SUSPECT ADVERSE REACTION REPORT

NI-Tolmar-TLM-2025-01067

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
AGLE	NICARAGUA	21	Jul	2015	9	Female	18	Jul	2024

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

1) Acanthosis nigricans (Acanthosis nigricans (10000350), Acanthosis nigricans (10000350))
(/Feb/2025 -) - Not Recovered/Not Resolved/Ongoing
2) Eligard 22.5 mg every 3 months for Central Precocious Puberty (Off label dosing (10074165), Off label use (10053762))
(18/Jul/2024 -) - Not Recovered/Not Resolved/Ongoing
3) Weight gain (Weight increased (10047899), Weight increased (10047899))
(/Feb/2025 -) - 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)

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) (18/Jul/2024 - Ongoing)	

III. CONCOMITANT DRUG(S) AND HISTORY

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

1)METFORMIN(METFORMIN)(/Feb/2025 -)

Cont..

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)

Cont..

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

Name : Tolmar, Inc
701 Centre Avenue
Fort Collins, CO, 80526, UNITED STATES OF AMERICA
debbie.maierhofer@tolmar.comand+1-4129158447

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-TLM-2025-01067
24c. DATE RECEIVED BY MANUFACTURER: 23/Apr/2025	24d. REPORT SOURCE: ☑ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT: 06/May/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...)

Event Description :

This study report from Nicaragua was received by Adium (reference number: NI-ADIUM-NI-0039-20250423) via the ‘ASOFARMA A TU LADO' Patient Support Program on 23-Apr-2025 from a consumer (patient's mother) (non-healthcare professional) regarding a child of 09-year-old female patient who experienced non-serious events of ‘Acanthosis nigricans' (Acanthosis nigricans), ‘weight gain' (weight increased) and ‘Eligard 22.5 mg every 3 months for Central Precocious Puberty ‘ (Off label use) during Eligard (leuprolide acetate) 22.5 mg 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 25-Apr-2025.

The patient's medical history included insulin resistance and current condition included precocious puberty.

Concomitant medication included metformin.

On 18-Jul-2024, the patient began receiving Eligard 22.5 mg, every 3 months via subcutaneous route for precocious puberty (Lot numbers and Expiration dates were not provided).

On an unknown date in Feb-2025, the patient gained 5 pounds in 2 months and had acanthosis nigricans, so the physician prescribed metformin. No further details were available.

Corrective treatment was not reported.

Relevant test results included:
On an unknown date in Feb-2025: Weight: gained 5 pounds (Ref. range: Not provided).

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

The outcome of weight increased, acanthosis nigricans and off-label use was not resolved.

The reporter did not assess the seriousness of weight increased, acanthosis nigricans and off label use.

The reporter did not provide the causality of weight increased, acanthosis nigricans, off label use in relationship to Eligard and Eligard unspecified device.

No further queries were raised.

Listedness:

Acanthosis nigricans>Eligard>Unlisted as per CCDS>07-Nov-2024
Acanthosis nigricans>Eligard>Unlisted as per USPI>Feb-2025
Acanthosis nigricans>Eligard unspecified device>Unlisted as per USPI>Feb-2025
Acanthosis nigricans>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
Off-label use>Eligard>Unlisted as per Canadian monograph>02-Apr-2025

Weight increased>Eligard>listed as per CCDS>07-Nov-2024
Weight increased>Eligard>listed as per USPI>Feb-2025
Weight increased>Eligard unspecified device>listed as per USPI>Feb-2025
Weight increased>Eligard>listed as per Canadian monograph>02-Apr-2025

Company Remarks (Sender's Comments) :

Evaluator comment (Tolmar): This is regarding a female child 09-year-old who experienced acanthosis nigricans (Acanthosis nigricans), weight increased (weight gain) and off label use (Eligard 22.5 mg every 3 months for Central Precocious Puberty) during Eligard (leuprolide acetate) 22.5 mg therapy for precocious puberty. Tolmar assessed the reported events as non-serious since they did not meet the ICH seriousness criteria and are not IME events. The reported events acanthosis nigricans and weight gain were assessed as not related to Eligard (drug and device) as the events can be explained by medical history of insulin resistance and patient being put on metformin. Event off label use was assessed as not related to Eligard (drug and device) as the event occurred with the product and not due to drug.

Additional Information (Continuation...)

Lab Result :

Continuation Sheet for CIOMS report

Test Name	Test Date	Test Result	Normal Value
WEIGHT	/Feb/2025		

Test Result (Code) / Result Unstructured Data (free text) :

1) Test Name: WEIGHT

Result Unstructured Data (free text) : gained 5 pounds in 2 months

Test Date: /Feb/2025

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 : 18/Jul/2024 To :Continuing
Action(s) Taken With Drug : Dose not changed

Causality

1) Acanthosis nigricans (Acanthosis nigricans - 10000350, Acanthosis nigricans - 10000350)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

2) Eligard 22.5 mg every 3 months for Central Precocious Puberty (Off label dosing - 10074165, Off label use - 10053762)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

3) Weight gain (Weight increased - 10047899, Weight increased - 10047899)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Acanthosis nigricans
CORE UnLabeled

2) Eligard 22.5 mg every 3 months for Central Precocious Puberty
CORE UnLabeled

3) Weight gain
CORE Labeled

2) 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 [10073186 - Central precocious puberty]
Action(s) Taken With Drug : Not applicable

Causality

1) Acanthosis nigricans (Acanthosis nigricans - 10000350, Acanthosis nigricans - 10000350)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

2) Eligard 22.5 mg every 3 months for Central Precocious Puberty (Off label dosing - 10074165, Off label use - 10053762)
Causality as per reporter : Not Reported

Continuation Sheet for CIOMS report

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

3) Weight gain (Weight increased - 10047899, Weight increased - 10047899)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Acanthosis nigricans
CORE
2) Eligard 22.5 mg every 3 months for Central Precocious Puberty
CORE
3) Weight gain
CORE

22.CONCOMITANT DRUG(S) (Continuation...)

1). Drug : METFORMIN
Active Substance : 1) METFORMIN
Form Strength :
Daily Dose : 1) (500 milligram(s), 1 in 12 Hour)
Indications : 1) Product used for unknown indication [10070592 - Product used for unknown indication]
Therapy Dates : 1) From : /Feb/2025 To :

23. OTHER RELEVANT HISTORY (Continuation...)

2) INSULIN RESISTANCE (10022489 , Insulin resistance)