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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

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Product Name:	Orencia (abatacept)
Subjects:	Angioedema Fatal hypersensitivity
Application Type/Number:	BLA 125118
Applicant/Sponsor:	Bristol-Myers Squibb
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EXECUTIVE SUMMARY

This review provides the Division of Pharmacovigilance I's (DPV-I) assessment of cases of (1) angioedema, and (2) anaphylaxis events with a fatal outcome in the FDA Adverse Event Reporting System (FAERS) database and medical literature following the identification of a pediatric case of angioedema with Orencia (abatacept). This review will inform whether the current labeling for abatacept adequately reflects the nature and severity of hypersensitivity events that have been reported in the postmarketing setting. The results of this review will be shared with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to assess whether regulatory action is necessary.

DPV-I searched the FAERS database for reports of angioedema with abatacept through August 20, 2019, and medical literature through November 29, 2019. Our case series included 83 cases of angioedema; the majority of these were from the United States (n=61, 73.5 percent). Cases were identified with acute onset of angioedema symptoms and delayed-onset symptoms following the first abatacept exposure (n=32, 38.5 percent) or subsequent abatacept exposures (n=37, 44.6 percent). Angioedema was reported with a variety of doses and both intravenous (IV) and subcutaneous (SC) routes of administration. The symptoms reported in this case series have the potential for clinically significant or life-threatening outcomes, with respiratory symptoms defined as shortness of breath, wheezing, or difficulty breathing being reported in 24 (28.9 percent) of our cases. Furthermore, the majority of the cases within our case series reported a serious outcome (n=54, 65.1 percent), with two identified cases reporting intubation for airway protection. A positive dechallenge was reported in 27 cases (32.5 percent) and 6 cases (7.2 percent) described a positive rechallenge. The results from this analysis were limited by administration of concomitant medications with known associations with angioedema (n=16, 19.2 percent), potential for underreporting (e.g., cases with a delayed onset), database query limitations (e.g., Preferred Term coding), and limited data quality associated with postmarketing reporting.

DPV-I also searched the FAERS database for reports of anaphylaxis events with fatal outcomes with abatacept through November 8, 2019, and medical literature through November 29, 2019. Our assessment of anaphylaxis events with fatal outcomes identified one case that was previously identified by the Applicant and submitted to the FDA. This case demonstrated a probable association between abatacept administration and the anaphylactic reaction with the fatal outcome.

In conclusion, our assessment of postmarketing data suggests an association between abatacept and both acute- and delayed-onset angioedema. Some cases of acute-onset angioedema were associated with other symptoms of hypersensitivity (e.g., hypotension and rash) that are labeled or implied in the current warning for hypersensitivity with abatacept; however, the occurrences of delayed-onset hypersensitivity reactions and delayed-onset angioedema are not labeled. Because angioedema can be life-threatening and some cases occurred with a delayed onset (following abatacept administration) that is not usually associated with hypersensitivity events, it is important to inform prescribers of this safety issue. Furthermore, our search of the FAERS database for cases of anaphylaxis with a fatal outcome identified one case that the Applicant provided to FDA previously. Because postmarketing data cannot be used to define an incidence

or prevalence of an event, we recommend removing case counts (i.e., “a case of…”) from the description within labeling of this event.

Based on the findings of this review, DPV-recommends an update to Section 5.2 Hypersensitivity and 6.4 Postmarketing Experience to reflect the risk of angioedema with abatacept. Additionally, we recommend removal of qualifier indicating that only one case (“a case of”) of anaphylaxis with a fatal outcome has been reported because postmarketing data are limited to describe the incidence of adverse events.

1 INTRODUCTION

This review provides the Division of Pharmacovigilance I's (DPV-I) assessment of cases of (1) angioedema, and (2) anaphylaxis events with fatal outcomes in the FDA Adverse Event Reporting System (FAERS) database and medical literature following the identification of a pediatric case of angioedema with Orencia (abatacept). This review will inform whether the current labeling for abatacept adequately reflects the nature and severity of hypersensitivity events that have been reported in the postmarketing setting. The results of this review will be shared with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to assess whether regulatory action is necessary.

1.1 BACKGROUND

Abatacept is a fusion protein that inhibits T cell activation.[1] It is available for intravenous (IV) and subcutaneous (SC) administration. Abatacept is indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and psoriatic arthritis (PsA).

1.1.1 Angioedema

Angioedema is defined as deep dermal, subcutaneous, and/or mucosal membrane (including the respiratory and gastrointestinal tracts) swelling that is abrupt in onset.[2-4] Although angioedema can occur in any part of the body, it most frequently involves the face (e.g., eyes, lips, mouth, tongue), extremities, or genitalia.[5] Angioedema is typically self-limiting with most lesions resolving within 72 hours and the involved tissue returning to baseline without sequalae.[4] Complications of angioedema, however, can be fatal as edema involving the respiratory tract[a] can lead to impaired oxygenation and asphyxiation.[4,5] Angioedema has multiple etiologies and may actually describe a group of disorders with a common clinical expression.[2] Types of angioedema are numerous and include hereditary and acquired angioedema, idiopathic angioedema, chronic urticaria-associated angioedema, vasculitis-induced angioedema, drug-induced angioedema, and others.[4] Current labeling for abatacept does not describe angioedema as a known adverse event (see Section 1.3).[1]

Drug-induced angioedema can demonstrate various pathophysiologic mechanisms, including (1) allergic angioedema, (2) bradykinin-induced angioedema, and (3) potentially other unknown mechanisms.

1. Allergic angioedema, the most common form of drug-induced angioedema, typically occurs with a close temporal relationship to the inciting agent and includes other histamine-related sequalae such as urticaria.[6] Medications that are associated with allergic angioedema include the beta-lactam antibiotics, iodinated contrast media, neuromuscular blocking agents, and quinolones.[2] Drugs of abuse, such as cocaine, have also been associated with a possible allergy-mediated angioedema.[7] Additionally, allergic angioedema may also be associated with foods or venom from insects.[4]

[a] Angioedema of the uvula is also referred to as Quincke's disease.

2. Drug-induced angioedema that is mediated by bradykinin (e.g., angiotensin converting enzyme (ACE) inhibitor-induced angioedema), a potent vasodilatory peptide, does not involve histamine or other mast cell mediators and therefore is not usually associated with pruritis, urticaria, or therapeutic improvement with antihistamine therapy.[4,6] Although less publicized than ACE inhibitors, the following medications have been associated with bradykinin-mediated angioedema: angiotensin receptor blockers, dipeptidyl peptidase-4 inhibitors, fibrinolytic agents, and others.[2,8]
3. Cases of drug-induced angioedema with an unknown or multifactorial mechanism are described in published literature. For example, urticaria and angioedema have been described with nonsteroidal anti-inflammatory drugs (NSAIDs) through both allergic and non-allergic pathways.[2] A published case report attributing angioedema to amiodarone describes a patient who took uninterrupted amiodarone for 8 years and experienced facial angioedema symptoms intermittently during the most recent year of therapy, discontinued the drug for an unknown duration of time, then reinitiated amiodarone therapy; within 30 minutes of amiodarone rechallenge, the patient experienced facial flushing and angioedema.[9] The adverse events described in this amiodarone case had characteristics both consistent with an allergic angioedema (e.g., symptoms within 30 minutes after rechallenge) and inconsistent with allergic angioedema (e.g., amiodarone therapy for 7 years prior to angioedema symptoms). Similar cases of delayed-onset angioedema reactions have been reported with calcium channel blockers.[10]

1.1.2 Anaphylaxis Events With Fatal Outcomes

Abatacept was labeled for hypersensitivity within the Warnings and Precautions Section 5.2 Hypersensitivity after hypersensitivity reactions were observed in the abatacept clinical development programs. Furthermore, the label describes a fatal postmarketing case of anaphylaxis that occurred following the first infusion.[1] Anaphylaxis, a severe hypersensitivity reaction, is a systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance and can be fatal.[11] The administration of biologic medications, such as abatacept, has been associated with development of hypersensitivity to the biologic medication via various mechanisms.[12] Immunoglobulin E (IgE)-mediated hypersensitivity reactions (e.g., anaphylaxis) generally require a period of sensitization and therefore are not usually associated with the first exposure to an allergen.[11] Non-IgE-related hypersensitivity, on the other hand, is mediated through IgG activation of cell lines such as basophils and macrophages or the complement system.[12] Because non-IgE-related hypersensitivity does not require sensitization, the first exposure of a drug can be sufficient to induce a reaction. Interestingly, an epidemiologic study evaluating hypersensitivity reactions with biologic immunosuppressants in the Medicare claims database found that abatacept hypersensitivity reactions were more likely to occur with the first exposure of abatacept when compared with other drugs in the study (such as infliximab and tocilizumab), where patients were more likely to experience hypersensitivity reactions with subsequent exposures of the drug.[13]

1.2 PERTINENT REGULATORY HISTORY

Table 1 lists the abatacept approval dates for adult and pediatric indications by formulation.

Table 1. Abatacept Approval Dates for Adult and Pediatric Indications, by Formulation			
Indication	**Formulation**	**Adult Approval Date**	**Pediatric Approval Date**
RA	**IV**	December 23, 2005	N/A
	SC	July 29, 2011	N/A
JIA	**IV**	N/A	April 7, 2008 (*patients ≥6 years of age*);
	SC	N/A	March 30, 2017 (*patients ≥2 years of age*)
PsA	**IV**	June 30, 2017	Not approved
	SC	June 30, 2017	Not approved
Abbreviations: IV=intravenous, JIA=juvenile idiopathic arthritis, N/A=not applicable, PsA=psoriatic arthritis, RA=rheumatoid arthritis, SC=subcutaneous			

The following describes regulatory history relevant to the safety issues under review.

1.2.1 Anaphylaxis Events With Fatal Outcomes

On July 11, 2013, the Applicant submitted a Change Being Effective (CBE)-0 supplement (later updated to a Prior Approval Supplement) which, in part, addressed hypersensitivity reactions. Within this supplement, the Applicant proposed adding information regarding a fatal case of anaphylaxis. To support this labeling change, the Applicant performed an analysis focused on cases of anaphylaxis (i.e., at least one Preferred Term (PT) was mapped to the *Standard MedDRA Query (SMQ) Anaphylactic reactions*) that had a fatal outcome in their Corporate safety database (includes clinical trial, postmarketing, and literature cases) that listed abatacept as a suspect or interacting drug. Cases where abatacept was received *within 24 hours preceding the onset*[b] of the anaphylaxis event were further reviewed to assess the causality of death. The Applicant identified one postmarketing fatal anaphylaxis case: a 74-year-old female experienced an anaphylactic reaction that was complicated by a grand mal seizure within minutes of her first abatacept infusion and subsequently died within 2 hours of abatacept administration. As a result, FDA approved a labeling update on December 30, 2014, which stated that a fatal postmarketing case associated with the first abatacept dose had been reported and instructed prescribers to immediately stop therapy with abatacept if a serious allergic reaction occurs.

1.2.2 Angioedema

On January 6, 2014, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) met to discuss the potential safety signal of angioedema with abatacept[14] after identifying 13 angioedema individual case safety reports (ICSRs) with abatacept in EudraVigilance. The EMA PRAC subsequently opened safety signal number 17765 and requested that the Applicant: submit a cumulative review of cases of angioedema, discuss the possible mechanisms for angioedema with abatacept, and consider whether further actions are necessary. On February 10, 2014, the Applicant submitted Periodic Benefit Risk Evaluation Report (PBRER) #11 (reporting period of December 23, 2012, through December 22, 2013),[15] which described the Applicant's assessment of events coded within the MedDRA *SMQ*

[b] Of note, the Applicant's decision to limit their analysis to cases where abatacept was administered within 24 hours preceding the onset of the event could result in the exclusion of hypersensitivity reactions with an onset >24 hours following drug administration.

Angioedema (narrow) with abatacept during the reporting period. The Applicant identified 22 reports of angioedema that were coded with the following PTs: Urticaria (n=9), Angioedema (n=3), Eye swelling (n=3), Pharyngeal oedema (n=3), Lip swelling (n=2), Swelling face (n=2), Laryngeal oedema (n=1), and Face oedema (n=1). The Applicant assessed that the causality of abatacept for angioedema was likely in the three cases coded with the PT Angioedema during the 1-year reporting period; however, complications of angioedema with potential for clinically significant outcomes (e.g., dyspnea) were already labeled events for abatacept. On July 10, 2014, the PRAC finalized their PBRER #11 assessment report for abatacept[16] and concluded that there was not enough evidence to suggest a causal relationship with abatacept for angioedema based upon the data described in PBRER #11.

The Applicant subsequently closed the safety signal for angioedema following additional assessments described in PBRER #12 (included an assessment of angioedema with abatacept irrespective of route of administration) and PBRER #14.[17,18,c]

On May 29, 2019, FDA issued an information request (IR) to the Applicant requesting their full analysis of the angioedema safety signal reported in PBRER #14 and opened a Tracked Safety Issue (TSI #2077).[19,20]

On July 23, 2019, the Applicant responded to FDA's IR[21] and provided: (1) an assessment of clinical trial data for angioedema reported with abatacept, (2) disproportionality analyses conducted on the FAERS (data through 2018Q3) and VigiBase (data through 2019Q1) databases, and (3) a cumulative assessment of reports of angioedema coded within MedDRA (version 22.0) *SMQ Angioedema (narrow)* from their Corporate safety database through May 31, 2019.

1. The Applicant concluded that clinical trial data did not show an increased risk of angioedema in abatacept-treated patients compared to placebo; furthermore, the incidence of angioedema did not increase with long-term exposure when compared to short-term trials.
2. Disproportionality analyses of the FAERS and VigiBase databases did not identify safety signals (i.e., EB05 $\geq$ 2) with abatacept and terms identified as related to angioedema.
3. The Applicant provided their analysis of 1,366 cases (encompassing 1,478 events) from their Corporate safety database search, which included 42 cases that were coded with the PT Angioedema (see Appendix A for a summary of Corporate safety database search results and a line listing of cases coded with the PT Angioedema).[d] Of the 1,366 cases, 642 (47 percent) reported urticaria without any additional PT, and the Applicant assessed these cases to be unlikely to represent angioedema. The remaining 724 cases are summarized in Table 2.

[c] PBRER #12 and PBRER #14 describe the Applicant's assessment of the reporting period December 23, 2013, through December 24, 2014, and December 23, 2013, through December 24, 2016, respectively.
[d] Of the 42 Applicant-identified cases coded with the PT Angioedema, 25 were not identified within the FAERS search described in Section 2.3.1.

Table 2. Applicant-Submitted Analysis of the Bristol-Myers Squibb Corporate Safety Database for Angioedema Cases Without Urticaria Only, Cumulative Data Through May 21, 2019 N=724	
Serious, n	163
Concurrent event related to allergic reaction, n*	324
Action reported with abatacept, n	
Unknown	289
Withdrawn	192
Drug interrupted	148
No change	88
Dose increased	4
Dose decreased	2
Not applicable	1
Insufficient information for assessment, n	474
Alternate etiology for angioedema reported,† n	247
Concomitant medication associated with angioedema‡	225
Past medical history of angioedema or like symptoms	25
Concomitant nephrotic syndrome	5
Positive rechallenge, n	5
Fatal cases, n	2
* Concurrent events related to allergic reactions were described as erythema, urticaria, pruritus, etc. † A case can report more than one alternate etiology for angioedema. ‡ Medications with a known association with angioedema were reported as ACE inhibitors, NSAIDS, calcium channel blockers, monoclonal antibodies, opioids, metoprolol, and paroxetine.	

The Applicant determined that approximately 15 percent of the 724 angioedema cases described in Table 2 occurred during or shortly after abatacept administration, suggesting a possible drug-event relationship. Despite identifying cases of angioedema that had a temporal relationship to abatacept administration or positive rechallenge, the Applicant concluded that their evaluation did not support an association between abatacept and angioedema. Furthermore, the Applicant did not support updating the abatacept labeling to describe angioedema because the cases in their Corporate safety database were consistent with labeled hypersensitivity adverse events (e.g., dyspnea, hypotension, urticaria).

1.3 RELEVANT PRODUCT LABELING

The following is the relevant safety labeling for the adverse event under investigation. Labeling information abstracted from the Orencia label, updated March 21, 2019.[1]

WARNINGS AND PRECAUTIONS

5.2 Hypersensitivity

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis or anaphylactoid reactions. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event

of a reaction. Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life threatening. In postmarketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA has been reported. If an anaphylactic or other serious allergic reaction occurs, administration of ORENCIA should be stopped immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

ADVERSE REACTIONS

6.1 Clinical Studies Experience in Adult RA Patients Treated with Intravenous Orencia

Infusion-Related Reactions and Hypersensitivity Reactions

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies III, IV, and V were more common in the ORENCIA-treated patients than the placebo patients (9% for ORENCIA, 6% for placebo). The most frequently reported events (1%-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with ORENCIA included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild (68%) to moderate (28%). Fewer than 1% of ORENCIA-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 ORENCIA-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis or anaphylactoid reactions. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients and generally occurred within 24 hours of ORENCIA infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction.

2 METHODS AND MATERIALS

2.1 CASE SELECTION CRITERIA

2.1.1 Angioedema

Inclusion criteria—Reports were included as cases of angioedema if they describe a fast progression of:

- Edema of the larynx, pharynx, tongue, or uvula
  OR
- Edema of the face with reported area of lax tissue (e.g., lips)
  OR
- Non-specified face or throat swelling associated with symptoms of difficulty swallowing, shortness of breath, or trouble breathing
  OR
- Bowel wall edema supported by imaging

Exclusion criteria

- The presence of dermatologic sequala after edema resolution (e.g., blisters, skin peeling)

OR

- Eye swelling without surrounding tissue swelling described

2.1.2 Anaphylaxis Events With Fatal Outcomes

To support thorough evaluation of the labeled warning for hypersensitivity reactions (5.2), we aimed to assess cases of anaphylaxis events that had a fatal outcome. Cases of anaphylaxis events with fatal outcomes were included in our case series if the outcome of the report included the serious outcome of death and the adverse event met at least one of the following criteria:

1. Clinical diagnosis of anaphylaxis or anaphylactic shock as stated by the reporter
2. Description of clinical criteria for diagnosing anaphylaxis as stated by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (often referred to as the Sampson criteria, for the first author of the published version, see Table 3)[11]

Table 3. Clinical Criteria for Anaphylaxis[11]
Anaphylaxis is highly likely when any *one* of the following *three* criteria are fulfilled:[11]
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:** a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia) b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly (i.e., minutes to several hours) after exposure to a likely allergen for that patient: a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30 percent decrease in systolic BP* b. Adults: systolic BP of less than 90 millimeters mercury (mmHg) or greater than 30 percent decrease from that person's baseline
*Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years

2.2 CAUSALITY ASSESSMENT

We assessed cases of angioedema events or anaphylaxis events with fatal outcomes for a causal relationship with abatacept using a modified version of the World Health Organization-Uppsala

Monitoring Center (WHO-UMC) causality assessment tool (see Table 4).[22] Cases with unlikely or unassessable causality were excluded from further review.

Table 4. Causality Classification and Criteria Based on the WHO-UMC System	
Causality Term	**Assessment Criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.3 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 5.

Table 5. FAERS Search Strategies*	
Query 1: Angioedema	
Date of search	August 20, 2019
Time period of search	All reports through August 19, 2019
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Search
Product term	Product Active Ingredient: Abatacept
MedDRA search terms (Version 22.0)	PTs: Swelling face, Angioedema, Swollen tongue, Lip swelling, Eye swelling, Pharyngeal swelling, Pharyngeal oedema, Face oedema, Laryngeal oedema, Swelling of eyelid, Mouth swelling, Eyelid oedema, Periorbital oedema, Oedema mouth, Allergic oedema, Periorbital swelling, Tongue oedema, Circumoral oedema, Circumoral swelling, Lip oedema, Scleral oedema, Throat tightness, Soft tissue swelling, Localised oedema

Table 5. FAERS Search Strategies*	
Query 2: Fatal hypersensitivity	
Date of search	November 8, 2019
Time period of search	All reports through November 7, 2019
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Search
Product term	Product Active Ingredient: Abatacept
MedDRA search terms (Version 22.1)	*Anaphylactic reaction (Standard MedDRA Query) Broad search*
Reported outcomes	Serious outcome of death
* See Appendix B for a description of the FAERS database.	

2.4 LITERATURE SEARCH

DPV-I searched the medical literature with the strategy described in Table 6.

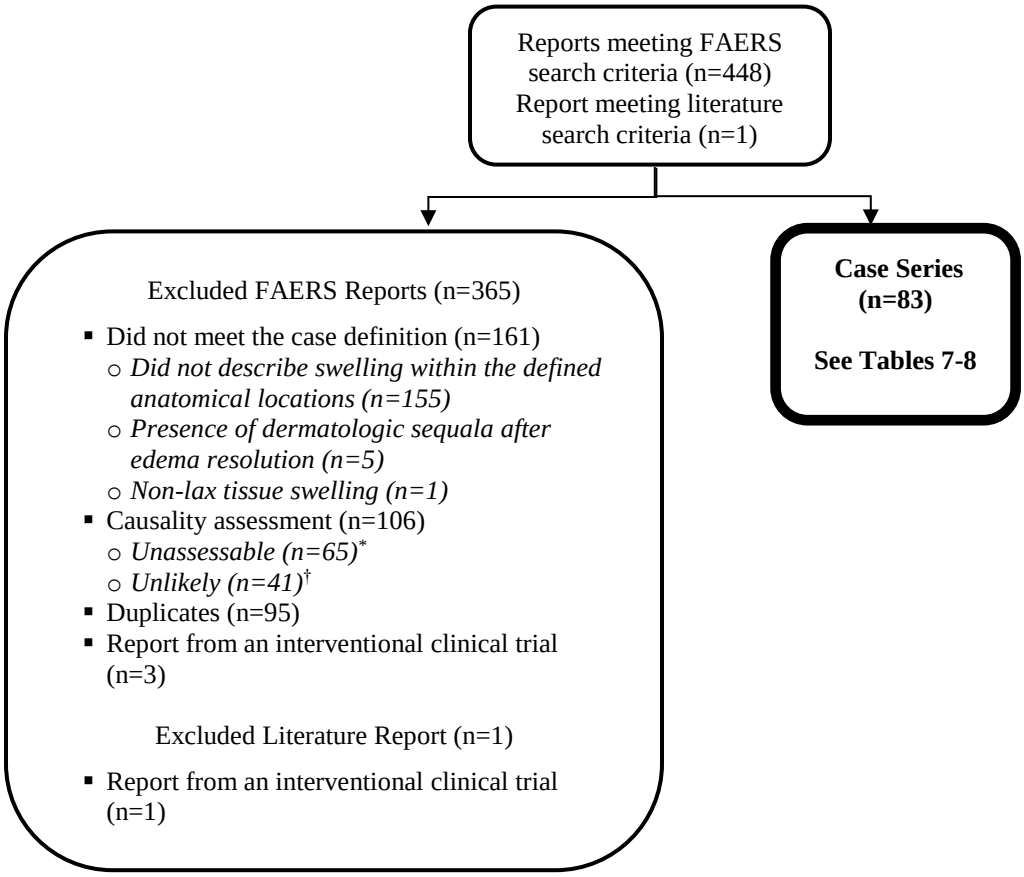
Table 6. Literature Search Strategies		
Angioedema Searches		
Date of searches	November 29, 2019	
	Angioedema Query 1	Angioedema Query 2
Database	PubMed@FDA	Embase
Search terms	("Abatacept"[Mesh]) AND "Angioedema"[Mesh]	'angioneurotic edema'/exp AND 'abatacept'/exp AND 'adverse event'/exp
Years included in search	All years	All years
Fatal Hypersensitivity Searches		
Date of searches	November 29, 2019	
	Fatal Hypersensitivity Query 1	Fatal Hypersensitivity Query 2
Database	PubMed@FDA	Embase
Search terms	((("Fatal Outcome"[Mesh]) AND "Hypersensitivity"[Mesh]) AND "Abatacept"[Mesh]) OR ((("death") AND "hypersensitivity") AND "abatacept")	('fatality'/exp AND 'abatacept'/exp AND 'hypersensitivity'/exp) OR ('anaphylaxis'/exp AND 'death'/exp AND 'abatacept'/exp)
Years included in search	All years	All years

3 RESULTS

3.1 FAERS AND LITERATURE CASE SELECTION FOR ANGIOEDEMA

The FAERS search retrieved 448 reports. After applying the case selection criteria in Section 2.1.1, assessing for causality per Section 2.2, and accounting for duplicate reports, 83 cases were included in the case series of angioedema with abatacept use (see Figure 1). The literature search identified one report of angioedema with abatacept; however, this report was excluded from the case series as it described a subject enrolled in an interventional clinical trial.

Figure 1. FAERS Case Selection for Angioedema Case Series



* The 65 unassessable reports did not contain adequate information for causality assessment.

† Of the 41 reports with an "unlikely" causal relationship, 39 had a strong alternative cause for the reported symptoms (symptoms associated with a concomitant infection (n=13), angioedema associated with the exposure of another product (n=11), the report described a concomitant diagnosis that likely caused the reported symptoms (n=7: nephrotic syndrome n=2, clogged salivary gland n=1, lymphoma n=1, dermatologist-diagnosed dermatitis n=1, sun burn n=1, and fire ant bite n=1), the swelling was associated with a surgical procedure or trauma (n=4), or the swelling was associated with a reported dental problem (n=4)), and 2 had an unsupportive temporal relationship (i.e., the onset of swelling was prior to abatacept exposure).

Table 7 summarizes descriptive characteristics of the 83 FAERS cases of angioedema reported with abatacept for this case series (see Appendix C for a line listing of these cases).

Table 7. Descriptive Characteristics of Angioedema With Abatacept in This FAERS Case Series, Received by FDA Through August 19, 2019 (N=83)	
Age, years, median (range), n=71	59 (16-83)
Sex, n (%)	
Female	75 (90.4)
Male	6 (7.2)
Not reported	2 (2.4)

Table 7. Descriptive Characteristics of Angioedema With Abatacept in This FAERS Case Series, Received by FDA Through August 19, 2019 (N=83)	
Abatacept indication, n (%)	
Rheumatoid arthritis	61 (73.5)
Arthritis	2 (2.4)
Spondyloarthritis	1 (1.2)
Arthralgia	1 (1.2)
Not reported	18 (21.7)
Prior abatacept exposure, n (%)	
No previous abatacept exposure (event followed 1st exposure)	32 (38.6)
Previous abatacept exposure (event followed 2nd or later exposure)	37 (44.6)*
Prior exposure unable to be determined/not reported	14 (16.9)
Time to onset of event from most recent abatacept exposure, n (%)†	
Acute-onset: within 24 hours or same day as administration	34 (41.0)
Delayed-onset: greater than or equal to 24 hours, or 1 or more days following administration	26 (31.3)
Not reported/unable to assess	23 (27.7)
Serious, n (%)‡	54 (65.1)
Hospitalization	14
Life-threatening	9
Disability	1
Other	42
Dechallenge, n (%)	
Positive	27 (32.5)
Negative	3 (3.6)
Not reported/unable to assess	53 (63.9)
Rechallenge, n (%)	
Positive	6 (7.2)
Negative	4 (4.8)
Not reported/unable to assess	73 (88.0)
Causality assessment, n (%)	
Probable	16 (19.3)
Possible	67 (80.7)
Report type, n (%)	
Direct	10 (12.0)
Expedited	38 (45.8)
Non-expedited	35 (42.2)
Year reported, n (%)	
2006-2008	13 (15.7)
2009-2011	8 (9.6)
2012-2014	22 (26.5)
2015-2017	25 (30.1)
2018-2019	15 (18.1)
Country, n (%)	
United States	61 (73.5)
Foreign	22 (26.5)

Table 7. Descriptive Characteristics of Angioedema With Abatacept in This FAERS Case Series, Received by FDA Through August 19, 2019

(N=83)

* Includes patients who have tolerated one or more dose(s) of ongoing abatacept therapy (n=35), a patient who was previously treated with abatacept and experienced symptoms upon re-initiation (n=1), and a patient who previously tolerated SC abatacept and experienced symptoms upon switching to IV (n=1).

† Time to onset was calculated from the administration of the most recent dose of abatacept to the time when reported symptoms met the case selection criteria described in Section 2.1.1.

‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, and other serious important medical events. A case can have more than one serious outcome.

Of the 26 cases that described a delayed-onset of angioedema following abatacept administration, the median time to onset was 2 days after the most recent dose (range of 1 to 14 days).

Table 8 provides the clinical presentation, medical management, and concomitant angioedema risk factors for the 83 cases of angioedema, by time-to-onset from abatacept administration.

Table 8. Event, Treatment, and Risk Factor Characteristics of Angioedema With Abatacept in This FAERS Case Series by Time to Onset of Event, Received by FDA Through August 19, 2019 (N=83)

	All Reports N=83	Time to Onset of Event From Last Exposure		
		Acute (<24 h) N=34	Delayed (≥24 h) N=26	Not Reported N=23
Abatacept dose, mg, n (%)				
125	27 (32.5)	7	6	14
250	2 (2.4)	1	0	1
500	5 (6.0)	4	1	0
750	13 (15.7)	9	3	1
1000	3 (3.6)	2	1	0
Not reported	33 (39.8)	11	15	7
Abatacept route, n (%)				
IV	45 (54.2)	24	17	4
SC	29 (34.9)	7	8	14
Not reported	9 (10.8)	3	1	5
Prior abatacept exposure, n (%)				
No previous abatacept exposure	32 (38.5)	20	8	4
Previous abatacept exposure	37 (44.6)*	11	15	11
Prior exposure unable to be determined	14 (16.9)	3	3	8
Area of swelling reported, n†				
Lips	26	10	10	6
Tongue	26	9	10	7
Larynx‡	23	13	5	5
Eye and surrounding area	18	8	5	5
Face and/or cheeks	13	3	4	6
Extremities	4	0	2	2
Uvula (Quincke's disease)	1	0	1	0
Dermatologic events: hives, urticaria, or rash, n (%)	26 (31.3)	11	7	8

Table 8. Event, Treatment, and Risk Factor Characteristics of Angioedema With Abatacept in This FAERS Case Series by Time to Onset of Event, Received by FDA Through August 19, 2019 (N=83)

	All Reports N=83	Time to Onset of Event From Last Exposure		
		Acute (<24 h) N=34	Delayed (≥24 h) N=26	Not Reported N=23
Concordance of timing of dermatologic events and swelling, n (%)‡	n=26	n=11	n=7	n=8
Yes	15 (57.7)	10	4	1
Not reported/unknown	11 (42.3)	1	3	7
Respiratory symptoms, n (%)§	24 (28.9)	12	8	4
Gastrointestinal symptoms, n (%)	6 (7.2)	3	3	0
Pharmacologic interventions, n†				
Antihistamine	27	14	8	5
Corticosteroid	23	13	8	2
Epinephrine	7	6	1	0
Intubation, n (%)	1 (1.2)	0	1	0
Concomitant medication associated with angioedema, n†	16	10	4	2
NSAID	9	5	3	1
ACE inhibitors or ARBs	8	6	1	1
Bisphosphonate	4	4	0	0
History of medication allergies	21 (25.3)	8	10	3

* Includes patients who have tolerated 1 or more dose(s) of ongoing abatacept therapy (n=35), a patient who was previously treated with abatacept and experienced symptoms upon re-initiation (n=1), and a patient who previously tolerated SC abatacept and experienced symptoms upon switching to IV (n=1).
† A case can have one or more areas of swelling, pharmacologic interventions, or concomitant medications associated with angioedema.
‡ The DPV reviewer classified cases describing 'throat swelling with shortness of breath' OR 'throat swelling with difficulty breathing' as 'laryngeal swelling' for purposes of this review.
§ Respiratory symptoms included shortness of breath, wheezing, or difficulty breathing.

Three representative cases from our case series are described below. One case illustrates acute-onset angioedema associated with anaphylaxis. The other two cases demonstrate delayed-onset angioedema with abatacept; one case reported a patient who was evaluated by an allergy specialist and one case required intubation and hospitalization.

FAERS Case#12457016, serious outcome—hospitalization, life-threatening, and other medically serious event, Brazil, 2016: This case described a 64-year-old female patient with a past medical history of hypertension and RA. Her home medications included methotrexate, leflunomide, and hydroxychloroquine. After finishing her first dose of abatacept 750 mg IV, she was reported to have had anaphylactic shock, a cutaneous rash on the chest and face, glottis edema, hypotension, and convulsions. She was hospitalized and treated with hydrocortisone 500 mg (unknown route), diazepam 10 mg (unknown route) and phenytoin four vials (unknown dose and route). The patient was reported to have recovered from the event an unknown time after abatacept administration. **This case was coded with the following PTs: Anaphylactic shock, Hypotension, Laryngeal edema, Rash, Seizure.**

Reviewer comment: This case describes a 64-year-old female patient who experienced glottal edema (i.e., meeting our case definition for angioedema) with anaphylaxis after abatacept administration. Her symptoms met the clinical criteria for anaphylaxis (mucocutaneous involvement and hypotension) starting after her first abatacept infusion, indicating a close temporal relationship between the drug administration and the development of anaphylaxis. The events described within this case are well-documented within the current abatacept label, which describes events of anaphylaxis, hypotension, and urticaria within Warnings and Precautions Section 5.2 Hypersensitivity. Although glottal edema and convulsions are not labeled, in this case they can reasonably be associated with the constellation of symptoms of the labeled event of anaphylactic reaction. The causality of this case was assessed to be probable for the association between abatacept and the anaphylactic reaction.

FAERS Case#7451249, serious outcome—life-threatening and other medically serious event, United States, 2010: This pharmacist-reported case was submitted directly to the FDA and describes a 46-year-old female patient who received one dose of IV abatacept (dose unknown) for polyarthritis. Her concomitant medications included hydroxychloroquine, omeprazole, mesalamine, metformin, levothyroxine, alprazolam, imipramine, and citalopram. Her past medical history was reported as inflammatory polyarthritis, psoriasis, depression, fibromyalgia, type 2 diabetes, and hypothyroidism. She had a history of drug allergies to sulfonamides, codeine, and meperidine (reactions not reported). The day following the patient's first abatacept infusion, the patient experienced a sore throat. Two days post-abatacept, she presented to the emergency department (ED) with a swollen upper lip and was treated with oral prednisone and diphenhydramine (doses not reported). Three days post-abatacept, the patient's bottom lip began to swell. Four days post-abatacept, she experienced eye, tongue, and throat swelling and was admitted to the hospital for angioedema. The patient was evaluated by "allergy/immunology staff" and was treated with methylprednisolone, hydroxyzine, and famotidine (doses and routes not reported). Her C1 esterase level was reported as normal. She was reported to have significant improvements in her symptoms allowing for hospital discharge after 2 days (post-abatacept day 6). Abatacept therapy was not resumed. **This case was coded with the PT Angioedema.**

Reviewer comment: This case describes angioedema in a female patient after her first dose of abatacept with progressive symptoms requiring hospitalization. The patient did not describe any changes to her other medications and she was assessed by an allergy specialist. Importantly, her workup revealed a normal C1 esterase level, making hereditary angioedema unlikely to be an alternative etiology for her angioedema symptoms. No other symptoms of a hypersensitivity reaction such as rash were reported. The causal relationship between abatacept and angioedema was assessed to be probable because of the temporal association and the assessment by the allergy specialist, which ruled out hereditary angioedema as an alternative etiology.

FAERS Case#13557016, serious outcome—life-threatening, United States, 2017: This pharmacist-reported case was submitted directly to the FDA and describes a 16-year-old female who was treated with IV abatacept every 4 weeks (unreported dose) for spondyloarthritis. The patient was previously treated with a TNF inhibitor but "experienced a delayed anaphylactic reaction" to the drug and was switched to abatacept. Her other medication intolerance was to

diclofenac with a reaction of hair loss and transaminitis. Her concomitant medications included medroxyprogesterone, as needed ibuprofen, and as needed acetaminophen. The patient received her fifth infusion of abatacept and presented to the ED 3 days later complaining of swelling and tingling that initially started on the left infraorbital area and spread to the tongue and lips. The patient was treated with IV methylprednisolone 125 mg and famotidine 20 mg (route not reported) and was discharged from the ED. The following day (4 days post-abatacept administration), the patient returned to the ED with tongue swelling and a feeling of "throat closing off." She was drooling slightly with no wheezing or respiratory distress. She was treated with epinephrine (unknown route and dose), methylprednisolone 80 mg IV, diphenhydramine 25 mg (unknown route), famotidine (unknown dose and route), and an unspecified fluid bolus. The patient was reported to be "doing better" after these interventions and she was admitted to a pediatric step-down inpatient unit. After admission, she had a return of her lip and tongue swelling without respiratory distress or drooling over 6 to 8 hours requiring three doses of intramuscular (IM) epinephrine (dose not reported) followed by a continuous epinephrine infusion of 0.1 mcg/kg/min. The epinephrine infusion was titrated up to 0.16 mcg/kg/min without resolution of lip or tongue swelling and the patient was intubated for airway protection. The reporter noted that the patient did not respond to steroids or epinephrine and remained intubated at the time of reporting, which was 3 days after her initial tongue and lip symptoms. **This case was coded with the following PTs: Drooling, Eye swelling, Lip swelling, Paraesthesia oral, Swollen tongue, Throat tightness.**

Reviewer comment: This healthcare-professional reported case describes symptoms consistent with angioedema beginning 3 days after her fifth dose of abatacept and her symptoms progressed to require intubation for airway protection. The patient did not respond to steroids and epinephrine therapy which is consistent with a non-histamine induced angioedema mechanism, and no other symptoms consistent with anaphylaxis (e.g., skin or gastrointestinal symptoms) were reported. The patient used ibuprofen as needed, however, no ibuprofen administration was reported. Additionally, she had a history of a "delayed anaphylaxis" reaction to another biologic agent without additional information regarding the assessment, which potentially represented a baseline risk factor for angioedema. Therefore, ibuprofen-induced angioedema and hereditary angioedema cannot be ruled out as possible alternative etiologies. The causality of the angioedema within this case was assessed to be <u>probably</u> related to abatacept because of the temporal relationship with the most recent administration. Of note, this case was not coded with the PT Angioedema despite the description of the event being consistent with the diagnosis.

In addition to the cases identified within our case series, a physician-reported case of delayed-onset angioedema was identified in the FAERS search for anaphylaxis events with fatal outcomes and is described below.

FAERS Case#6388817, serious outcome—hospitalization,[e] United States, 2007: This physician-reported case described a 42-year-old female patient who received abatacept 1000 mg IV once for RA. Her past medical history included systemic lupus and an allergy to sulfasalazine (unreported reaction). Her concomitant medications included hydroxychloroquine,

[e] Of note, this case is coded with the serious outcomes of death and hospitalization; the outcome of death was added in error and subsequently deleted from the narrative.

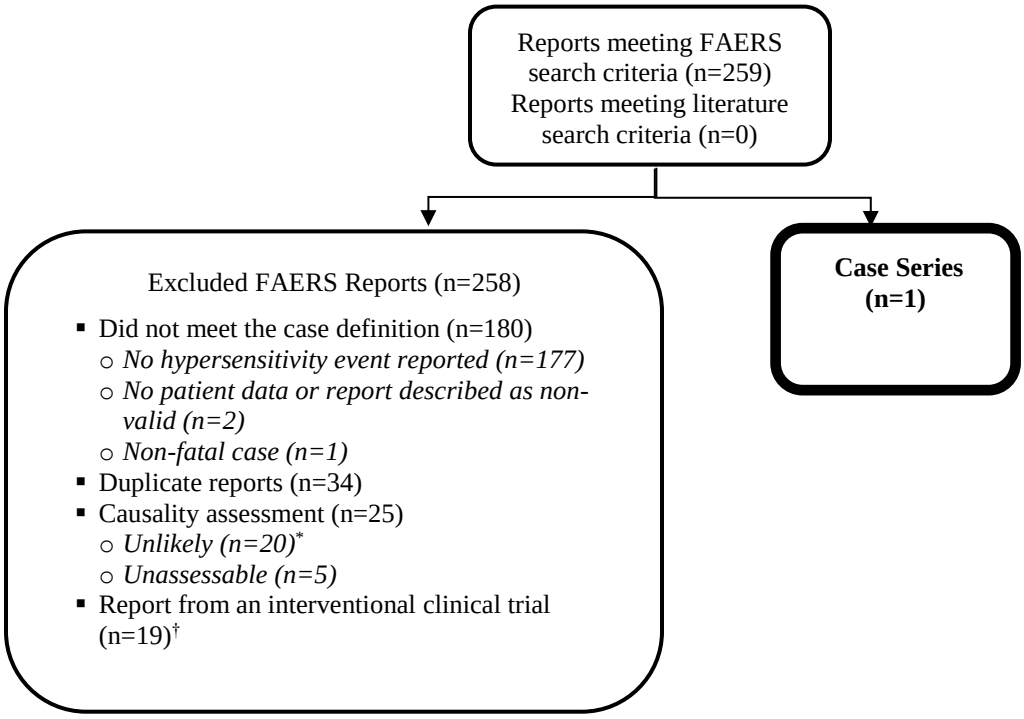
folic acid, amitriptyline, hydrocodone/acetaminophen, docusate, prednisone, methotrexate, warfarin, and ferrous sulfate. It was reported that no new medication was given around the time of the event. One day after the patient's first abatacept dose, she experienced throat swelling and vomiting requiring hospitalization. The reporting physician diagnosed the patient's symptoms as an anaphylactic reaction with angioedema. A computed tomography scan of the neck revealed soft tissue edema without evidence of abscess and clusters of normal appearing lymph nodes. During her hospitalization, she was treated with IV ranitidine, diphenhydramine, and dexamethasone (doses not reported) and she also required intubation and admission to the intensive care unit for 2 days. She was reported to be hypertensive with a diastolic blood pressure greater than 100 mmHg for which she was treated with metoprolol and lisinopril. After extubation, her examination revealed only minimal swelling of the vocal cords, no shortness of breath, rashes, or symptoms of an allergic reaction. **This case was coded with the PT Anaphylactic reaction.**

Reviewer comment: This case describes throat swelling requiring intubation 1 day after abatacept administration. Although the physician described this event as anaphylaxis with angioedema, the report was coded only with the PT Anaphylactic reaction. The presence of vomiting supports a diagnosis of anaphylaxis; however, the onset of illness was not acute (i.e., occurred the day after abatacept administration), and no other symptoms of a hypersensitivity reaction (e.g., hypotension, rash) were reported. Additionally, the swelling symptoms resolved within 72 hours without sequalae, which is typical for angioedema.[4] The patient was treated with lisinopril for hypertension during her hospitalization; however, lisinopril was not listed as a medication she took at home and is therefore unlikely to be the cause of her angioedema based upon the temporal information described within the case. The relationship between abatacept administration and the event of angioedema was assessed to be probable.

3.2 FAERS AND LITERATURE CASE SELECTION FOR ANAPHYLAXIS EVENTS WITH FATAL OUTCOMES

The FAERS search for anaphylaxis events with fatal outcomes with abatacept retrieved 259 reports with 1 case meeting the case selection criteria in Section 2.1.2 and causality assessment in Section 2.2, see Figure 2. The literature search did not identify any reports of anaphylaxis events with fatal outcomes.

Figure 2. FAERS Case Selection for Anaphylaxis Events with Fatal Outcomes



* Reports assessed to be unlikely related to abatacept (n=20) described events consistent with an infectious etiology (n=14), an event related to an underlying disease (n=4), or an allergy associated with another agent (n=2).

† Within the interventional clinical trial cases, no death was attributed to a hypersensitivity event. Cases of death were reported as infectious causes (n=7), cardiac arrest (n=6), respiratory failure (n=2), fatal pneumothorax (n=1), lymphoma with CNS involvement (n=1), hepatorenal failure (n=1), or was not reported (n=1).

The one anaphylaxis event with a fatal outcome case identified from this FAERS search is described below. Of note, the Applicant previously provided this case to the FDA in a labeling supplement that was submitted on July 11, 2013 (see Section 1.2.1).

FAERS Case# 8306317, serious outcome—death, United States, 2012: This physician-reported case describes a 74-year-old female patient with seropositive RA who was prescribed abatacept 750 mg IV. The patient was reported to be a "healthy post-menopausal woman" with additional medical history that included obesity, urinary incontinence, autoimmune thyroid disease, osteoarthritis, and hypertension. She did not have a history of a seizure disorder, heart disease, diabetes, or cardiorespiratory disease. She had previously been treated with infliximab; however, infliximab was discontinued because of a reaction of chest pressure and hives. Her home medications included tolterodine, bumetanide, levothyroxine, celecoxib, metoprolol, hydrochlorothiazide, methotrexate, folic acid, eye drops, potassium bicarbonate, prednisone, and antibiotics as needed prior to dental work.

Proper abatacept administration and storage was documented by the rheumatology office, including preparation of the infusion with the provided syringe and use of an in-line filter for infusion. Approximately 2 minutes after starting her first infusion in her rheumatologist's office, she complained of "feeling prickly and being agitated" and she "did not look well." The infusion

was stopped. Within 1 minute, she developed a grand mal seizure. Emergency services were called, and she was treated with IV methylprednisolone and IM epinephrine. Within 2 minutes, she developed respiratory arrest, bradycardia, and became asystolic. Cardiopulmonary resuscitation was started, and the patient was transported to the ED. The patient was unable to be resuscitated and was pronounced dead within 2 hours of the start of the abatacept infusion. The ED physician's assessment was that the cause of death was "anaphylactic shock." Autopsy results showed IgE of 406 (reference range 0 to 99, no units reported), tryptase of 215 (reference range <11.5, no units reported), and showed "microscopic evidence of mast cell degranulation." The medical examiner concluded that the cause of death was anaphylaxis following abatacept administration. **This case was coded with the following PTs: Anaphylactic reaction and Generalised tonic-clonic seizure.**

Reviewer comment: This case describes an elderly female patient who developed an anaphylactic reaction during her first abatacept infusion and subsequently died. This case is well documented and describes a close temporal relationship between abatacept initiation and death and is supported by the ED physician and medical examiner assessments. This case was identified by the Applicant in a prior search of their safety database and provided to the FDA within a labeling supplement that led to the inclusion of language in labeling stating a fatal case of anaphylaxis following the first infusion has been reported. The relationship between fatal anaphylaxis and abatacept administration was reported as probable.

4 DISCUSSION

The purpose of this review is for DPV-I to provide DPARP an analysis of postmarketing data regarding angioedema with abatacept use after the identification of a pediatric case describing this adverse event. The Applicant has previously investigated angioedema as a potential signal with abatacept; however, they concluded that there was not enough evidence to suggest a causal relationship. Furthermore, the Applicant asserted that labeling changes are not necessary because the events identified within their assessment for angioedema most likely represent events that belong within the spectrum of hypersensitivity (e.g., dyspnea, hypotension, urticaria) and are already included within labeling. The current review; however, identified cases of angioedema associated with abatacept administration—some of which the Applicant may be unaware of as they were reported directly to the FDA (n=10 direct reports)—that are not described by the current warning for hypersensitivity within abatacept labeling.

The current DPV-I review identified 83 cases of angioedema with abatacept use; the majority of these were from the United States (n=61, 73.5 percent). Angioedema cases were further described as having an acute onset of angioedema symptoms (i.e., within 24 hours of abatacept administration or the same day as abatacept administration) (n=34), a delayed onset of symptoms (i.e., greater than or equal to 24 hours or the day following abatacept administration) (n=26), or an unknown time to symptom development (n=23). Of note, cases of delayed-onset angioedema described a median time-to-onset of angioedema symptoms of 2 days and ranged from 1 to 14 days. Our cases described angioedema that occurred following the first abatacept exposure (n=32, 38.5 percent) and with subsequent abatacept exposures (n =37, 44.6 percent). Furthermore, cases of both acute-onset and delayed-onset angioedema were reported with a variety of dosages and with both IV and SC routes of administration. These data suggest that

patients may be at risk of developing angioedema throughout therapy with abatacept regardless of dose, route, or prior exposure to abatacept. The symptoms reported in this case series have the potential for clinically significant outcomes (e.g., intubation, impaired respiration), with edema of the lip(s) (n=26, 31.3 percent), tongue (n=26, 31.3 percent), or larynx (n=23, 27.7 percent) being reported most frequently. Additionally, respiratory symptoms defined as shortness of breath, wheezing, or difficulty breathing were reported in 24 (28.9 percent) of our cases. Notably, the majority of cases within our case series reported a serious outcome (n=54, 65.1 percent), and two cases (angioedema FAERS search, n=1; anaphylaxis with a fatal outcome FAERS search, n=1) requiring intubation for airway protection. Importantly, the risk of serious outcomes may be increased because of lack of recognition of delayed-onset angioedema, because other hypersensitivity reactions typically have a closer temporal relationship to drug exposure. For example, some cases within our series described a progressive onset of angioedema (e.g., a sore throat developed the day following administration with tongue swelling and a feeling of throat closing off the following day). Delayed recognition of angioedema could result in emergent need for intervention (e.g., monitoring for airway protection versus emergent intubation). A positive dechallenge was reported in 27 (32.5 percent) of our cases, and 6 (7.2 percent) described a positive rechallenge.

The potential mechanism for angioedema associated with abatacept is unknown, and the current case series is unable to discern this information. Because angioedema represents a constellation of disorders with a common clinical expression, it is possible that the angioedema events identified within this case series represent more than one safety signal. For example, some angioedema cases described an acute onset from abatacept administration and reported dermatologic events (i.e., hives, urticaria, rash, or a combination of the three) (32.4 percent of the acute-onset cases); these characteristics are consistent with an IgE-mediated or histamine-induced reaction. The symptoms described in these cases are well-described in current hypersensitivity labeling of abatacept (5.2) or can be implied by the labeling of anaphylaxis, which includes swelling of the lips, tongue, or uvula as one diagnostic criteria.[11] Other cases, however, report a delayed onset (i.e., ≥24 hours) of symptoms without concomitant dermatologic findings (74.1 percent of the delayed-onset cases either did not report dermatologic events or were unable to be assessed for dermatologic events); these cases may be more consistent with a non-IgE mediated mechanism (e.g., bradykinin-induced angioedema). The events described in the delayed-onset cases are not described in or implied by current labeling. In fact, Section 6.1, subsection *Infusion-Related Reactions and Hypersensitivity Reactions* states that reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea "generally occurred within 24 hours" of abatacept administration, which is inconsistent with the results shown in our case series.

Limitations of abatacept-associated angioedema reporting, identification, and causality assessment are multifactorial and should be considered when assessing the current case series. Angioedema may be difficult to recognize by providers and patients, and therefore may not be reported because of a lack of recognition of the potential drug-related cause or attribution of the angioedema to a concomitant occurrence with another diagnosis (e.g., anaphylaxis). Underreporting is particularly important when considering a hypersensitivity reaction with an onset (from exposure) ≥24 hours, which may not be as readily attributed to medication administration as would be a reaction with a shorter onset from drug administration.

Additionally, less-severe, self-resolving angioedema may only be seen as a minor nuisance and not reported to physicians or to the FDA. We identified cases of angioedema that were not coded with the PT Angioedema, limiting our ability to identify potential cases of abatacept-associated angioedema within the FAERS database. For example, one case described in Section 4.1 contains a physician diagnosis of anaphylaxis and angioedema; however, the case was coded with only the PT Anaphylactic reaction and was not identified in search for angioedema. Other cases coded as anaphylactic events, but that described angioedema, would have been missed by our search due to our search strategy. Furthermore, more than half of the cases coded with the PT Angioedema identified by the Applicant's Corporate safety database search were not identified in our search of the FAERS database (25/42), including cases with a serious outcome. As a result, our case series may underestimate the true scope (e.g., clinical description, seriousness) of angioedema events with abatacept. Finally, although our case series described positive dechallenge (n=27, 32 percent) or rechallenge (n=6, 7.1 percent), the significance of dechallenge and rechallenge is difficult to determine because of the intermittent and episodic natural course of angioedema as an adverse event. Finally, causality assessment for abatacept for cases of angioedema is complicated by concomitant administration of medications with known associations with angioedema (n=16, 19.3 percent). Spontaneous adverse event reports frequently have insufficient information to explicitly rule out alternate etiologies for an event.

Our search for cases of anaphylaxis events with fatal outcomes identified one case with a probable causal relationship to abatacept administration that was previously identified by the Applicant and submitted to the FDA. Because postmarketing data cannot be used to define the incidence or prevalence of an event, the current labeling which quantifies the number of *reported* cases of anaphylaxis with a fatal outcome requires knowledge of the difference between incidence rates and case counts within postmarketing reporting and may therefore be misleading to clinicians.

5 CONCLUSION

In conclusion, our assessment of postmarketing data suggests an association between abatacept and angioedema. The case series demonstrates both acute- and delayed-onset cases of angioedema associated with abatacept administration, with some cases describing serious or clinically significant outcomes. Although the events described within cases of acute-onset angioedema associated with other symptoms of hypersensitivity (e.g., hypotension and rash) are largely labeled or implied in current labeling for hypersensitivity describing anaphylaxis, delayed-onset angioedema and angioedema that was not associated with other hypersensitivity-related events are not labeled. Furthermore, describing cases of angioedema with a delayed onset or progressive nature of events, may prompt providers to monitor for worsening of angioedema symptoms or provide additional patient counseling. Because angioedema is a potentially life-threatening adverse event and was seen across various doses, routes of administration, and without regard for prior abatacept administration, it is important to inform prescribers of this safety issue.

6 RECOMMENDATIONS

Based on this review, DPV-I recommends an update to Section 5.2 Hypersensitivity and 6.4 Postmarketing Experience to reflect the potential risk of angioedema, including angioedema with a delayed onset after administration, with abatacept as seen below. Additionally, we recommend removing the reference to the number of cases reported as postmarketing data are limited to describe the incidence of adverse events.

Strikethrough text represents DPV-I recommended deletions. Blue text represents DPV-I recommended additions.

WARNINGS AND PRECAUTIONS

5.2 Hypersensitivity

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis or anaphylactoid reactions. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction. Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life threatening. In postmarketing experience, ~~**a case of**~~ fatal anaphylaxis following the first infusion of ORENCIA has been reported. **In the postmarketing experience, life-threatening cases of angioedema have occurred. Angioedema has occurred as early as after the first dose of ORENCIA, but also has occurred with subsequent doses. Angioedema reactions have occurred within hours of administration and in some instances had a delayed onset (i.e., days).** If an anaphylactic or other serious allergic reaction occurs, administration of ORENCIA should be stopped immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

ADVERSE REACTIONS

6.6 Postmarketing Experience

Adverse reactions have been reported during the postapproval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. Based on the postmarketing experience ~~in adult RA patients~~**with ORENCIA**, the following adverse reaction**s have** ~~has~~ been identified ~~during postapproval use with ORENCIA~~:

- Vasculitis (including cutaneous vasculitis and leukocytoclastic vasculitis)
- New or worsening psoriasis
- **Angioedema reactions [*see Warnings and Precautions (5.2)*]**

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8 APPENDICES

8.1 APPENDIX A. APPLICANT-SUBMITTED ASSESSMENT OF ANGIOEDEMA WITH ABATACEPT

Applicant-Submitted Analysis of the Bristol-Myers Squibb Corporate Safety Database, Cumulative Data Through May 21, 2019 **N=1,366**			
Case origin, n			
Spontaneous case			655
Solicited case			614
Clinical trial case			95
Literature case			2
Preferred terms (PTs), n			
Urticaria	670	Laryngeal swelling	10
Urticaria alone (without other reported PTs)	642	Eyelid oedema	10
		Periorbital oedema	7
Swelling face	232	Eye oedema	6
Eye swelling	103	Pharyngeal oedema	5
Lip swelling	93	Lip oedema	5
Swollen tongue	74	Periorbital swelling	5
Pharyngeal swelling	70	Oedema mouth	4
Face oedema	49	Tongue oedema	3
Angioedema	42	Epiglottic oedema	2
Swelling of eyelid	31	Circumoral oedema	1
Mouth swelling	24	Gingival oedema	1
Gingival swelling	24	Conjunctival oedema	1
Laryngeal swelling	14	Sclaral oedema	1
Age, years, mean (range), n=1,155			58 (8-92)
Sex, n			
Female			1,166
Male			144
Unknown			56
Time to onset of event from first dose, days, mean (range), n=522			259 (1 -3650)
Time to onset of event from last dose, days, mean (range), n=180			7 (1-392)
Outcome, n			
Unknown			826
Recovering/resolving			527
Not recovered			123
Fatal			2
Seriousness, n			
Nonserious			907
Serious			459
Action taken, n			
Unknown			626
Withdrawn			406
Drug interrupted			265
No change			173
Dose decreased			3
Dose increased			5

Applicant-Submitted Line Listing of Cases Coded With the PT Angioedema Within the Bristol-Myers Squibb Corporate Safety Database, Cumulative Data Through May 21, 2019 N=42								
	Applicant Case Number	**FAERS Case Number**	**Sex**	**Age (Years)**	**Route**	**# Doses Before Angioedema**	**Event Latency From Recent Dose**	**Edema Location and Symptoms**
1	11674819	Not identified	F	52	IV	Not reported	Not reported	Not reported
2	11898350	Not identified	F	57	IV	13 doses	18 days	Not reported
3	13121033	Not identified	F	56	IV	2.5 years	Not reported	Tongue swelling and difficulty swallowing
4	13290390	Not identified	F	46	IV	Not reported	Not reported	2 episodes of swelling: face, difficulty swelling
5	13984026	Not identified	F	25	IV	0	4 days before abatacept	Angio-neurotic edema
6	14539936	6950171	F	52	SC	11 months	>2 weeks	Stridor and subglottic edema
7	14598254	Not identified	F	40	IV	3 doses	Not reported	Not reported
8	14609796	Not identified	Unk	Unk	IV	8 months	10-11 days	Quincke's edema with lip and tongue edema
9	14632137	Not identified	F	52	IV	3 doses	7 days	Fatal tongue swelling
10	14636724	7004973	F	74	IV	1 dose	14 min into infusion	Swelling of eyes, nose, throat
11	14762983	7106040	F	55	Unk	1 dose	8 days	Not reported
12	15227689	Not identified	F	42	IV	3 doses	Shortly after loading dose	Swelling of lip and tongue
13	15291545	7616351	F	63	IV	10 months	7 days	Face swelling
14	15444649	Not identified	F	62	IV	1 dose	25 minutes into infusion	Lump in throat, difficulty breathing through mouth
15	16373128	Not identified	F	62	Unk	2.5 years	Not reported	Quincke's edema

Applicant-Submitted Line Listing of Cases Coded With the PT Angioedema Within the Bristol-Myers Squibb Corporate Safety Database, Cumulative Data Through May 21, 2019 N=42								
	Applicant Case Number	**FAERS Case Number**	**Sex**	**Age (Years)**	**Route**	**# Doses Before Angioedema**	**Event Latency From Recent Dose**	**Edema Location and Symptoms**
16	16695660	Not identified	F	53	IV	12 doses	12 hours after infusion	Face and eye edema, urticaria, pharyngeal discomfort
17	17037177	Not identified	F	59	IV	Not reported	During infusion	Swollen lip, urticaria, pruritus
18	19913722	Not identified	F	42	IV	1 dose	During infusion	Eyelid, face, and hand swelling, flushing,
19	19913946	Not identified	F	48	Unk	Not reported	Not reported	Angio-neurotic edema
20	20102828	Not identified	F	18	IV	7 months	48 hours	Eye and mouth swelling, urticaria
21	20343786	10005522	F	58	IV	Not reported	Not reported	Not reported
22	20691085	Not identified	F	Unk	IV	7 years	During infusion	Throat swelling
23	20951117	10927667	F	52	IV	19 months	14 days	Extremities
24	21200779	Not identified	F	Unk	SC	1 dose	<1 day	Swollen tongue, face, hand
25	BMS-2011-000052	Not identified	F	33	IV	Not reported	3 hours	Face, tongue, and larynx edema; dysphagia, dyspnea
26	BMS-2015-006644	10798342	F	29	IV, SC	3 months	9 days	Edema and laryngeal discomfort
27	BMS-2015-056744	11200640	F	73	Unk	6 months	Not reported	Not reported
28	BMS-2015-057342	Not identified	F	43	SC	5 months	Not reported	Edema to mouth and throat, dysphonia, dysphagia

Applicant-Submitted Line Listing of Cases Coded With the PT Angioedema Within the Bristol-Myers Squibb Corporate Safety Database, Cumulative Data Through May 21, 2019

N=42

	Applicant Case Number	FAERS Case Number	Sex	Age (Years)	Route	# Doses Before Angioedema	Event Latency From Recent Dose	Edema Location and Symptoms
29	BMS-2015-079183	Not identified	F	49	SC	2 doses	Not reported	Tongue swelling
30	BMS-2016-034885	12347782	F	70	IV	Not reported	Not reported	Not reported
31	BMS-2016-077469	Not identified	F	48	SC	8 months	<1 day	Lip and glottis edema
32	BMS-2016-091229	11200640	F	73	IV	6 months	Not reported	Not reported
33	BMS-2016-094499	14534107	F	74	SC	Not reported	Not reported	Not reported
34	BMS-2017-044031	Not identified	F	62	IV	18 months	About 20 days	Not reported
35	BMS-2018-059571	15113150	F	65	Unk	Not reported	Not reported	Not reported
36	BMS-2017-062024	13744537	F	78	IV	6 months	Not reported	Not reported
37	BMS-2017-079401	Not identified	F	50	IV	1 dose	After infusion	Not reported
38	BMS-2018-035687	15070312	F	Unk	Unk	Not reported	Not reported	Not reported
39	BMS-2019-031843	16142767	F	71	Unk	Not reported	Not reported	Not reported
40	BMS-2018-106895	15615427	F	60	SC	5 doses	Not reported	Face swelling
41	BMS-2017-053671	Not identified	F	56	SC	3 months	Not reported	Intensive facial angioedema
42	BMS-2019-043440	16302855	F	Unk	Unk	Not reported	Not reported	Not reported

Abbreviations: Unk=Unknown

8.2 APPENDIX B. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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.

8.3 APPENDIX C. FAERS LINE LISTING OF ABATACEPT AND ANGIOEDEMA OR HYPERSENSITIVITY WITH FATAL OUTCOME CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
Immediate-Onset Angioedema Cases									
1	03/20/2014	10025797	3	MX-BRISTOL-MYERS SQUIBB COMPANY-20475042	EXPEDITED	40.00	Female	MEX	HO, OT
2	02/19/2013	9111891	1	US-BRISTOL-MYERS SQUIBB COMPANY-16537722	NON-EXPEDITED	45.00	Female	USA	
3	10/10/2018	15483851	2	BR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-091000	EXPEDITED	45.00	Female	BRA	LT, OT
4	03/27/2008	6595921	2	US-BRISTOL-MYERS SQUIBB COMPANY-14064174	NON-EXPEDITED	49.00	Female	USA	
5	12/19/2016	13040967	1	BR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-107133	EXPEDITED	50.00	Female	BRA	OT
6	03/30/2016	12223552	3	BR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-022558	EXPEDITED	50.40	Female	BRA	OT
7	07/05/2017	13720891	1		DIRECT	51.88	Female	USA	OT
8	12/13/2007	6497629	2	FR-BRISTOL-MYERS SQUIBB COMPANY-14008569	EXPEDITED	52.00	Female	FRA	HO, OT
9	04/04/2012	8502632	1		DIRECT	53.00	Female	USA	OT
10	05/11/2017	13535568	1	JP-BRISTOL-MYERS SQUIBB COMPANY-BMS-2017-032548	EXPEDITED	54.00	Female	JPN	OT
11	04/19/2016	12280229	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-026806	EXPEDITED	54.47	Female	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
12	02/19/2013	9110691	1	US-BRISTOL-MYERS SQUIBB COMPANY-16713000	NON-EXPEDITED	55.00	Female	USA	
13	08/05/2011	8070787	3	AU-BRISTOL-MYERS SQUIBB COMPANY-15900152	EXPEDITED	55.00	Male	AUS	OT
14	06/05/2006	6064229	1		DIRECT	57.00	Female	USA	HO, LT
15	03/26/2018	14679063	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-024040	EXPEDITED	58.78	Female	USA	OT
16	12/31/2008	6870580	2	US-BRISTOL-MYERS SQUIBB COMPANY-14456750	EXPEDITED	59.00	Female	USA	HO
17	04/07/2015	10997044	1		DIRECT	62.00	Female	USA	
18	05/30/2006	6054217	2	US-BRISTOL-MYERS SQUIBB COMPANY-13380761	EXPEDITED	63.00	Female	USA	OT
19	02/19/2013	9137241	1	US-BRISTOL-MYERS SQUIBB COMPANY-17142811	NON-EXPEDITED	64.00	Female	USA	OT
20	06/10/2016	12457016	3	BR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-043751	EXPEDITED	64.00	Female	BRA	HO, LT, OT
21	11/07/2018	15596004	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-101584	EXPEDITED	66.90	Female	USA	HO
22	01/23/2019	15857274	1	FR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2019-003371	EXPEDITED	67.00	Female	FRA	OT
23	04/04/2016	12237015	1		DIRECT	69.00	Male	USA	HO
24	02/13/2014	9895205	2	US-BRISTOL-MYERS SQUIBB COMPANY-19345552	NON-EXPEDITED	72.00	Female	USA	
25	03/23/2016	12206059	3	BR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-018618	EXPEDITED	72.43	Female	BRA	HO, OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
26	06/18/2018	15026643	1	GB-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-051961	EXPEDITED	73.00	Male	GBR	OT
27	05/28/2009	7004973	1	US-BRISTOL-MYERS SQUIBB COMPANY-14636724	EXPEDITED	74.00	Female	USA	HO
28	11/11/2016	12932480	2	CH-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-093183	EXPEDITED	79.29	Female	CHE	LT, OT
29	06/25/2007	6341313	1	US-BRISTOL-MYERS SQUIBB COMPANY-13743034	NON-EXPEDITED		Female	USA	LT
30	02/22/2010	7288043	1	US-BRISTOL-MYERS SQUIBB COMPANY-14545479	NON-EXPEDITED		Female	USA	OT
31	02/25/2010	7294474	1	US-BRISTOL-MYERS SQUIBB COMPANY-14444665	NON-EXPEDITED		Female	USA	OT
32	02/19/2013	9110749	1	US-BRISTOL-MYERS SQUIBB COMPANY-16942039	NON-EXPEDITED		Female	USA	OT
33	04/02/2019	16149693	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2019-029407	EXPEDITED		Female	USA	OT
34	07/12/2019	16565596	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2019-068621	EXPEDITED		Female	USA	HO, LT
Delayed-Onset Angioedema Cases									
35	05/17/2017	13557016	1		DIRECT	16.00	Female	USA	LT
36	02/16/2015	10798342	1	FR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-006644	EXPEDITED	29.00	Not Reported	FRA	OT
34	12/27/2017	14329883	2	CA-BRISTOL-MYERS SQUIBB COMPANY-BMS-2017-113778	EXPEDITED	35.89	Female	CAN	OT
38	09/15/2011	8145139	1		DIRECT	41.00	Female	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
39	02/19/2013	9112047	1	US-BRISTOL-MYERS SQUIBB COMPANY-16356750	NON-EXPEDITED	43.00	Female	USA	
40	02/19/2013	9110990	1	US-BRISTOL-MYERS SQUIBB COMPANY-16425605	NON-EXPEDITED	44.00	Female	USA	
41	03/19/2010	7451249	1		DIRECT	46.32	Female	USA	HO, LT
42	12/13/2017	14281540	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2017-108552	EXPEDITED	51.56	Female	USA	OT
43	06/30/2008	6686906	1	US-BRISTOL-MYERS SQUIBB COMPANY-14148274	NON-EXPEDITED	53.00	Female	USA	
44	08/05/2014	10361750	1	US-BRISTOL-MYERS SQUIBB COMPANY-21237045	EXPEDITED	55.00	Female	USA	OT
45	08/21/2018	15301191	1	CA-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-088619	EXPEDITED	55.86	Female	CAN	OT
46	02/04/2014	9868261	1	US-BRISTOL-MYERS SQUIBB COMPANY-20084026	EXPEDITED	57.00	Female	USA	OT
47	02/13/2014	9896319	1	US-BRISTOL-MYERS SQUIBB COMPANY-18834085	NON-EXPEDITED	57.00	Female	USA	OT
48	02/22/2010	7288023	1	US-BRISTOL-MYERS SQUIBB COMPANY-14523393	NON-EXPEDITED	61.00	Female	USA	
49	12/22/2009	7226250	2	SE-BRISTOL-MYERS SQUIBB COMPANY-14898993	EXPEDITED	62.00	Female	SWE	OT
50	09/26/2007	6427860	1	US-BRISTOL-MYERS SQUIBB COMPANY-13863212	NON-EXPEDITED	63.00	Female	USA	
51	08/09/2016	12634006	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-063293	NON-EXPEDITED	65.00	Female	USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
52	09/29/2008	6773906	1	US-BRISTOL-MYERS SQUIBB COMPANY-14265979	NON-EXPEDITED	67.00	Female	USA	LT, OT
53	11/26/2015	11780541	2	SE-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-078830	EXPEDITED	67.00	Female	SWE	OT
54	09/26/2015	11557579	1	JP-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-054356	EXPEDITED	67.80	Female	JPN	HO, DS
55	12/21/2007	6512169	1	US-BRISTOL-MYERS SQUIBB COMPANY-13963970	NON-EXPEDITED	69.00	Female	USA	
56	02/13/2014	9895566	1	US-BRISTOL-MYERS SQUIBB COMPANY-17293945	NON-EXPEDITED	70.00	Female	USA	
57	05/06/2017	13519850	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2017-037279	EXPEDITED	74.00	Female	USA	OT
58	01/30/2018	14456564	6	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-007948	NON-EXPEDITED	76.00	Female	USA	
59	02/19/2013	9110367	1	US-BRISTOL-MYERS SQUIBB COMPANY-16575730	NON-EXPEDITED	83.00	Male	USA	
60	02/13/2014	9895098	1	US-BRISTOL-MYERS SQUIBB COMPANY-18695718	NON-EXPEDITED		Female	USA	
Unknown Time-to-Onset Angioedema Cases									
61	03/27/2008	6595945	1	US-BRISTOL-MYERS SQUIBB COMPANY-14078455	NON-EXPEDITED	46.00	Female	USA	
62	08/25/2014	10406944	2	SE-BRISTOL-MYERS SQUIBB COMPANY-21318464	EXPEDITED	48.73	Female	SWE	OT
63	02/13/2014	9896122	2	US-BRISTOL-MYERS SQUIBB COMPANY-19680057	NON-EXPEDITED	49.00	Female	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
64	06/01/2016	12429069	1		DIRECT	50.00	Female	USA	
65	05/22/2013	9302984	1	US-BRISTOL-MYERS SQUIBB COMPANY-17293028	EXPEDITED	52.00	Female	USA	OT
66	08/19/2016	12667835	3	GB-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-067305	EXPEDITED	53.00	Female	GBR	OT
67	11/09/2015	11715680	3	BR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-074760	EXPEDITED	55.00	Female	BRA	OT
68	09/29/2008	6773938	1	US-BRISTOL-MYERS SQUIBB COMPANY-14316871	NON-EXPEDITED	59.00	Female	USA	
69	10/08/2014	10505829	1	US-SA-2014SA014125	NON-EXPEDITED	61.00	Male	USA	HO
70	06/04/2016	12436006	2	AU-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-042417	EXPEDITED	62.74	Female	AUS	OT
71	01/23/2012	8348133	1	US-BRISTOL-MYERS SQUIBB COMPANY-16349920	EXPEDITED	64.00	Male	USA	HO
72	02/14/2017	13229856	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2017-010417	NON-EXPEDITED	65.00	Female	USA	
73	06/11/2019	16414911	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2019-045780	EXPEDITED	70.00	Female	USA	OT
74	02/05/2018	14489713	3	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-009980	NON-EXPEDITED	71.00	Female	USA	
75	04/02/2019	16285208	1		DIRECT	73.30	Female	USA	
76	10/26/2018	15553660	4	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-100681	NON-EXPEDITED	78.00	Female	USA	
77	10/05/2016	12812141	3	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-082428	NON-EXPEDITED	79.64	Female	USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
78	04/12/2018	14750471	7	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-033778	NON-EXPEDITED	82.04	Female	USA	
79	06/25/2007	6341314	1	US-BRISTOL-MYERS SQUIBB COMPANY-13743109	NON-EXPEDITED		Female	USA	
80	05/22/2013	9302957	1	US-BRISTOL-MYERS SQUIBB COMPANY-18892521	EXPEDITED		Female	USA	OT
81	12/05/2014	10632391	1	US-BRISTOL-MYERS SQUIBB COMPANY-21274881	NON-EXPEDITED		Female	USA	
82	01/09/2015	10699752	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-006984	NON-EXPEDITED		Female	USA	
83	05/17/2019	16323272	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2019-047317	NON-EXPEDITED		Not Reported	USA	
Angioedema Case Identified From the Hypersensitivity With A Fatal Outcome Search (Not Included In Case Series)									
84	12/21/2007	6388817	5	US-BRISTOL-MYERS SQUIBB COMPANY-13882824	NON-EXPEDITED	42	Female	USA	HO†
Hypersensitivity With a Fatal Outcome									
85	07/12/2012	8306317	5	US-BRISTOL-MYERS SQUIBB COMPANY-16280653	EXPEDITED	74	Female	USA	DE

*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. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.

† Of note, this case is coded with the serious outcomes of death and hospitalization; the outcome of death was added in error and subsequently deleted from the narrative.

Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, OT=Other Medically Significant

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