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:	June 23, 2025
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Associate Division Director:	Sara Camilli, PharmD, BCPS DPV II
Product Names:	Nucynta (tapentadol hydrochloride), Nucynta ER (tapentadol hydrochloride)
Pediatric Labeling Approval Dates:	July 3, 2023 (Nucynta), June 14, 2024 (Nucynta ER)
Application Type/Number:	NDA 022304, NDA 203794, NDA 200533
Applicant:	Collegium Pharmaceutical, Inc.
TTT Record ID:	2025-14493

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for tapentadol hydrochloride (Nucynta, Nucynta ER) 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 United States (U.S.) serious unlabeled adverse events associated with tapentadol in pediatric patients.

Tapentadol hydrochloride (Nucynta, Nucynta ER) is an opioid analgesic. Tapentadol immediate release (IR) oral tablet and oral solution were initially approved in the U.S. on November 20, 2008, and October 15, 2012, respectively. Tapentadol extended release (ER) oral tablet was approved in the U.S. on August 25, 2011.

Tapentadol IR oral tablet formulation is currently indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults and pediatric patients aged 6 years and older with a body weight of at least 40 kg. Tapentadol IR oral solution extended this indication to include use in patients aged 6 years and older with a body weight of at 16 kg. Of note, the applicant for tapentadol IR oral solution has never marketed the product. Tapentadol ER is currently indicated for the management of:

- severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.
- severe and persistent neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

This pediatric postmarketing safety review was prompted by the following:

- July 3, 2023, pediatric labeling for tapentadol IR that expanded the indication to include use in pediatric patients aged 6 years and older with a body weight of at least 40 kg.
- June 14, 2024, approval for a tapentadol ER supplemental new drug application submission that fulfilled the requirements of a Written Request issued by FDA to obtain pediatric information on tapentadol ER from birth through 16 years of age for the management of moderate to severe acute pain. There were no related labeling changes associated with this supplement. The safety and efficacy of tapentadol ER in pediatric patients <18 years old have not been established.

A pediatric postmarketing safety review for tapentadol has not previously been presented to the Pediatric Advisory Committee

DPV reviewed all U.S. serious FAERS reports with tapentadol in pediatric patients less than 18 years of age from November 20, 2008 - April 24, 2025, and identified 57 reports; however, all reports were excluded from further discussion. These reports were excluded because they described labeled adverse events or adverse events more likely caused by concomitant medications or comorbidities, described transplacental exposures, did not contain sufficient information to assess causality, did not describe a pediatric patient, or were a duplicate report.

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

DPV did not identify any new pediatric safety concerns for tapentadol at this time and will continue routine pharmacovigilance monitoring for tapentadol.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for tapentadol hydrochloride (Nucynta, Nucynta ER) 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 United States (U.S.) serious unlabeled adverse events associated with tapentadol in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Tapentadol hydrochloride (Nucynta,[1,2] Nucynta ER[3]) is an opioid analgesic. Tapentadol immediate release (IR) oral tablet[1] and oral solution[2] were initially approved in the U.S. on November 20, 2008, and October 15, 2012, respectively. Tapentadol extended release (ER) oral tablet[3] was approved in the U.S. on August 25, 2011.

Tapentadol IR oral tablet formulation[1,] is currently indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults and pediatric patients aged 6 years and older with a body weight of at least 40 kg. Tapentadol IR oral solution[2] extended this indication to include use in patients aged 6 years and older with a body weight of at 16 kg. Of note, the applicant for tapentadol IR oral solution has never marketed the product (89 FR 18946). Tapentadol ER[3] is currently indicated for the management of:

- severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.
- severe and persistent neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

This pediatric postmarketing safety review was prompted by the following:

- July 3, 2023[1], pediatric labeling for tapentadol IR that expanded the indication to include use in pediatric patients aged 6 years and older with a body weight of at least 40 kg.
- June 14, 2024[4], approval for a tapentadol ER supplemental new drug application submission that fulfilled the requirements of a Written Request issued by FDA to obtain pediatric information on tapentadol ER from birth through 16 years of age for the management of moderate to severe acute pain. There were no related labeling changes associated with this supplement. The safety and efficacy of tapentadol ER in pediatric patients <18 years old have not been established.

A pediatric postmarketing safety review for tapentadol has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Nucynta tablet formulation,[1] Nucynta oral solution,[2] and Nucynta ER[3] tablet labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the Pediatric Use subsection.

1.2.1 Nucynta IR Tablets

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF NUCYNTA TABLETS

See full prescribing information for complete boxed warning.

- **NUCYNTA tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and reassess regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially upon initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA tablets are essential. (5.2)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.3, 7)**
- **Accidental ingestion of NUCYNTA tablets, especially by children, can result in a fatal overdose of tapentadol. (5.2)**
- **If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.4)**
- **Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.5)**

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

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to tapentadol (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. (4)

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

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation. (5.6)
- Serotonin Syndrome with Concomitant Use of Serotonergic Drugs: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA tablets if serotonin syndrome is suspected. (5.7)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate, particularly during initiation and titration. (5.8)

- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of NUCYNTA tablets in patients with circulatory shock. (5.10)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA tablets in patients with impaired consciousness or coma. (5.11)

----------ADVERSE REACTIONS----------
The most common adverse reactions were
- Adults (incidence ≥10%) were nausea, dizziness, vomiting and somnolence. (6.1)
- Pediatric patients 6 years and older (incidence ≥5%): vomiting, constipation, nausea, pruritus, and pyrexia

8.4 PEDIATRIC USE

The safety and effectiveness of NUCYNTA (tapentadol) tablets in pediatric patients ages 6 years and older who weigh at least 40 kg have been established. Use of NUCYNTA (tapentadol) tablets in pediatric patients ages 6 years and older who weigh at least 40 kg is based on one randomized, double-blind, placebo-controlled, multiple-dose efficacy and safety study of NUCYNTA (tapentadol) oral solution in 175 pediatric patients from birth to 17 years of age who had undergone surgery that would reliably produce moderate to severe pain and supported by pharmacokinetic and safety data from three open-label, single-dose studies of NUCYNTA (tapentadol) oral solution in 129 patients from birth to 17 years of age with moderate to severe acute pain from a surgical procedure [see Clinical Studies (14.2)].

The safety and effectiveness of NUCYNTA (tapentadol) tablets in pediatric patients less than 6 years of age have not been established. In pediatric patients less than 6 years of age, NUCYNTA (tapentadol) oral solution did not demonstrate efficacy compared to placebo when evaluated in one randomized, double-blind, placebo-controlled, multiple-dose study in 175 pediatric patients from birth to 17 years of age who had undergone surgery that would reliably produce moderate to severe pain [see Clinical Studies (14.2)].

The safety and effectiveness of NUCYNTA (tapentadol) tablets in pediatric patients who weigh less than 40 kg have not been established because the recommended dosage cannot be achieved with available tablet strengths. Consider use of another NUCYNTA product, such as NUCYNTA (tapentadol) oral solution, in patients who cannot swallow oral tablets or who weigh less than 40 kg [see Dosage and Administration (2.3)].

NUCYNTA (tapentadol) tablets have not been studied in pediatric patients with hepatic or renal impairment; therefore, use in these populations is not recommended [see Dosage and Administration (2.4)].

1.2.2 Nucynta Oral Solution

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF NUCYNTA ORAL SOLUTION

See full prescribing information for complete boxed warning.

- **Ensure accuracy when prescribing, dispensing, and administering NUCYNTA oral solution. Dosing errors due to confusion between mg and mL, and other tapentadol oral solutions of different concentrations can result in accidental overdose and death. (2.1, 5.1)**
- **NUCYNTA oral solution exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and reassess regularly for these behaviors and conditions. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially when initiation and following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA oral solution are essential. (5.3)**
- **Accidental ingestion of NUCYNTA oral solution, especially by children, can result in a fatal overdose of tapentadol. (5.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.4, 7)**
- **If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome which may be life threatening if not recognized and treated. Ensure that neonatology experts will be available at delivery. (5.5)**
- **Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.6)**

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

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or gastrointestinal obstruction, including suspected paralytic ileus. (4)
- Hypersensitivity to tapentadol. (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. (4)

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

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.7)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate patients, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA oral solution if serotonin syndrome is suspected. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)

- Severe Hypotension: Regularly evaluate patients during dosage initiation and titration. Avoid use of NUCYNTA oral solution in patients with circulatory shock. (5.11)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA oral solution in patients with impaired consciousness or coma. (5.12)

----------ADVERSE REACTIONS----------
The most common adverse reactions were
- Adults (incidence ≥10%): nausea, dizziness, vomiting and somnolence. (6.1)
- Pediatric patients 6 years and older (incidence ≥5%): vomiting, constipation, nausea, pruritus, and pyrexia.

8.4 PEDIATRIC USE

The safety and effectiveness of NUCYNTA (tapentadol) oral solution in pediatric patients ages 6 years and older who weigh at least 16 kg have been established. Use of NUCYNTA (tapentadol) oral solution in pediatric patients ages 6 years and older who weigh at least 16 kg is based on one randomized, double-blind, placebo controlled, multiple-dose efficacy and safety study in 175 pediatric patients from birth to 17 years of age who had undergone surgery that would reliably produce moderate to severe pain and supported by pharmacokinetic and safety data from three open-label, single-dose studies in 129 patients from birth to 17 years of age with moderate to severe acute pain from a surgical procedure [see Clinical Studies (14.2)].

The safety and effectiveness of NUCYNTA (tapentadol) oral solution in pediatric patients less than 6 years of age or who weigh less than 16 kg have not been established. In pediatric patients less than 6 years of age or who weigh less than 16 kg, NUCYNTA (tapentadol) oral solution did not demonstrate efficacy compared to placebo when evaluated in one randomized, double-blind, placebo-controlled, multiple-dose study in 175 pediatric patients from birth to 17 years of age who had undergone surgery that would reliably produce moderate to severe pain [see Clinical Studies (14.2)].

NUCYNTA (tapentadol) oral solution has not been studied in pediatric patients with hepatic or renal impairment; therefore, use in these populations is not recommended [see Dosage and Administration (2.4)].

1.2.3 Nucynta ER Tablets

WARNING: SERIOUS LIFE-THREATENING RISKS FROM USE OF NUCYNTA ER
See FULL PRESCRIBING INFORMATION for complete boxed warning.

- **NUCYNTA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and reassess regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially upon initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA ER are essential. Instruct patients to swallow NUCYNTA ER tablets whole to avoid exposure to a potentially fatal dose of tapentadol. (2.1, 5.2)**
- **Accidental ingestion of NUCYNTA ER, especially in children, can result in fatal overdose of tapentadol. (5.2)**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking NUCYNTA ER because co-ingestion can result in fatal plasma tapentadol levels. (5.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.3, 7)**
- **If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.4) Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.5)**

———————CONTRAINDICATIONS———————

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to tapentadol or to any other ingredients of the product (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. (4)

———————WARNINGS AND PRECAUTIONS———————

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.6)
- Serotonin Syndrome with Concomitant Use of Serotonergic Drugs Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA ER if serotonin syndrome is suspected. (5.7)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of NUCYNTA ER in patients with circulatory shock. (5.10)

- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA ER in patients with impaired consciousness or coma. (5.11)

———————————— ADVERSE REACTIONS————————————

The most common (≥10%) adverse reactions were nausea, constipation, dizziness, headache, and somnolence. (6)

8.4 PEDIATRIC USE

The safety and efficacy of NUCYNTA ER in pediatric patients less than 18 years of age have not been established.

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	April 25, 2025
Time period of search	November 20, 2008† - April 24, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: TAPENTADOL, TAPENTADOL HYDROCHLORIDE
MedDRA search terms (Version 27.1)	All Preferred Terms
Other criteria	Case Seriousness: Serious‡ Country Derived: USA

* See **Appendix 7.1** for a description of the FAERS database.
† U.S. approval date of Nucynta oral tablets (NDA 022304).
‡ 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.
Abbreviations: DPV = Division of Pharmacovigilance, ER = extended release, MedDRA=Medical Dictionary for Regulatory Activities, USA=United States of America

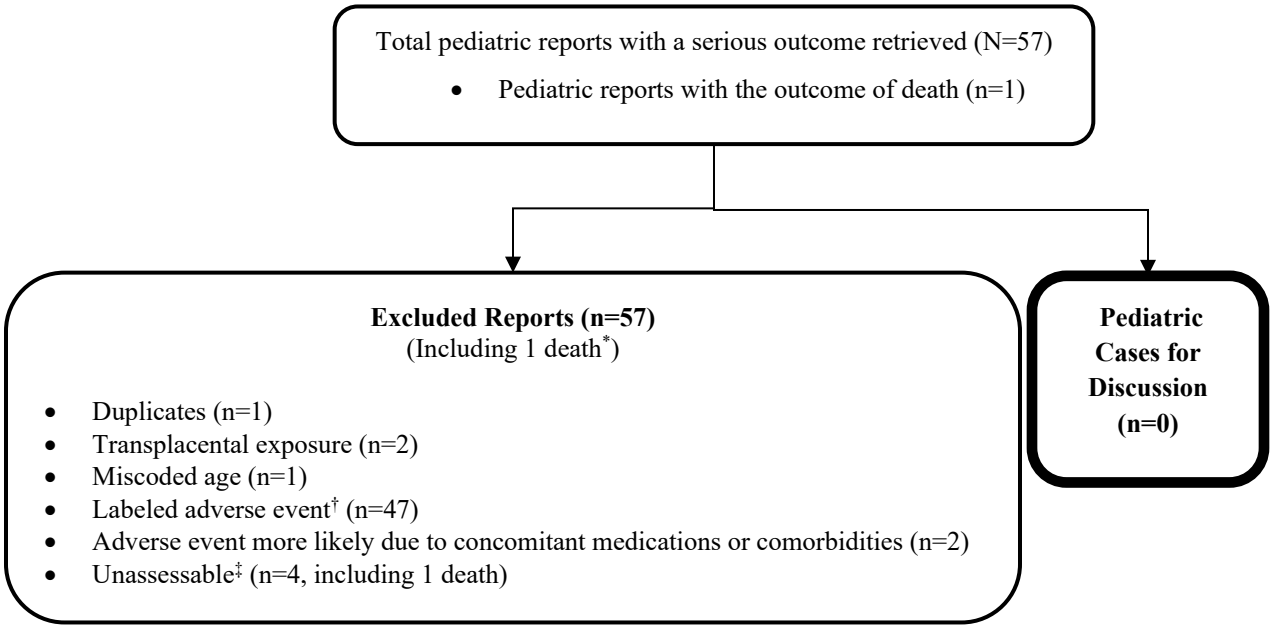
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 57 U.S. serious pediatric reports for patients less than 18 years old from November 20, 2008, through April 24, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all reports from the case series for the reasons listed in Figure 1.

Figure 1. Selection of U.S. Serious Pediatric Cases with Tapentadol



* We identified one case describing a fatal outcome. The case described a 17-year-old female who was prescribed tapentadol for an unknown indication. The patient died from a possible overdose of unknown products. It was unknown whether the patient ingested tapentadol, illicit substances, or other unprescribed products as part of the suspected overdose, therefore, causality for the fatal event and tapentadol is unassessable.
† Labeled adverse event does not represent increased severity.
‡ 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.
Abbreviations: AE = adverse event

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with tapentadol in pediatric patients less than 18 years of age from November 20, 2008 - April 24, 2025, and identified 57 reports; however, all reports were excluded from further discussion.

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

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for tapentadol at this time and will continue routine pharmacovigilance monitoring for tapentadol.

6 REFERENCES

1. Nucynta (tapentadol oral tablets) [Package insert]. Stoughton; Collegium Pharm, Inc, December 2023.
2. Nucynta (tapentadol oral solution) [Package insert]. Stoughton; Collegium Pharm, Inc, December 2023.
3. Nucynta ER (tapentadol) [Package insert]. Stoughton; Collegium Pharm, Inc, December 2023.
4. U.S. Food and Drug Administration (FDA). Letter to Applicant – Supplement Approval. June 14, 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/200533Orig1s029ltr.pdf.

7 APPENDICES

7.1 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.