CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

NI-Tolmar-TLM-2025-04576

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6 REACTION ONSET		
		Day	Month	Year	Years		Day	Month	Year
XSSH	NICARAGUA	09	May	2016	9	Female	03	Jul	2025

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

1) Heavy vaginal bleeding (Vaginal haemorrhage (10046910), Vaginal haemorrhage (10046910)) (03/Jul/2025 -) - Not Recovered/Not Resolved/Ongoing
2) Off-label use for non-approved indication (Off label use in unapproved indication (10084345), Off label use (10053762)) Unknown

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) (22.5 Milligram, 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 [10058084 - Precocious puberty]

18. THERAPY DATE(S) (from/to)	19. THERAPY DURATION
1) (19/Jun/2025 -)	

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 (10058084, 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-TLM-2025-04576
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE
09/Jul/2025	☑ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE
12/Jul/2025	☑ 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 via an electronic form through the Jazz Safety tool of the Patient Support Program “ASOFARMA A TU LADO” (reference number: NI-ADIUM-NI-0056-20250709) on 09-Jul-2025 from a Consumer regarding a Child 9 Years old Female patient who experienced a “Heavy vaginal bleeding" (Vaginal haemorrhage) and “Off-label use for non-approved indication” (Off label use), 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 10-Jul-2025.

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

Concomitant medications were not reported.

On 19-Jun-2025, the patient began receiving Eligard 22.5 milligram for 3 months, via subcutaneous route of administration for Central Precocious puberty (Lot numbers and Expiration dates were not provided).

On 03-Jul-2025, the patient suffered Heavy vaginal bleeding. No further details were provided.

Corrective treatment was not reported.

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

The outcome of Vaginal haemorrhage was not Recovered.

The outcome of Off label use was Unknown.

The reporter did not assess the seriousness of Vaginal haemorrhage and Off label use in relationship to Eligard.

The reporter did not provide the causality of Vaginal haemorrhage and Off label use in relationship to Eligard and Eligard unspecified device.

No follow up queries were raised.

Vaginal haemorrhage>Eligard>Listed as per CCDS>07-Nov-2024
Vaginal haemorrhage>Eligard>Unlisted as per USPI>Feb-2025
Vaginal haemorrhage>Eligard unspecified device>Unlisted as per USPI>Feb-2025
Vaginal haemorrhage>Eligard>Listed 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

Company Remarks (Sender's Comments) :

Evaluator comment (Tolmar): This case is regarding a child, 9 years old female patient who experienced vaginal haemorrhage (heavy vaginal bleeding) and off label use (off-label use for non-approved indication), during Eligard (Leuprolide acetate) 22.5 milligram therapy for central 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 causality for the reported event vaginal haemorrhage is assessed as related with Eligard (drug) (not related to device) based on plausible temporality and known safety profile of the drug stating vaginal bleeding may be observed during the first weeks of therapy or after subsequent doses due to rise in gonadotropins and sex steroids above baseline because of the initial stimulatory effect of the drug. The causality of the event off label use is assessed as not related with Eligard (drug and device) components as the event had happened due to human action, rather due to drug.

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

Product-Reaction Level

1) Drug	: Eligard® (Leuprolide acetate)
Active Substance	: 1) Leuprolide acetate
Drug Characterization	: Suspect
Form Strength	: 1) 22.5 Milligram
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 [10058084 - Precocious puberty]

Continuation Sheet for CIOMS report

Therapy Dates : 1) From : 19/Jun/2025 To :Continuing
Action(s) Taken With Drug : Dose not changed

Causality

1) Heavy vaginal bleeding (Vaginal haemorrhage - 10046910, Vaginal haemorrhage - 10046910)
Causality as per reporter : Related
Causality as per Mfr : Related
DeChallenge : Not applicable
ReChallenge : Not Applicable
2) Off-label use for non-approved indication (Off label use in unapproved indication - 10084345, Off label use - 10053762)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Heavy vaginal bleeding
CORE Labeled
2) Off-label use for non-approved indication
CORE UnLabeled

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

Causality

1) Heavy vaginal bleeding (Vaginal haemorrhage - 10046910, Vaginal haemorrhage - 10046910)
Causality as per reporter : Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable
2) Off-label use for non-approved indication (Off label use in unapproved indication - 10084345, Off label use - 10053762)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Heavy vaginal bleeding
CORE
2) Off-label use for non-approved indication
CORE