SUSPECT ADVERSE REACTION REPORT

NI-TOLMAR, INC.-23NI043670

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE Years	3. SEX	4-6 REACTION ONSET		
		Day	Month	Year			Day	Month	Year
ICMM	NICARAGUA	11	Mar	2016	7	Female	11	Sep	2023

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data)

1) Anxiety (Anxiety (10002855), Anxiety (10002855))
(/Apr/2025 -) - Not Recovered/Not Resolved/Ongoing
2) HEADACHES (Headache (10019211), Headache (10019211))
(11/Sep/2023 -) - Not Recovered/Not Resolved/Ongoing
3) BODY ACHES (General body pain (10048971), Pain (10033371))
(11/Sep/2023 -) - Not Recovered/Not Resolved/Ongoing
4) A LOT OF HAIR IS FALLING OUT (Hair loss (10019045), Alopecia (10001760))
(11/Sep/2023 -) - Not Recovered/Not Resolved/Ongoing

Cont..

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ LIFE THREATENING
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ RESULTS IN PERSISTENCE OR SIGNIFICANT DISABILITY/INCAPACITY
- ☐ CONGENITAL ANOMALY
- ☐ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S)INFORMATION

14. SUSPECT DRUG(S)(include generic name)

1) Eligard® (Leuprolide acetate, Leuprolide acetate) (Suspect) (Injection)(Unknown)

Cont..

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☑ NA

15. DAILY DOSE(S)

1) (22.5 milligram(s), 1 in 3 Month)

Cont..

16. ROUTE(S) OF ADMINISTRATION

1) Subcutaneous

Cont..

21. DID EVENT REAPPEAR AFTER REINTRODUCTION ☐ YES ☐ NO ☑ NA

(NA : Not Applicable)

17. INDICATION(S) FOR USE

1) Puberty precocious [10037282 - Puberty precocious]

Cont..

18. THERAPY DATE(S) (from/to)	19. THERAPY DURATION
1) (03/Aug/2023 -)	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

No concomitants used/reported

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

1) PUBERTY PRECOCIOUS (10037282, Puberty precocious) (Continuing: Yes)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

Name : Tolmar, Inc
701 Centre Avenue
Fort Collins, CO, 80526, UNITED STATES OF AMERICA
Anjan.Chatterjee@tolmar.comand+1-9702124900

Study Information
Study Name: NA
EudraCT Number:
Protocol No.: NA
Center No.:
Subject Id :

24.REPORT NULLIFIED	24b. MFR CONTROL NO.
☐ YES ☐ NO	NI-TOLMAR, INC.-23NI043670
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE
14/Jun/2025	☑ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE
23/Jun/2025	☑ INITIAL ☐ FOLLOWUP

= Continuation attached sheet(s)..

Continuation Sheet for CIOMS report

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data) (Continuation...)

5) Depression (Depression (10012378), Depression (10012378)(/Apr/2025 -) - Not Recovered/Not Resolved/Ongoing)

Event Description :

This Study report from NICARAGUA was received by Adium (reference number: NI-ADIUM-NI-0158-20230927) on 27-SEP-2023 from a Consumer regarding a Child 7 Years old Female patient who experienced Headaches (Headache), Body aches (General body pain), A lot of hair is falling out (Hair loss) during Eligard (Leuprolide acetate) 22.5 milligram therapy for Puberty precocious. The needle component of the constituent device was not identified in the report. The report was sent to Tolmar on 28-SEP-2023.

The patient's medical history and current conditions included Precocious puberty.

Concomitant medications were not reported.

On 03-AUG-2023, the patient began receiving Eligard 22.5 milligram, q 3 month via Subcutaneous use for Puberty precocious (Lot numbers and Expiration dates not provided). On 11-SEP-2023 (also reported as for the last 15 days), 1 month 9 days after the most recent dose of Eligard, the patient experienced a lot of hair loss, at first it was occasional, but then a lot of hair was falling out. Also, she was having headaches and body aches. Corrective treatment was not reported. Action taken with Eligard in response to the events was Dose Not Changed. De-challenge and re-challenge were Not applicable. The outcome of Headache, General body pain and Hair loss was Not Recovered/Not Resolved.

The reporter did not assess the seriousness or causality of the events in relationship to Eligard.

On 14-Jun-2025 and 16-Jun-2025 follow-up information was received by Adium via Patient Support Program (reference number:NI-ADIUM-NI-0158-20230927) from a consumer (non-healthcare professional) and sent to Tolmar on 16-Jun-2025. New information included: Added new dose of Eligard (45 mg) and two new non-serious events of "Anxiety" (Anxiety) and "Depression"(Depression). Action taken of Eligard (22.5 mg) was updated from 'dose not changed' to 'unknown'. New treatment details were also added.

On an unknown date, the patient received a dosage change from Eligard 22.5 mg to Eligard 45 mg, every 6 months via subcutaneous route for precocious puberty (Lot numbers and Expiration dates not provided).

On an unknown date in Apr-2025, the patient experienced anxiety and depression. No further information was available.

Corrective treatment included piracetam and fluoxetine for anxiety and depression.

Action taken with Eligard (22.5 mg) in response to the events was unknown. De-challenge and re-challenge were not applicable.

Action taken with Eligard (45 mg) in response to the events was dose not changed. De-challenge and re-challenge were not applicable.

The outcome of anxiety, headache, pain, alopecia and depression was not recovered.

The reporter did not assess the seriousness of anxiety, headache, pain, alopecia and depression was not recovered.

The reporter did not provide the causality of anxiety, headache, pain, alopecia and depression in relationship to Eligard (22.5 mg) and Eligard unspecified device.

The reporter did not provide the causality of headache, pain, and alopecia while assessed the causality of anxiety and depression in relationship to Eligard (45 mg) and Eligard unspecified device as not related.

No further query was raised.

Listedness:
anxiety>Eligard>Unlisted as per CCDS>07-Nov-2024
anxiety>Eligard>Unlisted as per USPI>Feb-2025
anxiety>Eligard unspecified device>Unlisted as per USPI>Feb-2025
anxiety>Eligard>Unlisted as per Canadian monograph>02-Apr-2025

depression >Eligard>Listed as per CCDS>07-Nov-2024
depression >Eligard>Listed as per USPI>Feb-2025
depression >Eligard unspecified device>Listed as per USPI>Feb-2025
depression >Eligard>Listed as per Canadian monograph>02-Apr-2025

Listedness of events headache, pain, and alopecia was retained as per previous assessement.

Company Remarks (Sender's Comments) :

Evaluator comment (Tolmar): Causality
headache - Not related to drug and not related to device

Continuation Sheet for CIOMS report

pain - Not related to drug and not related to device
alopecia - related to drug and not related to device

FU- Events anxiety (Anxiety) and depression (Depression) were added. This is regarding 7 Years old female child patient who had anxiety (Anxiety) and depression (Depression) during Eligard (leuprolide acetate) 45 mg therapy for precocious puberty. Tolmar assessed the events as non-serious since they do not meet the ICH seriousness criteria and are not IME events. The reported event anxiety was assessed as not related to Eligard (drug and device) considering inconsistency with drug's safety profile. The reported event depression was assessed as related to Eligard (drug) considering the known safety profile of the drug and not related to device. Underlying precocious puberty is a confounder for causality assessment. Causality of the events headache, pain, and alopecia is retained as per previous assessment.

14.SUSPECT DRUG(S) (Continuation...)

Product-Reaction Level

1) Drug	:	Eligard® (Leuprolide acetate)
Active Substance	:	1) Leuprolide acetate
Drug Characterization	:	Suspect
Form of Admin	:	1) Injection
Lot Number	:	1) Unknown
Daily Dose	:	(22.5 milligram(s), 1 in 3 Month)
Route of Admin	:	1) Subcutaneous
Indications	:	1) Puberty precocious [10037282 - Puberty precocious]
Therapy Dates	:	1) From : 03/Aug/2023 To :Unknown
Action(s) Taken With Drug	:	Unknown

Causality

1) Anxiety (Anxiety - 10002855, Anxiety - 10002855)

Causality as per reporter	:	Not Reported
Causality as per Mfr	:	Not Related
DeChallenge	:	Not applicable
ReChallenge	:	Not Applicable

2) HEADACHES (Headache - 10019211, Headache - 10019211)

Causality as per reporter	:	Not Reported
Causality as per Mfr	:	Not Related
DeChallenge	:	Not applicable
ReChallenge	:	Not Applicable

3) BODY ACHES (General body pain - 10048971, Pain - 10033371)

Causality as per reporter	:	Not Reported
Causality as per Mfr	:	Not Related
DeChallenge	:	Not applicable
ReChallenge	:	Not Applicable

4) A LOT OF HAIR IS FALLING OUT (Hair loss - 10019045, Alopecia - 10001760)

Causality as per reporter	:	Not Reported
Causality as per Mfr	:	Related
DeChallenge	:	Not applicable
ReChallenge	:	Not Applicable

5) Depression (Depression - 10012378, Depression - 10012378)

Causality as per reporter	:	Not Reported
Causality as per Mfr	:	Not Related
DeChallenge	:	Not applicable
ReChallenge	:	Not Applicable

Labeling :

1) Anxiety	
CORE	UnLabeled
2) HEADACHES	
CORE	Labeled
3) BODY ACHES	
CORE	Labeled
4) A LOT OF HAIR IS FALLING OUT	
CORE	Labeled
5) Depression	
CORE	Labeled

2) Drug	:	Eligard® (Leuprolide acetate)
Active Substance	:	1) Leuprolide acetate

Continuation Sheet for CIOMS report

Drug Characterization : Suspect
Form of Admin : 1) Injection
Lot Number : 1) Unknown
Daily Dose : (45 milligram(s), 1 in 6 Month)
Route of Admin : 1) Subcutaneous
Indications : 1) Central Precocious Puberty [10037282 - Puberty precocious]
Action(s) Taken With Drug : Dose not changed

Causality

1) Anxiety (Anxiety - 10002855, Anxiety - 10002855)
Causality as per reporter : Not Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

2) HEADACHES (Headache - 10019211, Headache - 10019211)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

3) BODY ACHES (General body pain - 10048971, Pain - 10033371)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

4) A LOT OF HAIR IS FALLING OUT (Hair loss - 10019045, Alopecia - 10001760)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

5) Depression (Depression - 10012378, Depression - 10012378)
Causality as per reporter : Not Related
Causality as per Mfr : Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Anxiety
CORE UnLabeled
2) HEADACHES
CORE Labeled
3) BODY ACHES
CORE Labeled
4) A LOT OF HAIR IS FALLING OUT
CORE Labeled
5) Depression
CORE Labeled

3) Drug : Eligard® Unspecified Device (Leuprolide acetate)
Active Substance : 1) Leuprolide acetate
Drug Characterization : Suspect
Form of Admin : 1) Injection
Lot Number : 1) Unknown
Indications : 1) Central Precocious Puberty [10037282 - Puberty precocious]
Action(s) Taken With Drug : Not applicable

Causality

1) Anxiety (Anxiety - 10002855, Anxiety - 10002855)
Causality as per reporter : Not Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

2) HEADACHES (Headache - 10019211, Headache - 10019211)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

3) BODY ACHES (General body pain - 10048971, Pain - 10033371)

Continuation Sheet for CIOMS report

Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

4) A LOT OF HAIR IS FALLING OUT (Hair loss - 10019045, Alopecia - 10001760)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

5) Depression (Depression - 10012378, Depression - 10012378)
Causality as per reporter : Not Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Anxiety
CORE
2) HEADACHES
CORE
3) BODY ACHES
CORE
4) A LOT OF HAIR IS FALLING OUT
CORE
5) Depression
CORE

15. DAILY DOSE(S) (Continuation...)

Dosage Text :

Drug 1 :Eligard®

1) 22.5 milligram, q 3 month