Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date: February 23, 2024

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Pediatric Labeling Approval Date: December 4, 2020

Proprietary Name	Generic Name	New Drug Application (NDA)	Applicant
Januvia	Sitagliptin	021995	Merck Sharp and Dohme Corp.
Janumet	Sitagliptin and metformin hydrochloride	022044	Merck Sharp and Dohme Corp.
Janumet XR	Sitagliptin and metformin hydrochloride extended-release	202270	Merck Sharp and Dohme Corp.

TTT Record ID: 2023-7530

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Januvia (sitagliptin) tablets, Janumet (sitagliptin and metformin hydrochloride) tablets, and Janumet XR (sitagliptin and metformin hydrochloride extended-release) tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Januvia, Janumet, or Janumet XR in pediatric patients.

Januvia is a dipeptidyl peptidase-4 (DPP-4) inhibitor first approved in the United States on October 16, 2006. Janumet and Janumet XR are combinations of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin hydrochloride, a biguanide. Janumet was first approved by FDA on March 30, 2007, and Janumet XR was first approved on February 2, 2012. Currently all three products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Pursuant to PREA, FDA issued postmarketing requirements (PMRs) for pediatric studies (PMR 224-1, 856-1, 1802-1, 1082-2) concurrent with the initial approvals for Januvia, Janumet, and Janumet XR. Additionally, in 2007, the Applicant first submitted a proposed pediatric study request related to its sitagliptin products. The initial proposed pediatric study request led FDA to issue a Written Request (WR) for Januvia, Janumet, and Janumet XR under BPCA in 2012.

On June 4, 2020, the applicant submitted sNDA 021995/S047, sNDA 022044/S048, sNDA 202270/S022 to fulfil its PREA PMRs and meet the BPCA WR requirements. The Applicant submitted results of three randomized and placebo-controlled trials that evaluated 1) sitagliptin as monotherapy (NCT00730275) and 2) sitagliptin as add-on therapy to metformin (NCT01472367, NCT01760447) over 20 weeks followed by 34-week extensions.

Based on the results of the pediatric trials, FDA determined there was insufficient data to support broadening the indication for Januvia, Janumet, and Janumet XR to include glycemic control in pediatric patients with T2DM.

The labeling for Januvia, Janumet, and Janumet XR was updated on December 4, 2020, to reflect the clinical trial data and to specify that safety and effectiveness of these products have not been established in pediatric patients. This pediatric postmarketing safety review was prompted by the pediatric labeling on December 4, 2020. DPV has not previously presented sitagliptin products to the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with Januvia, Janumet, or Janumet XR in pediatric patients less than 18 years of age through December 12, 2023, and identified 48 reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Januvia, Janumet, or Janumet XR in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for Januvia, Janumet, or Janumet XR at this time and will continue routine pharmacovigilance monitoring for Januvia, Janumet, or Janumet XR.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Januvia (sitagliptin) tablets, Janumet (sitagliptin and metformin hydrochloride) tablets, and Janumet XR (sitagliptin and metformin hydrochloride extended-release) tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Januvia, Janumet, or Janumet XR in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Januvia is a dipeptidyl peptidase-4 (DPP-4) inhibitor first approved in the United States on October 16, 2006. Janumet and Janumet XR are combinations of sitagliptin and metformin hydrochloride, a biguanide. Janumet was first approved by FDA on March 30, 2007, and Janumet XR was first approved on February 2, 2012. Currently all three products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).[1,2,3]

Pursuant to PREA, FDA issued postmarketing requirements (PMRs) for pediatric studies (PMR 224-1, 856-1, 1802-1, 1082-2) concurrent with the initial approvals for Januvia, Janumet, and Janumet XR. Additionally, in 2007, the Applicant first submitted a proposed pediatric study request related to its sitagliptin products. The initial proposed pediatric study request led FDA to issue a Written Request (WR) for Januvia, Janumet, and Janumet XR under BPCA in 2012.[4,5]

On June 4, 2020, the Applicant submitted sNDA 021995/S047, sNDA 022044/S048, sNDA 202270/S022 to fulfil its PREA PMRs and meet the BPCA WR requirements. The applicant submitted results of three randomized and placebo-controlled trials that evaluated 1) sitagliptin as monotherapy (NCT00730275) and 2) sitagliptin as add-on therapy to metformin (NCT01472367, NCT01760447) over 20 weeks followed by 34-week extensions.

Based on the results of the pediatric trials, FDA determined there was insufficient data to support broadening the indication for Januvia, Janumet, and Janumet XR to include glycemic control in pediatric patients with T2DM.

The labeling for Januvia, Janumet, and Janumet XR was updated on December 4, 2020, to reflect the clinical trial data and to specify that safety and effectiveness of these products have not been established in pediatric patients. This pediatric postmarketing safety review was prompted by the pediatric labeling on December 4, 2020. DPV has not previously presented sitagliptin products to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Januvia and Janumet[a] labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Januvia, Janumet, or Janumet XR labeling information, please refer to the full prescribing information.[1,2,3]

[a] Safety information in the Highlights of Prescribing Information is identical for Janumet and Janumet XR.

1.2.1 Januvia

---------- CONTRAINDICATIONS ----------
History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema (5.5, 6.2)
---------- WARNINGS AND PRECAUTIONS ----------

- Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA. (5.1)
- Heart failure: Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of JANUVIA in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.2)
- Acute Renal Failure: Has been reported postmarketing, sometimes requiring dialysis. Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter. (5.3)
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues: Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Lower dose of insulin or insulin secretagogue may be required. (5.4, 7.1)
- Hypersensitivity Reactions: There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with JANUVIA such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Promptly stop JANUVIA, assess for other potential causes, institute appropriate monitoring and treatment. (5.5, 6.2)
- Severe and Disabling Arthralgia: Has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.6)
- Bullous Pemphigoid: There have been postmarketing reports requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue JANUVIA. (5.7)

---------- ADVERSE REACTIONS ----------
Adverse reactions reported in □5% of patients treated with JANUVIA and more commonly than in patients treated with placebo are upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with JANUVIA compared to placebo. (6.1)

8.4 Pediatric Use
The safety and effectiveness of JANUVIA have not been established in pediatric patients.

Three 20-week double-blind, placebo-controlled studies each with 34-week extensions were conducted to evaluate the efficacy and safety of sitagliptin in 410 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes, with or without insulin therapy (HbA1c 6.5-10% for patients not on insulin, HbA1c 7-10% for patients on insulin). At study entry, patients in study 1 were not treated with oral antihyperglycemic agents; patients in studies 2 and 3 were on maximally tolerated metformin therapy. The primary efficacy endpoint was the change from baseline in HbA1c after 20 weeks of therapy. The pre-specified primary efficacy analyses included data from study 1 and pooled data from studies 2 and 3, regardless of glycemic rescue or treatment discontinuation.

In both efficacy analyses, the effect of treatment with sitagliptin was not significantly different from placebo. In study 1, the mean baseline HbA1c was 7.5%, and 12% of patients were on insulin therapy. At week 20, the change from baseline in HbA1c in patients treated with JANUVIA (N=95) was 0.06% compared to 0.23% in patients treated with placebo (N=95), a difference of -0.17% (95% CI: -0.62, 0.28). In studies 2 and 3, the mean baseline HbA1c was 8.0%, 15% of patients were on insulin and 72% were on metformin HCl doses of greater than 1,500 mg daily. At week 20, the change from baseline in HbA1c in patients treated with sitagliptin (N=107) was -0.23% compared to 0.09% in patients treated with placebo (N=113), a difference of -0.33% (95% CI: -0.70, 0.05).

1.2.2 Janumet XR

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these highrisk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue JANUMET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

---------- CONTRAINDICATIONS ----------

- Severe renal impairment: eGFR below 30 mL/min/1.73 m2. (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4)
- History of a serious hypersensitivity reaction (e.g., anaphylaxis or angioedema) to JANUMET XR, sitagliptin, or metformin. (5.7, 6.2)

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

- Lactic Acidosis: See boxed warning. (5.1)
- Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis in patients treated with sitagliptin. If pancreatitis is suspected, promptly discontinue JANUMET XR. (5.2)
- Heart Failure: Has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of JANUMET XR in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.3)
- Acute Renal Failure: Has been reported postmarketing sometimes requiring dialysis. Before initiating JANUMET XR and at least annually thereafter, assess renal function. (5.4)
- Vitamin B12 Deficiency: Metformin may lower vitamin B12 levels. Measure hematologic parameters annually and vitamin B12 at 2 to 3 year intervals and manage any abnormalities. (5.5)
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues: Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. A lower dose of insulin or insulin secretagogue may be required. (5.6)
- Hypersensitivity Reactions: There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Promptly stop JANUMET XR, assess for other potential causes, institute appropriate monitoring and treatment. (5.7)
- Severe and Disabling Arthralgia: Has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.8)
- Bullous Pemphigoid: There have been postmarketing reports requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue JANUMET XR. (5.9)

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

The most common adverse reactions reported in ≥5% of patients simultaneously started on sitagliptin and metformin and more commonly than in patients treated with placebo were diarrhea, upper respiratory tract infection, and headache. (6.1)

8.4 Pediatric Use

The safety and effectiveness of JANUMET XR have not been established in pediatric patients.

Three 20-week double-blind, placebo-controlled studies each with 34-week extensions were conducted to evaluate the efficacy and safety of sitagliptin in 410 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes, with or without insulin therapy (HbA1c 6.5-10% for patients not on insulin, HbA1c 7-10% for patients on insulin). At study entry, patients in study 1 were not treated with oral antihyperglycemic agents; patients in studies 2 and 3 were on maximally tolerated metformin therapy. The primary efficacy endpoint was the change from baseline in HbA1c after 20 weeks of therapy. The pre-specified primary efficacy analyses included data from study 1 and pooled data from studies 2 and 3, regardless of glycemic rescue or treatment discontinuation.

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2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	December 13, 2023
Time period of search	All dates through December 12, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Januvia, Janumet, Janumet XR NDA: 021995, 022044, 202270
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

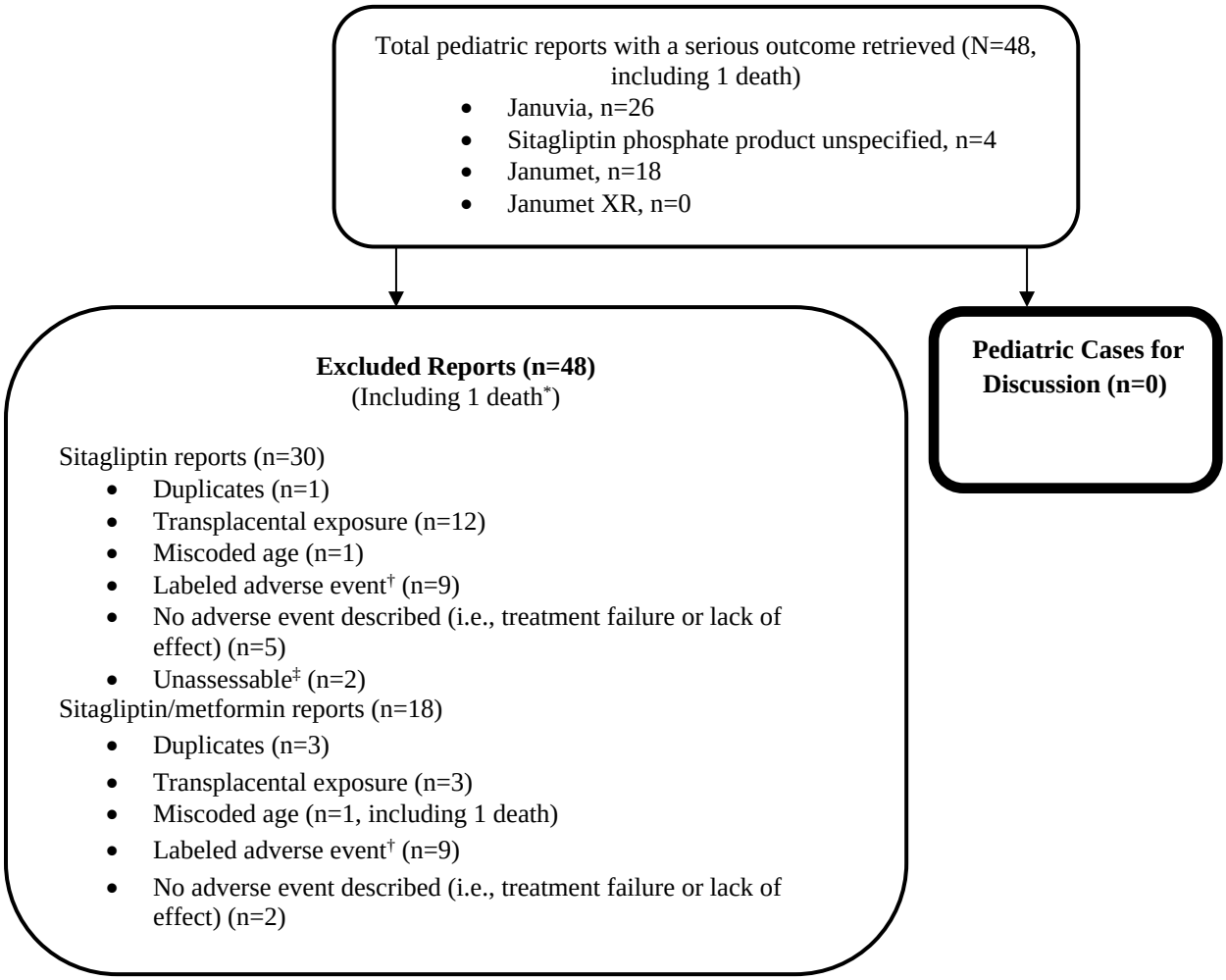
Table 2 presents the number of adult and pediatric FAERS reports through December 12, 2023, with Januvia, Janumet, or Janumet XR.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through December 12, 2023, With Januvia, Janumet, or Janumet XR			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	21,771 (11,732)	14,470 (4,569)	1,858 (483)
Pediatrics (0 - < 18 years)	59 (29)	48 (18)	1 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 48 serious pediatric reports through December 12, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all 48 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Januvia, Janumet, or Janumet XR



* One excluded FAERS report described a fatal outcome. The case described a 76-year-old patient who died from a heart attack; causality could not be attributed to sitagliptin.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all serious FAERS reports with Januvia, Janumet, or Janumet XR in pediatric patients less than 18 years of age through December 12, 2023, and identified 48 reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Januvia, Janumet, or Janumet XR in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Januvia, Janumet, or Janumet XR at this time and will continue routine pharmacovigilance monitoring for Januvia, Janumet, or Janumet XR.

6 REFERENCES

1. Januvia (sitagliptin) tablets. [Prescribing Information]. Whitehouse Station, NJ; Merck & Co., Inc: June 2022.
2. Janumet (sitagliptin and metformin hydrochloride) tablets. [Prescribing Information]. Whitehouse Station, NJ; Merck & Co., Inc: June 2022.
3. Janumet XR (sitagliptin and metformin hydrochloride extended-release) tablets. [Prescribing Information]. Whitehouse Station, NJ; Merck & Co., Inc: June 2022.
4. Shimy K. Clinical Review. NDA 021995/S-047, NDA 022044/S-048, NDA 202270/S-022. June 4, 2020. Available at: https://www.fda.gov/media/145531/download?attachment
5. Archdeacon P. NDA 021995/S-047, NDA 022044/S-048, NDA 202270/S-022. CDTL Review. June 4, 2020. Available at: https://www.fda.gov/media/145526/download?attachment

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.

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