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Pediatric Postmarketing Pharmacovigilance Review

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Product Name(s): Simponi (golimumab SC), Simponi Aria (golimumab IV)

**Pediatric Labeling
Approval Date:** June 22, 2017

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TABLE OF CONTENTS

Executive Summary	1
1 Introduction.....	2
1.1 Pediatric Regulatory History.....	2
1.2 Selected Labeled Safety Information	3
2 Methods and Materials.....	5
2.1 FAERS Search Strategy	5
3 Results.....	5
3.1 FAERS	5
3.1.1 Total Number of FAERS Reports by Age	5
3.1.2 Selection of Pediatric Cases in FAERS	5
3.1.3 Characteristics of Pediatric Cases.....	6
3.1.4 Summary of Fatal Pediatric Cases (N=0)	7
3.1.5 Summary of All Serious Pediatric Cases (N=3)	7
4 Discussion	9
5 Conclusion	10
6 Recommendation	10
7 References.....	11
8 Appendices.....	12
8.1 Appendix A. Select Safety Labeling for Simponi Aria (Golimumab Intravenous)	12
8.2 Appendix B. FDA Adverse Event Reporting System.....	13
8.3 Appendix C. FAERS Line Listing of the Pediatric Case Series (N=3).....	14

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for golimumab in pediatric patients through age 17. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with golimumab in pediatric patients.

Simponi (golimumab subcutaneous) is a human monoclonal antibody that binds both soluble and membrane-bound tumor necrosis factor (TNF), a key mediator of multiple inflammatory diseases.¹ Initially FDA approved April 24, 2009, golimumab subcutaneous (SC) is currently approved for treatment of active rheumatoid arthritis (RA) in combination with methotrexate (MTX), active psoriatic arthritis alone or in combination with MTX, ankylosing spondylitis, and moderate to severe ulcerative colitis in adult patients.¹ An intravenous (IV) formulation of golimumab, Simponi Aria, was FDA approved July 18, 2013. Currently approved indications for IV golimumab include active RA in combination with MTX, active psoriatic arthritis alone or in combination with MTX, or ankylosing spondylitis in adult patients.²

FDA issued a postmarketing requirement (PMR) study at the time of golimumab SC approval to fulfill PREA. PMR study CNTO148JIA3001 assessed the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab in pediatric patients ages 2-16 years with active polyarticular juvenile idiopathic arthritis (pJIA). The efficacy of golimumab SC in the treatment of pJIA was not demonstrated in this study; however, the results of this PMR study were incorporated in the labeling update for golimumab SC dated June 22, 2017.¹ Upon approval of golimumab IV in April of 2013, a PMR study was issued to assess the safety, efficacy, PK/PD and immunogenicity of IV golimumab in patients ages 2-17 years, 11 months with active JIA despite standard therapy with methotrexate. The trial is currently underway.³

Our FAERS search retrieved 127 pediatric reports with golimumab from April 24, 2009, through December 27, 2018. Of these, 87 reports included serious outcomes. No fatal cases describing unlabeled events were identified. We identified three foreign FAERS cases with golimumab in the pediatric population reporting a non-fatal serious unlabeled outcome. All cases occurred in patients receiving golimumab SC; no cases were identified with the IV product.

The three non-fatal serious cases identified described the unlabeled events of urethral prolapse, autoimmune hemolytic anemia (AIHA), and Crohn's disease. Of the three serious and unlabeled adverse events, no specific pattern of adverse events was noted. Regarding urethral prolapse and AIHA, singular reports of adverse events without supporting cases in the medical literature or the adult population do not necessarily constitute safety signals. FAERS searches for domestic reports of new-onset IBD associated with golimumab use in adults did not yield additional detailed cases at this time, and we did not identify additional detailed cases of new-onset IBD in adults or children in the medical literature. In conclusion, DPV will continue monitoring for all adverse events associated with the use of golimumab with routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for golimumab in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). Golimumab is not approved for use in pediatric patients in the United States. This review focuses on serious unlabeled adverse events associated with golimumab use in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Simponi (golimumab subcutaneous) is a human monoclonal antibody that binds both soluble and membrane-bound tumor necrosis factor (TNF), a key mediator of multiple inflammatory diseases. Initially FDA approved April 24, 2009, golimumab subcutaneous (SC) is currently approved for treatment of active rheumatoid arthritis (RA) in combination with methotrexate (MTX), active psoriatic arthritis alone or in combination with MTX, ankylosing spondylitis, and moderate to severe ulcerative colitis in adult patients. An intravenous (IV) formulation of golimumab, Simponi Aria, was FDA approved July 18, 2013. Currently approved indications for golimumab IV include active RA in combination with MTX, active psoriatic arthritis alone or in combination with MTX, or ankylosing spondylitis in adult patients.

FDA issued a postmarketing requirement (PMR) study at the time of golimumab SC approval to fulfill PREA. PMR study CNTO148JIA3001 assessed the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab in pediatric patients ages 2-16 years with active polyarticular juvenile idiopathic arthritis (pJIA). The efficacy of golimumab SC in the treatment of pJIA was not demonstrated because there was no statistical difference in the study's primary endpoint: the flare rate of golimumab SC-treated patients versus placebo between weeks 16 and 48.¹ In this study, the frequency and type of adverse reactions seen in children were generally similar to those observed in adults. The results of PMR study CNTO148JIA3001 assessing the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab in pediatric patients ages 2-16 years with active polyarticular juvenile idiopathic arthritis (pJIA) were incorporated in the labeling update for golimumab SC dated June 22, 2017 (see Section 1.2 below for specific verbiage).

Upon approval of golimumab IV in April of 2013, a PMR study was issued to assess the safety, efficacy, PK/PD, and immunogenicity of golimumab IV in patients ages 2-17 years and 11 months with active JIA despite standard therapy with methotrexate. The trial is currently underway.³

Golimumab SC was granted orphan drug designation for pediatric ulcerative colitis in March of 2012. In April of 2015, golimumab IV was granted FDA orphan drug designation for pJIA in patients 0-18 years of age.⁴

Of note, in the European Union (EU), the Committee for Medicinal Products for Human Use issued a positive opinion for a pJIA indication for golimumab SC, which was adopted by the EU Commission on June 24, 2016.⁵

Past DPV reviews for golimumab include the enhanced pharmacovigilance (ePV) for malignancy in pediatric and young adult patients (less than 30 years of age), completed for all TNF inhibitors for a 10-year interval.⁶ No labeling changes for golimumab have resulted from this review. This review was triggered by the June 22, 2017, labeling update for golimumab. DPV has not completed a pediatric-specific review of FAERS data for golimumab SC or IV for the Pediatric Advisory Committee (PAC).

1.2 SELECTED LABELED SAFETY INFORMATION

The BOXED WARNING, highlights of the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS, ADVERSE REACTIONS *Postmarketing Experience*, and USE IN SPECIFIC POPULATIONS *Pediatric Use* sections included in the product labeling for golimumab SC dated 3/2018 are listed below. See Appendix A for select labeling information for golimumab IV.

Golimumab SC

<p style="text-align: center;">WARNING: SERIOUS INFECTIONS AND MALIGNANCY</p> <p>SERIOUS INFECTIONS</p> <p>Patients treated with SIMPONI® are at increased risk for developing serious infections that may lead to hospitalization or death [see <i>Warnings and Precautions (5.1)</i>]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.</p> <p>Discontinue SIMPONI if a patient develops a serious infection.</p> <p>Reported infections with TNF blockers, of which SIMPONI is a member, include:</p> <ul style="list-style-type: none">• Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before SIMPONI use and during therapy. Initiate treatment for latent TB prior to SIMPONI use.• Invasive fungal infections including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric antifungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.• Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria. <p>Consider the risks and benefits of treatment with SIMPONI prior to initiating therapy in patients with chronic or recurrent infection.</p> <p>Monitor patients closely for the development of signs and symptoms of infection during and after treatment with SIMPONI, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see <i>Warnings and Precautions (5.1)</i>].</p> <p>MALIGNANCY</p> <p>Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member [see <i>Warnings and Precautions (5.2)</i>].</p>

-----**WARNINGS AND PRECAUTIONS**-----

- **Serious Infections:** Do not start SIMPONI during an active infection. If an infection develops, monitor carefully, and stop SIMPONI if infection becomes serious (5.1)
- **Invasive Fungal Infections:** For patients who develop a systemic illness on SIMPONI, consider empiric antifungal therapy for those who reside in or travel to regions where mycoses are endemic (5.1)
- **Hepatitis B Reactivation:** Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop SIMPONI and begin antiviral therapy (5.1)
- **Malignancies:** Incidence of lymphoma was greater than in the general U.S. population. Cases of other malignancies have been observed among patients receiving TNF blockers (5.2)
- **Congestive Heart Failure:** Worsening, or new onset, may occur. Stop SIMPONI if new or worsening symptoms occur (5.3)
- **Demyelinating Disorders:** Exacerbation or new onset may occur (5.4)
- **Lupus-like Syndrome:** Discontinue SIMPONI if symptoms develop (5.5)
- **Hypersensitivity Reactions:** Serious systemic hypersensitivity reactions including anaphylaxis may occur (5.11)

-----**ADVERSE REACTIONS**-----

Most common adverse reactions (incidence > 5%) are upper respiratory tract infection, nasopharyngitis, injection site reactions (6.1)

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of golimumab. 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 SIMPONI exposure.

Immune system disorders: Serious systemic hypersensitivity reactions (including anaphylactic reaction) [see Warnings and Precautions (5.11)], sarcoidosis

Neoplasms benign, malignant and unspecified: Melanoma, Merkel cell carcinoma [see Warnings and Precautions (5.2)]

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Skin and subcutaneous tissue disorders: Skin exfoliation, rash, bullous skin reactions

-----**USE IN SPECIFIC POPULATIONS**-----

8.4 Pediatric Use

Effectiveness of SIMPONI in pediatric patients less than 18 years of age has not been established.

The safety and efficacy of SIMPONI were evaluated in a multicenter, placebo-controlled, double-blind, randomized-withdrawal, parallel group study in 173 children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA) despite treatment with MTX for at least 3 months. Subjects were maintained on their stable dose of MTX at the same dose (mg/week) at study entry. Concurrent use of stable doses of oral corticosteroids (≤ 10 mg/day or 0.2 mg/kg/day prednisone or equivalent, whichever was less) and/or NSAIDs was permitted. In the 16 week open-label phase, all patients received MTX and SIMPONI 30 mg/m² (maximum 50 mg) subcutaneously every 4 weeks. Patients who achieved an ACR Ped 30 response at Week 16 entered the randomized-withdrawal phase of the study and received MTX and either SIMPONI 30 mg/m² (maximum 50 mg) or placebo every 4 weeks through Week 48.

The primary endpoint of the study was the proportion of patients who did not experience a flare between Week 16 and Week 48, among all subjects who entered the randomized withdrawal phase. The efficacy of SIMPONI in the

treatment of pJIA was not demonstrated in this study because there was no statistical evidence of differences in flare rate between SIMPONI-treated patients and placebo patients between Weeks 16 and 48.

In this study, the frequency and type of the adverse reactions seen in children were generally similar to those observed in adults.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Date of Search	December 28, 2018
Time Period of Search	April 24, 2009 [†] - December 27, 2018
Search Type	Quick Query
Product Terms	Product Active Ingredient: Golimumab
MedDRA Search Terms (Version 21.1)	All PT terms
Search Parameters	All ages, all outcomes, worldwide
* See Appendix B for a description of the FAERS database.	
[†] Date of U.S. approval	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from April 24, 2009, through December 27, 2018, with golimumab.

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	16,470 (5,598)	12,559 (1,821)	442 (61)
Pediatrics (0 - <17.99 years)	127 [‡] (55)	87 [‡] (17)	5 [‡] (2)
* May include duplicates and transplacental exposures, and have not been assessed for causality			
[†] For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.			
[‡] See Figure 1. 125 reports containing age resulted from our FAERS search. Two additional reports of pediatric deaths were identified among reports not containing age in the coded field, for a total of 127 reports. The two null age reports are also reflected in the totals for serious outcome and deaths.			

3.1.2 Selection of Pediatric Cases in FAERS

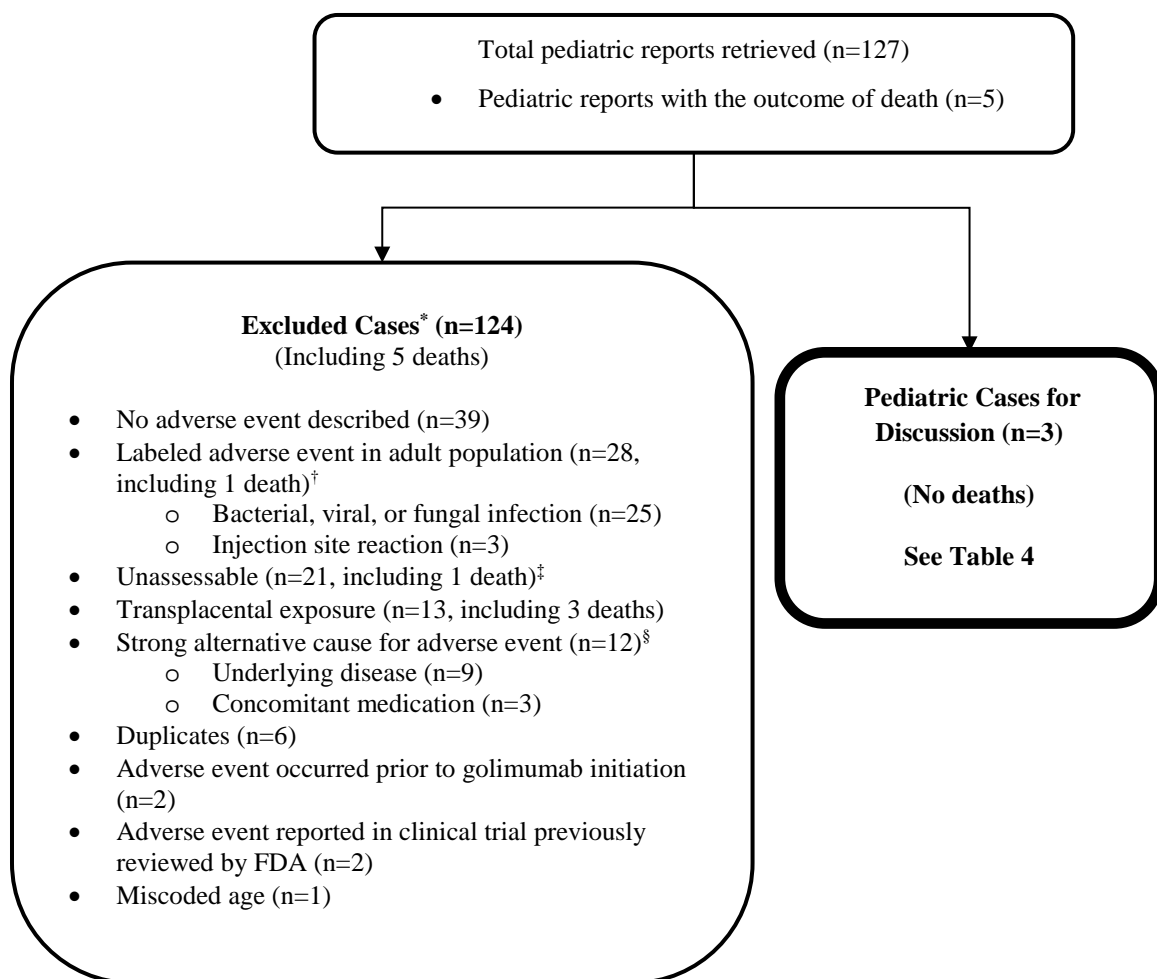
Our FAERS search retrieved 127 pediatric reports with golimumab from April 24, 2009, through December 27, 2018. Of these, 87 reports included serious outcomes. Thirteen reports were

submitted for the IV formulation. The remainder of reports were for the SC formulation or the formulation was not specified.

We reviewed all FAERS pediatric reports for golimumab SC and IV formulations.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Golimumab



*DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

† Labeled adverse events included in the current U.S. golimumab product labeling for adults. There was no increase in severity of labeled events in comparison with the adult population.

‡ These reports could not be assessed for causality because of insufficient or contradictory information.

§ Reports described uveitis in patients with JIA (n=2); worsening gastrointestinal symptoms (n=1), *C. difficile* infection (n=1), bloody diarrhea and subsequent anemia (n=1), tubulointerstitial nephritis (n=1) and pancreatitis (n=3) in patients with ulcerative colitis; benign lymphoid hyperplasia following a molar abscess (n=1); suicidal ideation in a patient with a history of suicidal behavior (n=1); and lymphopenia in patient on concomitant azathioprine (n=1).

3.1.3 Characteristics of Pediatric Cases

Appendix C contains a line listing of the three pediatric cases.

Table 4 summarizes the three FAERS cases in pediatric patients with golimumab received by FDA from April 24, 2009, through December 27, 2018.

Table 4. Characteristics of the FAERS Pediatric Cases with Golimumab Received by FDA from April 24, 2009, to December 27, 2018 (N=3)		
Age in years	12	1
	15	1
	16	1
Sex	Male	None
	Female	3
Country	United States	None
	Foreign	3
Reported Reason for Use	JIA	2
	Psoriatic arthritis	1
Serious Outcome*	Hospitalization	2
	Other serious	1
* 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 include any fatal pediatric adverse event cases in our case series.

3.1.5 Summary of All Serious Pediatric Cases (N=3)

We identified three foreign FAERS cases with golimumab in the pediatric population reporting a non-fatal, serious, unlabeled adverse event. All cases occurred in patients receiving golimumab SC; no cases were identified with the IV product.

FAERS Case # 9459658, Expedited, OT, SWE, 2013

A physician reported a 16-year-old female receiving golimumab for JIA developed Crohn's disease. The patient received golimumab SC 50 mg every three weeks for about a year and developed diarrhea, abdominal pain, and a 4-kilogram weight loss. Pathology confirmed Crohn's disease in the terminal ileum spreading to the colon. Treatment with golimumab was withdrawn. Past and current medications, comorbidities, and HLA-B27 status for this patient were not reported.

Reviewer's Comment:

Causality assessment of the potential association between golimumab and new-onset inflammatory bowel disease (IBD) in patients with rheumatic disease is hindered by multiple factors including whether IBD is a common disease-related comorbidity of the underlying indication for the TNF inhibitor and the use of previous or concomitant medications that may also be associated with secondary IBD.⁷

We searched for additional domestic cases of new-onset IBD with golimumab in the FAERS database in adults as well as in the medical literature for both pediatric and adult patients. Our

FAERS search for domestic reports of new-onset IBD associated with golimumab use in adult patients lacked additional cases with sufficient information for assessment.

We identified case reports in the literature of adult patients with rheumatic diseases manifesting with exacerbations of underlying IBD after treatment initiation with golimumab but did not identify detailed case reports of new-onset IBD with golimumab.^{8,9}

A 2015 publication reviewed FAERS data for the association between TNF inhibitor use and new-onset IBD in RA and juvenile rheumatoid arthritis patients (JRA).¹⁰ Between January 2003-December 2011, the authors identified 158 cases of TNF inhibitor-associated IBD (including one case associated with golimumab), and the Naranjo score was applied for causality assessment. The authors concluded that there was a weak association between new-onset IBD and TNF inhibitor use in RA patients and a moderately strong association between etanercept exposure and new-onset IBD^a in JRA patients. The authors did not supply sufficient information specifically regarding the case associated with golimumab use for additional independent assessment.

Due to limited information and multiple confounders, DPV will continue routine pharmacovigilance.

FAERS Case # 10678328, Expedited, HO, FIN, 2014

A physician reported a urethral mucosal prolapse in a 15-year-old female patient receiving golimumab 50 mg SC monthly for 10 months for the treatment of psoriatic arthritis. The patient also received methotrexate 20 mg SC weekly for 34 months. On an unknown date, the patient complained of a sore, growing lump at the end of her urethra that would occasionally bleed. A urethral mucosal prolapse was found upon cystoscopy and resected. Golimumab was stopped and the patient recovered.

Reviewer's Comment:

Urethral prolapse is a rare condition, with a suggested incidence of 1 in 3000 in girls, occurring most commonly in prepubescent or post-menopausal females. Low estrogen and increased intrabdominal pressure are proposed mechanisms for the development of urethral prolapse, however, the true underlying mechanism is not well understood.¹² This case lacks information about the patient's risk factors for urethral prolapse such as menarchal status or risk for increased intrabdominal pressure (e.g., cough, trauma, or constipation) to inform a thorough causality assessment.¹² To further assess the potential association between golimumab and urethral prolapse, we performed a FAERS search for golimumab and urethral prolapse in the adult population; our search retrieved no additional reports.

FAERS Case # 15271111, Expedited, HO, AUT, 2018

A physician reported autoimmune hemolytic anemia (AIHA) in a 12-year-old female receiving golimumab for treatment of extended oligoarthritis of pJIA. Approximately six months after the patient initiated golimumab, she was admitted to the hospital for treatment of severe AIHA. Her

^a Etanercept is the only TNF inhibitor labeled for IBD in ADVERSE REACTIONS *Postmarketing Experience*.¹¹

laboratory findings were hemoglobin 40 g/L (normal 118-152 g/L), lactate dehydrogenase 467 u/L (normal 104-257 u/L), indirect coombs test positive. Golimumab was discontinued, the patient was treated with corticosteroids, and she was discharged from the hospital five days after admission. The patient received MTX prior to golimumab initiation but MTX was discontinued when golimumab was introduced. Comorbid conditions included alopecia totalis. The patient's history was negative for lymphoproliferative disorders, systemic lupus erythematosus, inflammatory bowel diseases, previous similar episodes, and recent viral or respiratory infections.

Reviewer's Comment: Golimumab is labeled for pancytopenia, leukopenia, and thrombocytopenia, but not hemolytic anemia.¹ Hemolysis develops secondary to intrinsic erythrocyte abnormalities or extrinsic causes such as chemical, immunological, or physical forces that lead to erythrocyte damage. AIHA is a relatively rare form of hemolytic anemia and root causes include infections, immunodeficiency, lymphoproliferative disorders, and tumors. AIHA diagnosis depends on laboratory evidence of hemolysis and serologic evidence of autoantibody presence, both of which the narrative describes. The medical literature describes an association with AIHA and systemic autoimmune conditions, however, a link between AIHA and JIA has not been established.¹³ An additional FAERS search for adult cases of with PTs of Haemolytic anaemia and Autoimmune haemolytic anaemia yielded zero and two cases, respectively. Of the two cases coded with the PT Autoimmune haemolytic anaemia, one described pancytopenia and "suspected" AIHA and one described pancytopenia in the setting of a negative Coomb's test; both cases lacked information about specific laboratory diagnostic findings to confirm the diagnosis of AIHA.

4 DISCUSSION

DPV reviewed all FAERS reports with golimumab SC and IV in pediatric patients from April 24, 2009, to December 27, 2018. We identified three non-fatal serious cases describing the unlabeled events of urethral prolapse (n=1), AIHA (n=1), and Crohn's disease (n=1). No specific pattern of adverse events was noted from review of these cases, and the cases contained limited information for assessment.

For completeness, we reviewed the FAERS database for reports of urethral prolapse and AIHA associated with golimumab use occurring in the adult population. However, our additional searches did not yield sufficient information to constitute safety signals.

We also searched the FAERS database for reports of IBD occurring in the adult population and searched the medical literature for case reports in both pediatric and adult patients receiving golimumab. Our search of the FAERS database lacked additional reports of new-onset IBD in the adult population with sufficient information for causality assessment. We did not find additional detailed reports in the medical literature of new-onset IBD with golimumab.

Due to limited information in FAERS and multiple confounding factors limiting assessment, we will continue routine pharmacovigilance of the adverse events of urethral prolapse, AIHA, and new-onset IBD associated with golimumab use.

5 CONCLUSION

DPV-I analyzed all pediatric postmarketing events associated with golimumab use from April 24, 2009, through December 27, 2018. We identified the adverse events of new-onset Crohn's disease, urethral prolapse and AIHA with golimumab. DPV will continue routine pharmacovigilance for all adverse events reported with golimumab use.

6 RECOMMENDATION

DPV will continue monitoring for all adverse events associated with the use of golimumab.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. SELECT SAFETY LABELING FOR SIMPONI ARIA (GOLIMUMAB INTRAVENOUS)

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal (such as histoplasmosis), and other opportunistic infections have occurred in patients receiving SIMPONI ARIA (5.1).**
- **Discontinue SIMPONI ARIA if a patient develops a serious infection or sepsis (5.1).**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI ARIA (5.1).**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1).**
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member (5.2).**

-----WARNINGS AND PRECAUTIONS-----

- **Serious Infections:** Do not start SIMPONI ARIA during an active infection. If an infection develops, monitor carefully, and stop SIMPONI ARIA if infection becomes serious (5.1).
- **Invasive Fungal Infections:** For patients who develop a systemic illness on SIMPONI ARIA, consider empiric antifungal therapy for those who reside in or travel to regions where mycoses are endemic (5.1).
- **Hepatitis B Reactivation:** Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop SIMPONI ARIA and begin anti-viral therapy (5.1).
- **Malignancies:** More cases of lymphoma have been observed among patients receiving TNF blockers compared with patients in the control groups. Cases of other malignancies have been observed among patients receiving TNF blockers (5.2).
- **Congestive Heart Failure:** Worsening, or new onset, may occur. Stop SIMPONI ARIA if new or worsening symptoms occur (5.3).
- **Demyelinating Disorders:** Exacerbation or new onset may occur (5.4).
- **Lupus-like Syndrome:** Discontinue SIMPONI ARIA if symptoms develop (5.5).
- **Hypersensitivity Reactions:** Serious systemic hypersensitivity reactions including anaphylaxis may occur (5.11).

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence $\geq 3\%$) are: upper respiratory tract infection, alanine aminotransferase increased, viral infection, aspartate aminotransferase increased, neutrophil count decreased, bronchitis, hypertension, and rash (6.1).

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of golimumab. 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 golimumab exposure.

General Disorders and Administration Site Conditions: Infusion-related reactions [see Warnings and Precautions (5.11)]

Neoplasm benign and malignant: Melanoma, Merkel cell carcinoma [see Warnings and Precautions (5.2)]

Immune system disorders: Serious systemic hypersensitivity reactions (including anaphylactic reaction) [see Warnings and Precautions (5.11)], sarcoidosis

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Skin and subcutaneous tissue disorders: Skin exfoliation, bullous skin reactions

Section 8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of SIMPONI ARIA in pediatric patients less than 18 years of age have not been established. Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with other TNF-blocking agents [see Warnings and Precautions (5.2)].

8.2 APPENDIX B. 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.

8.3 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	12/29/2014	10678328	2	FI-JNJFOC- 20141216528	Expedited (15-Day)	15.543	F	FIN	HO
2	8/13/2018	15271111	2	AT-JNJFOC- 20180613168	Expedited (15-Day)	12	F	AUT	HO
3	8/15/2013	9459658	1	SE-JNJFOC- 20130806932	Expedited (15-Day)	16	F	SWE	OT
<p>*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. Abbreviations: HO=Hospitalization, OT=Other medically significant,</p>									

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/s/

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