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

Pediatric Postmarketing Pharmacovigilance Review

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Product Name:	Tirosint-SOL (Levothyroxine sodium) oral solution
Pediatric Labeling Approval Date:	December 15, 2016
Application Type/Number:	NDA 206977
Applicant:	IBSA Institut Biochimique SA
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tirosint-SOL (levothyroxine sodium) oral solution in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with levothyroxine in pediatric patients.

Tirosint-SOL (levothyroxine sodium) oral solution, a synthetic thyroxine (T4) hormone, was initially approved in the U.S. on December 15, 2016, and is available as unit dosed alcohol-free oral solution. Levothyroxine is currently indicated for pediatric patients, including neonates, with the hypothyroidism, and for the management of thyrotropin-dependent well-differentiated thyroid cancer.

This pediatric postmarketing safety review was stimulated by the pediatric labeling at initial approval on December 15, 2016. DPV has not previously presented an evaluation of postmarking adverse event reports for levothyroxine to the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with levothyroxine in pediatric patients less than 17 years of age through March 10, 2024, and identified 219 reports; however, all reports were excluded 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 levothyroxine in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tirosint-SOL (levothyroxine sodium) oral solution in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with levothyroxine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Tirosint-SOL (levothyroxine sodium) oral solution, a synthetic thyroxine (T4) hormone, was initially approved in the U.S. on December 15, 2016, and is available as unit dosed alcohol-free oral solution.[1] Levothyroxine is currently indicated for pediatric patients, including neonates, with the hypothyroidism, and for the management of thyrotropin-dependent well-differentiated thyroid cancer.

This pediatric postmarketing safety review was stimulated by the pediatric labeling at initial approval on December 15, 2016.[2,3]

DPV has not previously presented an evaluation of postmarking adverse event reports for levothyroxine to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The levothyroxine labeling contains the following safety information excerpted from the Highlights of Prescribing Information, ADVERSE REACTIONS section, and the *Pediatric Use* subsection. For additional levothyroxine labeling information, please refer to the full prescribing information.

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

See full prescribing information for complete boxed warning

- **Thyroid hormones, including TIROSINT-SOL, should not be used for the treatment of obesity or for weight loss.**
- **Doses beyond the range of daily hormonal requirements may produce serious or even life threatening manifestations of toxicity (6, 10).**

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

- Hypersensitivity to glycerol (4)
- Uncorrected adrenal insufficiency (4)

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

- Serious risks related to overtreatment or undertreatment with TIROSINT-SOL: Titrate the dose of TIROSINT-SOL carefully and monitor response to titration. (5.1)
- Cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease: Initiate TIROSINT-SOL at less than the full replacement dose because of the increased risk of cardiac adverse reactions, including atrial fibrillation. (2.3, 5.2, 8.5)
- Myxedema coma: Do not use oral thyroid hormone drug products to treat myxedema coma. (5.3)
- Acute adrenal crisis in patients with concomitant adrenal insufficiency: Treat with replacement glucocorticoids prior to initiation of TIROSINT-SOL treatment. (5.4)

- Worsening of diabetic control: therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing thyroid hormone therapy. (5.5)
- Decreased bone mineral density associated with thyroid hormone over-replacement: Overreplacement can increase bone resorption and decrease bone mineral density. Give the lowest effective dose. (5.6)

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

Adverse reactions associated with TIROSINT-SOL are primarily those of hyperthyroidism due to therapeutic overdosage including: arrhythmias, myocardial infarction, dyspnea, muscle spasm, headache, nervousness, irritability, insomnia, tremors, muscle weakness, increased appetite, weight loss, diarrhea, heat intolerance, menstrual irregularities, and skin rash (6)

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

Pregnancy may require the use of higher doses of TIROSINT-SOL (2.3, 8.1)

6 ADVERSE REACTIONS

Adverse Reactions in Pediatric Patients

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in pediatric patients receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants who have not undergone closure of the fontanelles, and in premature closure of the epiphyses in pediatric patients still experiencing growth with resultant compromised adult height.

8.4 Pediatric Use

TIROSINT-SOL is indicated in patients from birth to less than 17 years of age:

- As a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism
- As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer

Rapid restoration of normal serum T4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on cognitive development as well as on overall physical growth and maturation. Therefore, initiate TIROSINT-SOL therapy immediately upon diagnosis. Levothyroxine is generally continued for life in these patients [see Warnings and Precautions (5.1)].

Closely monitor infants during the first two weeks of TIROSINT-SOL therapy for cardiac overload and arrhythmias.

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	March 11, 2024
Time period of search	All dates through March 10, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: levothyroxine, levothyroxine sodium, levothyroxine sodium anhydrous, levothyroxine sodium/liothyronine sodium
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

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 March 10, 2024, with levothyroxine.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through March 10, 2024, With Levothyroxine

	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	30,329 (13,966)	22,325 (6,130)	1,652 (1,078)
Pediatrics‡ (0 - < 17 years)	803 (383)	629 (219)	107 (96)

* May include duplicates and transplacental exposures, and have not been assessed for causality

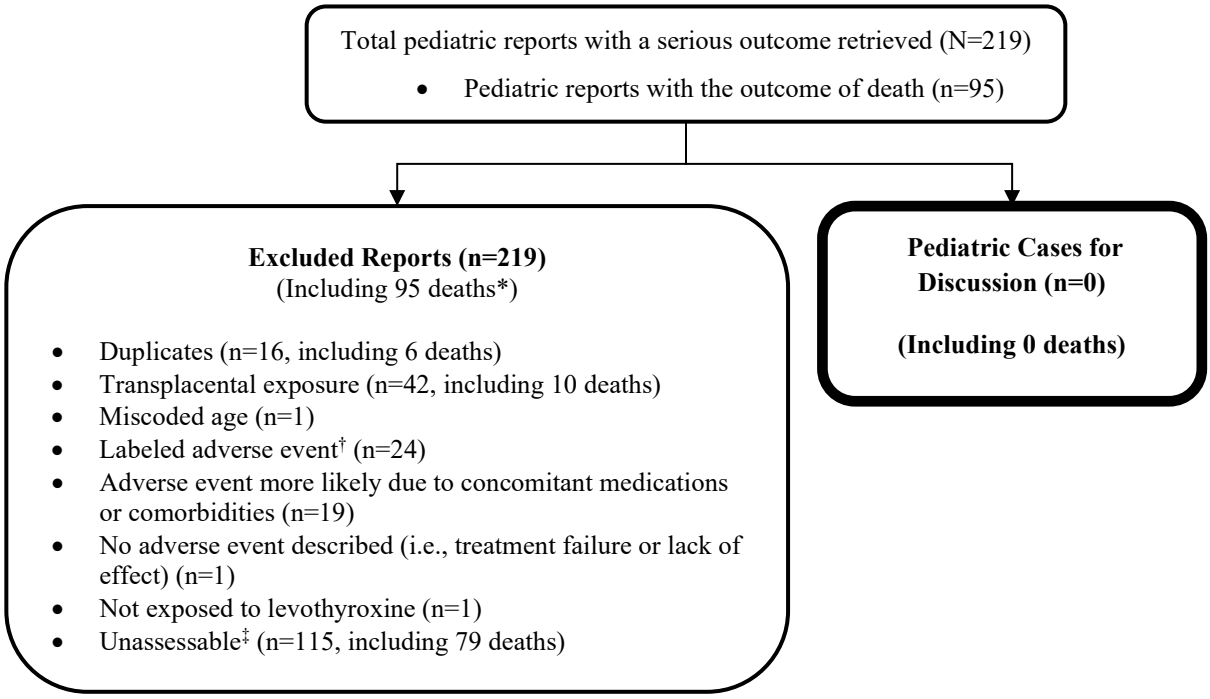
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

‡ See Figure 1. Seventy-nine additional reports of U.S. pediatric deaths were identified among reports not reporting an age. One additional report of U.S. pediatric death was identified among reports not coded with an outcome of death. These 80 reports are reflected in the counts of pediatric reports.

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

Our FAERS search retrieved 219 U.S. serious pediatric reports through March 10, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 219 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 U.S. Serious Pediatric Cases with Levothyroxine



* Of the excluded U.S. FAERS reports, 95 described fatal outcomes. After accounting for duplicate reports (n=6), we identified 89 individual cases with a fatal outcome. None of the deaths were determined to be attributed to levothyroxine. Ten cases described patients with prenatal exposure to levothyroxine and did not contain sufficient information to establish a causal relationship between levothyroxine and death. The remaining 79 cases did not provide sufficient clinical information to perform a causality assessment with levothyroxine. Notably, 72 of the unassessable death cases had identical verbatim text and lacked sufficient clinical data (i.e., no data on age, sex, clinical course, product indication, cause of death, concomitant exposures, comorbidities) to adequately assess; despite efforts to obtain additional information on these cases, no additional data were available.

† 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 U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 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 levothyroxine in pediatric patients less than 17 years of age through March 10, 2024, and identified 219 reports; however, all reports were excluded 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 levothyroxine in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Tirosint-SOL (levothyroxine sodium) oral solution [Prescribing Information]. Parsippany, NJ; IBSA Pharma Inc.: November 2023.

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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