue EUCRISA immediately and initiate appropriate therapy.
>
> ADVERSE REACTIONS
> 6.1 Clinical Trials Experience
> Table 1: Adverse Reaction Occurring in ≥1% of Subjects in Atopic Dermatitis Trials through Week 4

Adverse Reaction	EUCRISA N=1012 n (%)	Vehicle N=499 n (%)
Application site pain[a]	45 (4)	6 (1)

[a] Refers to skin sensations such as burning or stinging.

Additionally, the crisaborole labeling contains the following information in Section 8.4 Pediatric Use:

> **8.4 Pediatric Use**
> The safety and effectiveness of EUCRISA have been established in pediatric patients age 2 years and older for topical treatment of mild to moderate atopic dermatitis. Use of EUCRISA in this age group is supported by evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled 28-day trials which included 1,313 pediatric subjects 2 years and older [see Adverse Reactions (6.1) and Clinical Studies (14)]. The safety and effectiveness of EUCRISA in pediatric patients below the age of 2 years have not been established.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

The Division of Pharmacovigilance (DPV) searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	July 5, 2018
Time Period of Search	December 14, 2016† - July 4, 2018
Search Type	FBIS Quick Query
Product Terms	Product Active Ingredient: Crisaborole NDA: 207695
MedDRA Search Terms (Version 21.0)	All Preferred Terms

FBIS=FDA Business Intelligence Solution, FAERS=FDA Adverse Event Reporting System, MedDRA=Medical Dictionary for Regulatory Activities, NDA=new drug application
* See Appendix A for a description of the FAERS database.
† U.S. approval date

2.2 DRUG UTILIZATION

Proprietary drug utilization databases available to the FDA were used to conduct this analysis. Details and limitations of the databases are provided in Appendix B of this document.

2.2.1 Data Sources Used

The IQVIA National Sales Perspectives™ (NSP) database was used to determine the settings of care where crisaborole was sold from U.S. manufacturers to the various channels of distribution from December 2016 through July 2018.

The IQVIA Total Patient Tracker™ (TPT) database was used to provide national estimates of unique patients with a dispensed prescription for crisaborole from U.S. retail pharmacies, stratified by patient age (≤1, 2 – 17, 18+ years) from December 2016 through July 2018, annually.

The IQVIA National Prescription Audit™ (NPA) database was used to provide a national estimate of dispensed prescription for crisaborole from U.S. retail pharmacies, stratified by provider type, from December 2016 through July 2018, cumulative.

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from December 14, 2016 to July 4, 2018 with crisaborole.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from December 14, 2016 to July 4, 2018 with Crisaborole.

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	830 (830)	22 (22)	0 (0)
Pediatrics (0 - <18 years)	538 (538)	**9 (9)**	0 (0)

* 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.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved nine U.S. serious pediatric reports from December 14, 2016 to July 4, 2018. We reviewed all U.S. FAERS pediatric reports with a serious outcome. There were no deaths. The reported ages in these nine reports ranged from 3 to 16 years old.

Six cases were excluded from further analysis in this review because the adverse events were either labeled or attributed to an alternative etiology. Five of the six cases described labeled events of application site pain, including reports of a burning sensation. Two of the five cases additionally reported contact urticaria (hypersensitivity reaction). These adverse events are adequately described in the labeling, including hypersensitivity reactions in WARNINGS AND PRECAUTIONS and application site pain in ADVERSE REACTIONS (6.1 Clinical Trials Experience). The remaining case described the onset of a generalized rash while crisaborole was on hold; the rash had possible causal association with another medication, sulfamethoxazole/trimethoprim.[2]

We summarize the remaining three cases in the sections below.

3.1.3 Characteristics of Pediatric Cases

Table 3 summarizes the three FAERS cases in U.S. pediatric patients with the use of crisaborole, reporting a serious outcome and received by FDA from December 14, 2016 to July 4, 2018. Appendix C contains a line listing of the three pediatric cases.

Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases with Crisaborole from December 14, 2016 to July 4, 2018 (N=3)		
Age	3 years	1
	6 years	1
	13 years	1
Sex	Male	2
	Female	1
Reported Reason for Use	Atopic dermatitis	2
	Unknown	1
Serious Outcome*	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.

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports during this period.

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=3)

We identified three serious FAERS cases with crisaborole in the U.S. pediatric population reporting a non-fatal serious outcome.

Anaphylactic reaction/Angioedema (n=2)

One case reported a possible anaphylactic reaction, and one case of angioedema, with the use of crisaborole.

The first case reported a 3-year-old male who was prescribed crisaborole (dose and frequency not reported) for an unknown indication. The patient's medical history and concomitant medications were not reported. After an unknown duration of use, the patient developed "angioedema of the face" within five minutes of crisaborole application. There was no relief following treatment with oral diphenhydramine. The patient was taken to the emergency department where he was treated with unspecified antihistamines and steroids. The outcome of angioedema was not reported. Follow-up information from the physician stated that there was no causal association between crisaborole and angioedema; however, no further explanation was provided.

The second case reported a 6-year-old male who was switched from hydrocortisone to crisaborole for the treatment of atopic dermatitis. The patient's medical history included atopic dermatitis, allergic rhinitis, and food allergies. His concomitant medications were cetirizine, levocetirizine, and diphenhydramine. After two days of treatment with crisaborole, the patient developed "severe" erythema and pruritis. The affected area "looked like a bad burn." Additionally, "possible anaphylaxis symptoms, vomiting and breathing issues including

coughing" were reported by the healthcare providers. Treatment included cetirizine, levocetirizine, diphenhydramine, oral antibiotics, and moisturizing creams. Crisaborole was discontinued and the patient was recovering from the events.

Reviewer's comments: Both cases provided limited information, precluding a causality assessment. The first case reported a possible temporal association (angioedema occurred five minutes after the use of crisaborole), but the duration of use was unknown. The second case also reported a temporal association between the events and the use of crisaborole. However, the patient had a history of allergies and no urgent medical attention was reported for the possible anaphylactic symptoms and respiratory issues of an unspecified severity.

We further explored the potential safety signals of anaphylaxis and angioedema reported with the use of crisaborole. DPV expanded the FAERS search to identify additional reports of angioedema or anaphylaxis in all ages. We searched the FAERS database for crisaborole reports received through July 4, 2018 using: 1) High Level Term (HLT) Angioedemas and 2) Anaphylactic Reaction (Standardized MedDRA Query [SMQ]) algorithmic (see Appendices D and E for a list of the Preferred Terms [PTs] in the HLT and SMQ). The search retrieved 26 deduplicated cases, including the two cases described above. There were 11 pediatric cases and 10 adult cases; the age was not reported in 5 cases. Reported events included swelling of the face, eyelids, lips, or throat; no additional cases of anaphylaxis were retrieved. Of the 26 cases, 22 cases were non-serious. Four cases reported a serious outcome, including the two cases described above. The two remaining serious cases were not assessable. One additional case with a non-serious outcome reported a positive dechallenge (the adverse event resolved following the discontinuation of crisaborole). This case described the onset of facial swelling after the first dose of crisaborole; crisaborole was discontinued and the event resolved the following day without further treatment. Overall, the majority of these cases provided limited information regarding the medical history, concomitant medications, adverse events, time to onset, or clinical outcome. None of the cases met the case definition of angioedema or anaphylaxis, and the reported events appear to be consistent with the crisaborole labeling. DPV will continue to monitor for cases of facial swelling, angioedema, and anaphylaxis reported with crisaborole.

Application site exfoliation, Application site burn (n=1)

A 13-year-old female experienced burning and peeling on her face after the application of crisaborole. Her medical history included ADHD and eczema from an egg allergy. Her concomitant medication included methylphenidate hydrochloride. The patient was prescribed crisaborole twice a day as needed for eczema (off-label use). After the first application of crisaborole to her face, the patient had increased redness at the application site. This redness was initially attributed to worsening of the eczema, and crisaborole was continued. After two to three days of treatment with crisaborole, the patient's eyes became swollen and her face peeled off like a "chemical peel." There was no rash in other areas of the body outside of the application site. The dermatologist attributed the adverse event to crisaborole and it was discontinued. The patient was in pain and she was unable to attend school. As treatment, the dermatologist prescribed an unspecified steroid cream and injection. One week later, the patient recovered.

Reviewer's comments: Burning sensation is a labeled adverse event for crisaborole in the ADVERSE REACTIONS section of the labeling, but this case reported burning and peeling, which is an increased severity of the adverse event. DPV contacted the patient's mother for follow-up information and incorporated the additional information into the above case summary. To identify additional reports of application site burn or peeling in all ages, we searched FAERS for crisaborole reports received through July 4, 2018 using the PTs: Application site burn, Application site exfoliation, Skin exfoliation, and *Thermal burn. The search retrieved 59 deduplicated cases, including the case described above. Some cases reported both application site burns and peeling. There were 16 pediatric cases and 34 adult cases; the age was not reported in 9 cases. Of the 59 cases, 55 cases were non-serious. The majority of these cases provided limited information regarding the medical history, concomitant medications, adverse events, time to onset, or clinical outcome. The cases of application site burns (including two of the four serious cases) appear to be consistent with the crisaborole labeling. The third serious case reported worsening of the atopic dermatitis following the use of crisaborole and the occurrence of a "severe burn" after an unknown duration of use. The fourth serious case was reported above. No additional details were reported for the burn and the outcome was unknown. DPV will continue to monitor for cases of application site peeling reported with crisaborole.*

3.2 DRUG UTILIZATION

3.2.1 Settings of Care

From December 2016 through July 2018, approximately 90% of crisaborole was distributed to U.S. retail pharmacies, 7% to mail-order/specialty pharmacies, and 3% to non-retail settings.[a] Accordingly, we focused our efforts only on the retail pharmacy setting. Data from non-retail and mail-order/specialty pharmacy settings were not included in this analysis.

3.2.2 Patient-Level Data from U.S. Outpatient Retail Pharmacies

Table 4 shows the nationally estimated number of patients with a dispensed prescription for crisaborole stratified by age from U.S. outpatient retail pharmacies, December 2016 through July 2018, cumulative. Pediatric patients less than 18 years of age accounted for approximately 42% (130,000 patients) of total patients for crisaborole during the review period. The largest proportion of pediatric patients with a dispensed prescription for crisaborole were aged 2 – 17 years and accounted for approximately 94% of pediatric patients (122,000 patients). Off-label use in patients less than 2 years accounted for 7% of pediatric patients (8,900 patients).

[a] IQVIA, National Sales Perspectives™ Database. Dec 2016 – Jul 2018. Extracted September 2018. File NSP 2018-1584 Eucrisa by channel 8-30-18.xlsx

Table 4. Nationally Estimated Number of Patients with a Dispensed Prescription for Crisaborole from U.S. Outpatient Retail Pharmacies, Stratified by Patient Age, December 2016 - July 2018, Cumulative

	December 2016 - July 2018	
	Patient Count, N	**Share %**
Grand Total	**313,526**	**100.0%**
Age <18 years	129,979	41.5%
Age <2 years	8,930	6.9%
Age 2-17 years	121,595	93.6%
Age 18+ years	183,908	58.7%
Unknown Age	170	0.1%

Source: IQVIA, Total Patient Tracker™. December 2016 – July 2018. Extracted August 2018. File: TPT 2018-1594 Eucrisa by age 8-30-18.xlsx

*Subtotals may not sum exactly due to rounding. Due to aging of patients during the study period, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in double counting patients.

3.2.3 Provider Type

Table 5 shows the top provider types for crisaborole by the estimated number of total prescriptions dispensed regardless of age in U.S. outpatient retail pharmacies from December 2016 through July 2018. During the cumulative time examined, approximately 452,000 prescriptions were dispensed for crisaborole. Approximately 31% (140,000 prescriptions) of dispensed prescriptions for crisaborole were prescribed by dermatologists, followed by physician assistants at 17% (78,000 prescriptions) of dispensed prescriptions. Pediatricians accounted for approximately 11% (50,000 prescriptions) of dispensed prescriptions.

Table 5. Nationally Estimated Number of Dispensed Prescriptions by Top Provider Types for Crisaborole from U.S. Outpatient Retail Pharmacies, December 2016 – July 2018

	December 2016 – July 2018	
	TRx	**Share**
Crisaborole	**452,093**	**100.0%**
Dermatology	140,252	31.0%
Physician Assistant	77,961	17.2%
Nurse Practitioner	56,707	12.5%
Pediatrics	49,938	11.1%
GP/FP/IM*	46,798	10.4%
Osteopathic Medicine	32,485	7.2%
Allergy	31,381	6.9%
All Other (<1% respectively)	16,571	3.6%

Source: IQVIA National Prescription Audit™. December 2016 – July 2018. Extracted September 2018. File: NPA 2018-1584 Eucrisa by MD 9-13-18.xlsx

*GP/FP/IM – General Practice, Family Practice, and Internal Medicine

4 DISCUSSION

To provide context for the adverse event reports submitted to FAERS, drug utilization patterns for crisaborole were assessed. Drug utilization data showed pediatric patients accounted for approximately 42% of the total patients who received a prescription for crisaborole from U.S. outpatient retail pharmacies. Among pediatric patients, the largest use (94%) of crisaborole was in patients aged 2-17 years. Dermatologists and physician assistants were the top prescribing providers for crisaborole. Of note, the findings from the drug use analysis are national estimates and cannot be validated through medical chart review.

We reviewed all serious U.S. FAERS reports with crisaborole in the pediatric population from December 14, 2016 to July 4, 2018. Of the nine crisaborole cases reviewed, there were no new safety signals identified and there were no deaths reported. The reported ages in these nine cases ranged from 3 to 16 years old. The five cases of application site pain or contact urticaria were consistent with the known adverse events described in the crisaborole labeling. One additional case reported a rash that was likely attributed to another medication.

We identified anaphylactic reaction, angioedema, application site exfoliation, and application site burn as adverse events of interest among the three unlabeled, serious cases in our case series. We expanded our FAERS search for these adverse events of interest with related PTs to include non-serious cases in both the pediatric and adult population. The cases of application site burns appear to be consistent with the crisaborole labeling. The remainder of the cases were generally non-serious and provided limited information for assessment.

5 CONCLUSION

OSE did not identify any previously unrecognized pediatric safety concerns for crisaborole.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of crisaborole.

7 REFERENCES

1. Eucrisa [package insert]. New York, NY: Pfizer, Inc.; 2017.
2. Bactrim [package insert]. Philadelphia, PA: Mutual Pharmaceutical Company, Inc.; 2013.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

IQVIA National Sales Perspectives™: Retail and Non-Retail

The IQVIA 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.

IQVIA Total Patient Tracker™ (TPT)

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

IQVIA National Prescription Audit™

The IQVIA National Prescription Audit (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

8.3 APPENDIX C. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=3)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	4/18/2018	14776100	2	US-PFIZER INC-2018157584	Expedited (15-Day)	3	MALE	USA	OT
2	5/22/2018	14999655	1	(blank)	Direct	13	FEMALE	USA	OT
3	5/5/2017	13517619	2	US-PFIZER INC-2017193820	Expedited (15-Day)	6	MALE	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events.
Abbreviation: OT=Other medically significant

8.4 APPENDIX D. LIST OF PREFERRED TERMS IN HIGH LEVEL TERM *ANGIOEDEMAS*, MEDDRA 21.0

Acquired C1 inhibitor deficiency
Angioedema
Circumoral oedema
Circumoral swelling
Eyelid oedema
Face oedema
Gleich's syndrome
Hereditary angioedema
Hereditary angioedema with C1 esterase inhibitor deficiency
Hereditary angioedema with normal C1 esterase inhibitor
Idiopathic angioedema
Intestinal angioedema
Laryngeal oedema
Laryngotracheal oedema
Lip oedema
Lip swelling
Mouth swelling
Oculorespiratory syndrome
Oedema mouth
Oropharyngeal oedema
Oropharyngeal swelling
Periorbital oedema
Periorbital swelling
Pharyngeal oedema
Swelling face
Swelling of eyelid
Swollen tongue
Tongue oedema

8.1 APPENDIX E. LIST OF PREFERRED TERMS IN *ANAPHYLACTIC REACTION* (STANDARDIZED MEDDRA QUERY) ALGORITHMIC, MEDDRA 21.0

Algorithm: A or (B and C) or (D and (B or C))

A	Anaphylactic reaction
A	Anaphylactic shock
A	Anaphylactic transfusion reaction
A	Anaphylactoid reaction
A	Anaphylactoid shock
A	Circulatory collapse
A	Dialysis membrane reaction
A	Kounis syndrome
A	Procedural shock
A	Shock
A	Shock symptom
A	Type I hypersensitivity
B	Acute respiratory failure
B	Asthma
B	Bronchial oedema
B	Bronchospasm
B	Cardio-respiratory distress
B	Chest discomfort
B	Choking
B	Choking sensation
B	Circumoral oedema
B	Cough
B	Cyanosis
B	Dyspnoea
B	Hyperventilation
B	Irregular breathing
B	Laryngeal dyspnoea
B	Laryngeal oedema
B	Laryngospasm
B	Laryngotracheal oedema
B	Mouth swelling
B	Nasal obstruction
B	Oedema mouth
B	Oropharyngeal oedema
B	Oropharyngeal spasm
B	Oropharyngeal swelling
B	Pharyngeal oedema
B	Respiratory arrest
B	Respiratory distress
B	Respiratory dyskinesia
B	Respiratory failure
B	Reversible airways obstruction
B	Sensation of foreign body
B	Sneezing
B	Stridor
B	Swollen tongue
B	Tachypnoea
B	Throat tightness
B	Tongue oedema
B	Tracheal obstruction
B	Tracheal oedema
B	Upper airway obstruction
B	Wheezing
C	Acquired C1 inhibitor deficiency
C	Allergic oedema
C	Angioedema
C	Erythema
C	Eye oedema
C	Eye pruritus
C	Eye swelling
C	Eyelid oedema
C	Face oedema
C	Fixed eruption
C	Flushing
C	Generalised erythema
C	Hereditary angioedema with C1 esterase inhibitor deficiency
C	Injection site urticaria
C	Lip oedema
C	Lip swelling
C	Nodular rash
C	Ocular hyperaemia
C	Oedema
C	Oedema blister
C	Periorbital oedema
C	Pruritus
C	Pruritus allergic
C	Pruritus generalised
C	Rash
C	Rash erythematous
C	Rash generalised
C	Rash pruritic
C	Skin swelling
C	Swelling
C	Swelling face
C	Urticaria
C	Urticaria papular
D	Blood pressure decreased
D	Blood pressure diastolic decreased
D	Blood pressure systolic decreased
D	Cardiac arrest
D	Cardio-respiratory arrest
D	Cardiovascular insufficiency
D	Diastolic hypotension
D	Hypotension

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