CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

NI-TOLMAR, INC.-25NI056473

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
GBSL	NICARAGUA	06	Oct	2016	8	Female	30	Jan	2025

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

1) Diarrhea (Diarrhea (10012727), Diarrhoea (10012735))
(03/Feb/2025 -) - Unknown
2) Vaginal discharge of mucous appearance (Vaginal discharge (10046901), Vaginal discharge (10046901))
(04/Feb/2025 -) - Unknown
3) Cough (Cough (10011224), Cough (10011224))
(04/Feb/2025 -) - Unknown
4) Too sleepy/ excessive sleep (Sleep excessive (10041000), Hypersomnia (10020765))
(02/May/2025 - /Jun/2025) - Recovered/Resolved

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)

16. ROUTE(S) OF ADMINISTRATION

1) Subcutaneous

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

(NA : Not Applicable)

17. INDICATION(S) FOR USE

1) Central Precocious Puberty [10073186 - Central precocious puberty]

18. THERAPY DATE(S) (from/to)	19. THERAPY DURATION
1) (30/Jan/2025 - Ongoing)	

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) CENTRAL PRECOCIOUS PUBERTY (10073186, Central precocious puberty) (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.-25NI056473
24c. DATE RECEIVED BY MANUFACTURER: 29/Jul/2025	24d. REPORT SOURCE: ☑ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT: 05/Aug/2025	25a. REPORT TYPE: ☐ INITIAL ☑ FOLLOWUP

= Continuation attached sheet(s)..

Continuation Sheet for CIOMS report

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

5) Feeling exhausted (Exhaustion (10015667), Fatigue (10016256)(02/May/2025 - /Jun/2025) - Recovered/Resolved)

6) Off-label use for unapproved indication (Off label use (10053762), Off label use (10053762)(30/Jan/2025 -) - Unknown)

Event Description :

This Study report from NICARAGUA was received by Adium (reference number: NI-ADIUM-NI-0010-20250204) on 04-FEB-2025 from a Consumer/ Other Non-Health Prof regarding a Child 8 Years old Female patient who experienced diarrhea (Diarrhea), Vaginal discharge of mucous appearance (Vaginal discharge) during Eligard (Leuprolide acetate) 22.5 milligram therapy for Central precocious puberty. The needle component of the constituent device was not identified in the report. The report was sent to Tolmar on 05-FEB-2025.

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

Concomitant medications were not reported.

On 30-JAN-2025, the patient began receiving Eligard 22.5 milligram, q 3 month via Subcutaneous use for Central precocious puberty (Lot numbers and Expiration dates were not reported). On 03-FEB-2025, 5 days after the most recent dose of Eligard, the patient experienced diarrhea that persisted the following day. On 04-FEB-2025, 6 days after the most recent dose of Eligard, the patient experienced vaginal discharge of mucous aspect. 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 Diarrhea was Recovering/Resolving. The outcome of Vaginal discharge was Recovering/Resolving.

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

On 28-FEB-2025, follow-up information was received by Adium Patient support program (reference number: NI-ADIUM-NI-0010-20250204) from a Consumer/Other Non-Health Prof and sent to Tolmar on 03-MAR-2025. New information included: Added the new event Cough (Cough).

Reportedly, on 04-FEB-2025, 6 days after the most recent dose of Eligard, the patient experienced Cough, despite treatment and other care, the cough was persisting. Corrective treatment or further details were not provided. Action taken with Eligard treatment in response to the event was dose not changed, de-challenge and re-challenge were not applicable. The outcome of Cough was Not Recovered/Not Resolved.

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

On 29-Jul-2025, follow-up information was received by Adium via Patient Support Program “Asofarma a tu Lado” (reference number: NI-ADIUM-NI-0010-20250204 (2)) from a consumer (non-healthcare professional) and sent to Tolmar on 30-Jul-2025. New information included: added new non-serious event of "too sleepy/ excessive sleep" (Hypersomnia), "feeling exhausted"(Fatigue) and "Off-label use for unapproved indication" (Off label use).

On 30-Jan-2025, the patient began receiving Eligard 22.5 milligram, q 3 month via subcutaneous use for precocious puberty (Lot numbers and Expiration dates were not reported).

On 02-May-2025, the patient was feeling too sleepy and exhausted. No further details were provided.

Corrective treatment was unknown.

Action taken with Eligard in response to the event was dose not changed. De-challenge and re-challenge were not applicable.

The outcome of Hypersomnia and Fatigue was Recovered/Resolved.

The outcome of off label use was unknown.

The reporter did not assess the seriousness of hypersomnia, off label use and fatigue.

The reporter assesses the causality of hypersomnia and fatigue in relationship to Eligard and Eligard unspecified device as not related.

The reporter did not provide the causality for off label use in relationship to Eligard and Eligard Unspecified Device.

No further queries were raised.

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

off label use>Eligard>Unlisted as per CCDS>07-Nov-2024
off label use>Eligard>Unlisted as per USPI>Feb-2025
off label use>Eligard unspecified device>Unlisted as per USPI>Feb-2025

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off label use>Eligard>Unlisted as per Canadian monograph>02-Apr-2025

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

Listedness of events Diarrhea, Vaginal discharge and Cough is retained as per previous assessment.

Company Remarks (Sender's Comments) :

Evaluator comment (Tolmar): Causality
Diarrhea - Not related to drug and device
Vaginal discharge - Not related to drug and device
Cough - Related to drug and not related to device

Evaluator comment (Tolmar): This is regarding 08-year-old female child patient who had Hypersomnia ("too sleepy/ excessive sleep"), Fatigue ("feeling exhausted") and Off label use ("Off-label use for unapproved indication"), during Eligard (leuprolide acetate) 22.5 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 Hypersomnia was assessed as not related to Eligard (drug and device) considering inconsistency with known safety profile of the drug. The reported event Off label use was assessed as not related to Eligard (drug and device) as the event occurred with the product due to human action, rather due to the drug. The reported event Fatigue was assessed as related to Eligard (drug) considering the known safety profile of drug and not related to device. Causality and seriousness of events Diarrhea, Vaginal discharge and Cough was 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) Central Precocious Puberty [10073186 - Central precocious puberty]
Therapy Dates	:	1) From : 30/Jan/2025 To :Continuing
Action(s) Taken With Drug	:	Dose not changed

Causality

1) Diarrhea (Diarrhea - 10012727, Diarrhoea - 10012735)

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

2) Vaginal discharge of mucous appearance (Vaginal discharge - 10046901, Vaginal discharge - 10046901)

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

3) Cough (Cough - 10011224, Cough - 10011224)

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

4) Too sleepy/ excessive sleep (Sleep excessive - 10041000, Hypersomnia - 10020765)

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

5) Feeling exhausted (Exhaustion - 10015667, Fatigue - 10016256)

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

6) Off-label use for unapproved indication (Off label use - 10053762, Off label use - 10053762)

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

Labeling :

1) Diarrhea
CORE UnLabeled
2) Vaginal discharge of mucous appearance
CORE UnLabeled
3) Cough
CORE Labeled
4) Too sleepy/ excessive sleep
CORE UnLabeled
5) Feeling exhausted
CORE Labeled
6) Off-label use for unapproved indication
CORE UnLabeled

2) Drug : Eligard® Unspecified Device (Leuprolide acetate)
Active Substance : 1) Leuprolide acetate
Drug Characterization : Suspect
Lot Number : 1) Unknown
Indications : 1) Central Precocious Puberty [10073186 - Central precocious puberty]
Action(s) Taken With Drug : Not applicable

Causality

1) Diarrhea (Diarrhea - 10012727, Diarrhoea - 10012735)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable
2) Vaginal discharge of mucous appearance (Vaginal discharge - 10046901, Vaginal discharge - 10046901)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable
3) Cough (Cough - 10011224, Cough - 10011224)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable
4) Too sleepy/ excessive sleep (Sleep excessive - 10041000, Hypersomnia - 10020765)
Causality as per reporter : Not Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable
5) Feeling exhausted (Exhaustion - 10015667, Fatigue - 10016256)
Causality as per reporter : Not Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable
6) Off-label use for unapproved indication (Off label use - 10053762, Off label use - 10053762)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Diarrhea
CORE
2) Vaginal discharge of mucous appearance
CORE
3) Cough
CORE
4) Too sleepy/ excessive sleep
CORE

Continuation Sheet for CIOMS report

5) Feeling exhausted
CORE
6) Off-label use for unapproved indication
CORE

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

Dosage Text :

Drug 1 :Eligard®

1) 22.5 milligram, q 3 month