SUSPECT ADVERSE REACTION REPORT

CR-Tolmar-TLM-2025-01849

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
VSA	COSTA RICA	04	Dec	1931	93	Male			2022

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

1) diagnosed with prostate cancer with bone metastasis/ my grandfather's condition has worsened/ decay in his condition (Progression of prostate cancer (10066489), Prostate cancer (10060862))
Recovering/Resolving
2) Bone metastasis (Metastases to bone (10027452), Metastases to bone (10027452))
(//2022 -) - Not Recovered/Not Resolved/Ongoing
3) Eligard was no longer available in the country (Product supply issue (10077801), Product supply issue (10077801))
Unknown
4) Therefore, patient was switched to Zalodex 10.80 (Product substitution (10076753), Product substitution (10076753))
Unknown

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) (45 milligram(s), 1 in 6 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) Prostate cancer [10060862 - Prostate cancer]

18. THERAPY DATE(S) (from/to)	19. THERAPY DURATION
(25-Oct-2024 -)	

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) PROSTATE CANCER (10060862, Prostate cancer) (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	CR-Tolmar-TLM-2025-01849
24c. DATE RECEIVED BY MANUFACTURER: 26/Jun/2025	24d. REPORT SOURCE: ☑ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT: 03/Jul/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) Eligard was no longer having the expected effect/ lack of efficacy (Lack of drug effect (10023610), Drug ineffective (10013709)(27/Apr/2025 -) -

Unknown)

Event Description :

This study report from Brazil was received by Adium Patient Support Program (reference number: CR-ADIUM-CR-0166-20250514) on 14-May-2025 from a consumer (non-healthcare professional) regarding an elderly 93-year old male patient who experienced serious (medically significant) events of "Bone metastasis" (Metastases to bone) and "diagnosed with prostate cancer with bone metastasis/ my grandfather's condition has worsened/ decay in his condition" (Prostate cancer) and non-serious events of "Eligard was no longer having the expected effect" (Drug ineffective), "Eligard was no longer having the expected effect and was no longer available in the country" (Product supply issue), and "Therefore, patient was switched to Zalodex 10.8" (Product substitution) during Eligard (Leuprolide acetate) 45mg therapy for prostate cancer. The needle component of the constituent device was not identified in the report. The report was sent to Tolmar on 15-May-2025.

The patient's medical history was unknown and current condition included prostate cancer.

Concomitant medications were not provided.

On an unknown date, the patient began receiving Eligard of 45 mg strength in 6 months of frequency via subcutaneous route of administration for prostate cancer (Lot numbers and Expiration dates were not provided).

On an unknown date in 2022, the patient had been diagnosed with prostate cancer with bone metastasis for 3 years. He was unaware of his condition, so he was only told that the medication being administered is to keep his prostate healthy and allow him to urinate. In recent months, his condition had worsened, but he was now recovering. According to the latest tests performed, Eligard was no longer having the expected effect and was no longer available in the country.

On 25-Apr-2025, the patient was switched to Zalodex - 10.80 milligram dose - for prostate cancer.

Corrective treatment was not provided.

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

The outcome of metastases to bone was not recovered, prostate cancer was recovering and drug ineffective, product substitution and product supply issue was unknown.

The reporter did not assess the seriousness of metastases to bone, prostate cancer, drug ineffective and product substitution and product supply issue.

The reporter assessed the causality of drug ineffective and prostate cancer as related, metastases to bone as not related, product substitution and product supply issue as not reported in relationship to Eligard and Eligard unspecified device

No further queries were raised.

On 19-May-2025, Tolmar case ID QE-027981 was added to the case.

On 21-May-2025, the follow up was received by Adium Patient Support Program "ASOFARMA A TU LADO" (reference number: CR-ADIUM-CR-0166-20250514). New information included: dose administration date and lab test were added. Narrative was updated.

On 25-Oct-2024, the patient began receiving Eligard of 45 mg strength in 6 months of frequency via subcutaneous route of administration for prostate cancer (Lot numbers and Expiration dates were not provided).

Relevant lab test
On 25-Apr-2025, Blood testosterone: Unknown (Ref. range not provided).

No further queries were raised.

On 23-May-2025, Tolmar Quality Assurance number QE-027981 was added. This follow up information which was received on 23-May-2025 was considered as non-significant case.

On 26-Jun-2025, Tolmar Quality Assurance completed an evaluation of the technical complaint (QE-027981). Quality investigation report was added and narrative was updated.

Quality investigation report concluded that the root cause was considered as inconclusive.

Complaint assessment and conclusion:
A caregiver reported a unit of Eligard 45mg (lot number not reported) stating “According to the latest tests performed, Eligard was no longer having the expected effect" and he "Does not have the information" for the Suspect Lot(s). Per SOP-01003, complaints do not meet the criteria for QCC retain sample testing if a lot number is not reported.

Continuation Sheet for CIOMS report

Complaint QE-027676 documents the investigation of Eligard 45mg (unknown lot) with the failure mode "medical - lack of effect". QE-027676 was closed on 19-May-2025 and this complaint was received on 14-May-2025. Per SOP-00894, "Any complaint(s) received within 3 months of a previously completed investigation for the same product, lot number and complaint type, may reference the previous investigation." This complaint was received within 3 months of the closure of QE-027676 and therefore will not undergo reinvestigation.

The conclusion of QE-027676 is as follows: "Without an identified lot number, the executed manufacturing batch records could not be reviewed. However, the drug product must pass strict testing requirements prior to release; manufacturing records, analytical data and other applicable data reviews are performed prior to the release of each
lot. The stability data results for Eligard 45mg supports the product's expiration period. There was one Field Alert Report submission for all Eligard strengths within the past year related to the reported lack of efficacy. Reference Immediate Action VV- 026275 for discussion of the FAR and Deviation QE-023547. A one-year deviation search did not identify any other deviations that would have contributed to the reported defect."

Based on the data review and available information, there is no indication that the root cause of the reported lack of efficacy is related to the manufacturing or packaging process at Tolmar. The investigation of this event did not indicate any impaired quality of the product. Without the lot number, retain sample analysis could not be performed. The root cause is considered inconclusive. Further investigation is not required at this time and this complaint will be included in the system for tracking and trending purposes.

Listedness
Metastases to bone>Eligard® >listed as per CCDS Eligard®> 7-Nov-2024
Metastases to bone> Eligard® >listed as per Canadian Monograph Eligard®> 2-Apr-2025
Metastases to bone> Eligard®>listed as per USPI Eligard®>Feb-2025
Metastases to bone> Eligard® Unspecified Device> listed as per USPI Eligard®>Feb-2025

Prostate cancer>Eligard® >listed as per CCDS Eligard®> 7-Nov-2024
Prostate cancer> Eligard® >listed as per Canadian Monograph Eligard®> 2-Apr-2025
Prostate cancer> Eligard®>listed as per USPI Eligard®>Feb-2025
Prostate cancer> Eligard® Unspecified Device> listed as per USPI Eligard®>Feb-2025

Product supply issue >Eligard® >unlisted as per CCDS Eligard®> 7-Nov-2024
Product supply issue > Eligard® >unlisted as per Canadian Monograph Eligard®> 2-Apr-2025
Product supply issue > Eligard®>unlisted as per USPI Eligard®>Feb-2025
Product supply issue > Eligard® Unspecified Device>unlisted as per USPI Eligard®>Feb-2025

Product substitution >Eligard® >unlisted as per CCDS Eligard®> 7-Nov-2024
Product substitution> Eligard® >unlisted as per Canadian Monograph Eligard®> 2-Apr-2025
Product substitution> Eligard®>unlisted as per USPI Eligard®>Feb-2025
Product substitution> Eligard® Unspecified Device>unlisted as per USPI Eligard®>Feb-2025

Drug ineffective >Eligard® >listed as per CCDS Eligard®> 7-Nov-2024
Drug ineffective> Eligard® >listed as per Canadian Monograph Eligard®> 2-Apr-2025
Drug ineffective> Eligard®>listed as per USPI Eligard®>Feb-2025
Drug ineffective> Eligard® Unspecified Device>listed as per USPI Eligard®>Feb-2025

Company Remarks (Sender's Comments) :

Evaluator comment (Tolmar): The case is regarding an elderly 93-year old male patient who reported events of Metastases to bone (Bone metastasis), Prostate cancer(diagnosed with prostate cancer with bone metastasis/ my grandfather's condition has worsened/ decay in his condition), Drug ineffective (Eligard was no longer having the expected effect), Product supply issue (Eligard was no longer having the expected effect and was no longer available in the country), Product substitution (Therefore, patient was switched to Zalodex 10.8) during Eligard (Leuprolide acetate) 45mg therapy for prostate cancer. Tolmar assessed the events bone metastasis and prostate cancer as serious (medically significant) as these events are included in IME list and rest of the events were assessed as non-serious since they did not meet the ICH seriousness criteria. The causality of the events bone metastasis and prostate cancer were assessed as not related to suspect Eligard(Drug and device) as these events could be attributed to underlying prostate cancer which is known to progress despite treatment. The causality of event drug ineffective was assessed as related to suspect drug Eligard (not related to device) based on timeline association with Eligard administration and given that the effect of drug may vary from person to person. The causality of events product substitution due to product supply issue was assessed as not related to suspect Eligard(drug and device) as it was human action due circumstances.

Additional Information (Continuation...)

Lab Result :

Test Name	Test Date	Test Result	Normal Value
TESTOSTERONE	25/Apr/2025		

Continuation Sheet for CIOMS report

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

1) Test Name: TESTOSTERONE

Result Unstructured Data (free text) : Unknown

Test Date: 25/Apr/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 : (45 milligram(s), 1 in 6 Month)
Route of Admin : 1) Subcutaneous
Indications : 1) Prostate cancer [10060862 - Prostate cancer]
Action(s) Taken With Drug : Unknown

Causality

1) diagnosed with prostate cancer with bone metastasis/ my grandfather's condition has worsened/ decay in his condition (Progression of prostate cancer - 10066489, Prostate cancer - 10060862)
Causality as per reporter : Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

2) Bone metastasis (Metastases to bone - 10027452, Metastases to bone - 10027452)
Causality as per reporter : Not Related
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

3) Eligard was no longer available in the country (Product supply issue - 10077801, Product supply issue - 10077801)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

4) Therefore, patient was switched to Zalodex 10.80 (Product substitution - 10076753, Product substitution - 10076753)
Causality as per reporter : Not Reported
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

5) Eligard was no longer having the expected effect/ lack of efficacy (Lack of drug effect - 10023610, Drug ineffective - 10013709)
Causality as per reporter : Related
Causality as per Mfr : Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) diagnosed with prostate cancer with bone metastasis/ my grandfather's condition has worsened/ decay in his condition
CORE Labeled

2) Bone metastasis
CORE Labeled

3) Eligard was no longer available in the country
CORE UnLabeled

4) Therefore, patient was switched to Zalodex 10.80
CORE UnLabeled

5) Eligard was no longer having the expected effect/ lack of efficacy
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) Prostate cancer [10060862 - Prostate cancer]

Continuation Sheet for CIOMS report

Action(s) Taken With Drug : Not applicable

Causality

1) diagnosed with prostate cancer with bone metastasis/ my grandfather's condition has worsened/ decay in his condition (Progression of prostate cancer - 10066489, Prostate cancer - 10060862)
- Causality as per reporter : Related
- Causality as per Mfr : Not Related
- DeChallenge : Not applicable
- ReChallenge : Not Applicable

2) Bone metastasis (Metastases to bone - 10027452, Metastases to bone - 10027452)
- Causality as per reporter : Not Related
- Causality as per Mfr : Not Related
- DeChallenge : Not applicable
- ReChallenge : Not Applicable

3) Eligard was no longer available in the country (Product supply issue - 10077801, Product supply issue - 10077801)
- Causality as per reporter : Not Reported
- Causality as per Mfr : Not Related
- DeChallenge : Not applicable
- ReChallenge : Not Applicable

4) Therefore, patient was switched to Zalodex 10.80 (Product substitution - 10076753, Product substitution - 10076753)
- Causality as per reporter : Not Reported
- Causality as per Mfr : Not Related
- DeChallenge : Not applicable
- ReChallenge : Not Applicable

5) Eligard was no longer having the expected effect/ lack of efficacy (Lack of drug effect - 10023610, Drug ineffective - 10013709)
- Causality as per reporter : Related
- Causality as per Mfr : Not Related
- DeChallenge : Not applicable
- ReChallenge : Not Applicable

Labeling :

1) diagnosed with prostate cancer with bone metastasis/ my grandfather's condition has worsened/ decay in his condition
   CORE
2) Bone metastasis
   CORE
3) Eligard was no longer available in the country
   CORE
4) Therefore, patient was switched to Zalodex 10.80
   CORE
5) Eligard was no longer having the expected effect/ lack of efficacy
   CORE