CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

2023US019655

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
Masked	PANAMA	Masked	Masked	Masked	87	Male		Jan	2024

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

1) Loss of muscle tone (Muscle tone decreased (10028344), Hypotonia (10021118))
(/Jan/2024 -) - Not Recovered/Not Resolved/Ongoing
2) Urinary tract infection/ This infection became complicated (Complicated urinary tract infection (10080628), Urinary tract infection (10046571))
(/May/2025 -) - Recovering/Resolving
3) Dehydration (Dehydration (10012174), Dehydration (10012174))
Not Recovered/Not Resolved/Ongoing
4) Diarrhea (Diarrhea (10012727), Diarrhoea (10012735))
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) Enzalutamide (ENZALUTAMIDE, Enzalutamide) (Suspect) (Open-Label) (40 Milligram, Capsule)(Unknown)

Cont..

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

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
1) 160 milligram(s) (160 milligram(s), 1 in 1 Day)	1) Oral

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

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.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

Name : Astellas Pharma Global Development, Inc.
2375 Waterview Drive
Northbrook, IL, 60062-6111, UNITED STATES OF AMERICA

Study Information
Study Name: Enzalutamide Patient Support Progr (Cont..)
EudraCT Number:
Protocol No.: Enzalutamide_Astellas PSP
Center No.:
Subject Id :

24.REPORT NULLIFIED	24b. MFR CONTROL NO.
☐ YES ☐ NO	2023US019655
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE
04/Jun/2025	☑ STUDY ☐ LITERATURE ☑ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE
10/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) Weakness when walking (Weakness (10047862), Asthenia (10003549) - Not Recovered/Not Resolved/Ongoing)

6) Could not urinate due to infection (Unable to urinate (10076880), Urinary retention (10046555) - Unknown)

7) Obstructed urethra (Urethral obstruction (10046459), Urethral obstruction (10046459) - Unknown)

Event Description :

This case was received by Astellas business partner Tecnofarma S.A., on 28-Jun-2023, by an Other Health Professional (patient support manager) referring to an 87 years-old male patient and was received at Astellas from Tecnofarma S.A., on 28-Jun-2023 who was enrolled in post-marketing study: Enzalutamide Patient Support Program who was on Enzalutamide, Capsule (160 milligram(s), 1 every 1 Day). Indication for use was Prostate cancer.

Study no: Enzalutamide_Astellas PSP: Open label study.

The patient received enzalutamide for prostate cancer according to the following dosage regimen: (start date not provided) - (stop date not provided): Oral 160 mg, once daily.

The patient received Eligard (leuprorelin) for prostate cancer according to the following dosage regimen: 13-Oct-2022 - (ongoing): Subcutaneous 45 mg other (every 6 months) (Lyophilized for suspension).

Action taken with enzalutamide treatment in response to events (dehydration, diarrhea, weakness, urinary tract infection/ this infection became complicated, obstructed urethra and could not urinate) was withdrawn and action taken with leuprorelin treatment in response to events was no change.

Action taken with enzalutamide treatment in response to event loss of muscle tone was unknown.

On an unspecified date, the patient has had diarrhea for a week (no date indicated) and was taken to the hospital in an emergency because of dehydration due to diarrhea (dehydration). The patient continued with the symptoms mentioned above. They were not been able to make an appointment with the urologist because of current diarrhea.

On an unspecified date, the patient's wife reported that the patient had not been using the enzalutamide treatment for 2 weeks (no date indicated) by medical decision, because the medication caused a lot of diarrhea and this symptom caused a lot of weakness when walking. The patient's wife mentioned that patient will no longer continue with enzalutamide treatment but will continue with the leuprorelin treatment. She declined to provide further information.

Upon follow up, patient's relative (wife) reported that three months ago (in Jan-2024), the patient lost muscle tone and was now in bed, where all his daily needs must be taken care of. The use of other medication other than leuprorelin was not reported, but follow-up will be done to confirm if the patient was still being treated with enzalutamide 40 mg.

Upon follow up on 04-Jun-2025, The patient reported that he had a urinary tract infection (intensity: severe) that occurred in May-2025 and was hospitalized for 12 days. The patient treated with antibiotic treatment in hospital. This infection became complicated because his urethra became obstructed and he required bladder surgery to be able to urinate, as he was unable to urinate due to the infection.

The outcome of events dehydration, diarrhea, weakness when walking and loss of muscle tone was reported as not recovered/not resolved. The outcome of the event urinary tract infection/ this infection became complicated was reported as recovering/resolving (was in recovery) as of 24-May-2025, the outcome of the events obstructed urethra and could not urinate due to infection was unknown.

Medical history was not reported.

Past medications were not reported.

Concomitant medications were not reported.

No relevant lab data was reported.

The other health professional and patient's wife assessed the following events with respect to enzalutamide and leuprorelin:
- Dehydration (seriousness: Serious (Hospitalization); causality: Not Assessed)
- Diarrhea (seriousness: Serious (Hospitalization); causality: Not Assessed)
- Weakness when walking (seriousness: Serious (Medically Significant); causality: Not Assessed)
- Loss of muscle tone (seriousness: Serious (Disability); causality: Not Assessed)

The patient assessed the following events with respect to enzalutamide and leuprorelin:
- Urinary tract infection/ This infection became complicated (seriousness: Serious (Hospitalization); causality: Not Assessed)
- Obstructed urethra (seriousness: Serious (Hospitalization); causality: Not Assessed)
- Could not urinate due to infection (seriousness: Serious (Hospitalization, Disability); causality: Not Assessed)

Continuation Sheet for CIOMS report

Consent to contact patient and Other health professional for follow-up information was denied.

Tracking of changes:
28-Jun-2023: Initial information was received.

Follow-up information was received on 25-Jul-2023: New event (Weakness when walking) added, enzalutamide therapy details, action taken and clinical description updated.

Follow-up information was received by Astellas business partner Tecnofarma S.A.on 20-Mar-2024 from another healthcare professional via patient's wife and was received at Astellas from Tecnofarma S.A.on 21-Mar-2024: Added new event Loss of muscle tone, clinical description, updated seriousness of the event Weakness when walking from non-serious to Serious (Medically Significant) and added leuprorelin therapy details, updated action taken statement.

Follow-up information was received by Astellas business partner Adium on 04-Jun-2025, 05-Jun-2025 from patient and was received at Astellas from Adium on 05-Jun-2025, 06-Jun-2025: Reporter details, leuprorelin details (lot number, expiry date) added new events "urinary tract infection/ this infection became complicated", "obstructed urethra" and "could not urinate due to infection" added and narrative was updated.

Company Remarks (Sender's Comments) :

Event Information:
Unable to urinate was assessed as Serious due to Disability/Permanent Damage and Caused/Prolonged Hospitalization.
Weakness was assessed as Non-Serious, based on event not meeting ICH seriousness criteria.
Muscle tone decreased was assessed as Serious due to Disability/Permanent Damage.
Dehydration, Diarrhea, Urethral obstruction and Complicated urinary tract infection were assessed as Serious due to Caused/Prolonged Hospitalization.

All events coded to closest available MedDRA terms to reflect reported information.

Product: Enzalutamide
Astellas assessed Diarrhea and Weakness as Related based on temporal relationship. The confounders for Weakness include concurrent event: Diarrhoea, underlying malignancy and elderly age of patient. Dehydration was assessed as Not Related, as it can be attributed to Diarrhea. The de challenge was negative. Muscle tone decreased and Urethral obstruction as Not Related, based on available information for this case, a reasonable possibility to suggest a relationship between the suspect therapy and the reported events cannot be established. The confounders include elderly age of patient and underlying malignancy. Astellas assessed Complicated urinary tract infection as Not Related, as it can be attributed to Urethral obstruction and low immune state due to elderly age of patient, underlying malignancy. Unable to urinate as Not Related as it can be attributed to Urethral obstruction.

Product: Leuprorelin
Astellas assessed Dehydration, Weakness as Not Related, as these events were due to Diarrhoea. Additional confounders for Weakness include underlying malignancy and elderly age of patient. Diarrhoea as Not Related, as it can be attributed to enzalutamide. Muscle tone decreased and Urethral obstruction as Not Related, based on available information for this case, a reasonable possibility to suggest a relationship between the suspect therapy and the reported events cannot be established. The confounders include elderly age of patient and underlying malignancy. Astellas assessed Complicated urinary tract infection as Not Related, as it can be attributed to Urethral obstruction and low immune state due to elderly age of patient, underlying malignancy. Unable to urinate as Not Related as it can be attributed to Urethral obstruction.

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

Product-Reaction Level

1) Drug	: Enzalutamide (ENZALUTAMIDE)
Active Substance	: 1) Enzalutamide
Coding Class	: Open-Label
Drug Characterization	: Suspect
Form Strength	: 1) 40 Milligram
Form of Admin	: 1) Capsule
Lot Number	: 1) Unknown
Daily Dose	: 1) 160 milligram(s) (160 milligram(s), 1 in 1 Day)
Route of Admin	: 1) Oral
Indications	: 1) Prostate cancer [10060862 - Prostate cancer]
Action(s) Taken With Drug	: Drug withdrawn

Causality

1) Loss of muscle tone (Muscle tone decreased - 10028344, Hypotonia - 10021118)

Causality as per reporter	: Not assessed
Causality as per Mfr	: Not Related
ReChallenge	: Not Applicable

2) Urinary tract infection/ This infection became complicated (Complicated urinary tract infection - 10080628, Urinary tract infection - 10046571)

Continuation Sheet for CIOMS report

Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable

3) Dehydration (Dehydration - 10012174, Dehydration - 10012174)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Negative
ReChallenge : Not Applicable

4) Diarrhea (Diarrhea - 10012727, Diarrhoea - 10012735)
Causality as per reporter : Not assessed
Causality as per Mfr : Related
DeChallenge : Negative
ReChallenge : Not Applicable

5) Weakness when walking (Weakness - 10047862, Asthenia - 10003549)
Causality as per reporter : Not assessed
Causality as per Mfr : Related
DeChallenge : Negative
ReChallenge : Not Applicable

6) Could not urinate due to infection (Unable to urinate - 10076880, Urinary retention - 10046555)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable

7) Obstructed urethra (Urethral obstruction - 10046459, Urethral obstruction - 10046459)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable

Labeling :

1) Loss of muscle tone
CORE UnLabeled
IB UnLabeled

2) Urinary tract infection/ This infection became complicated
CORE UnLabeled
IB UnLabeled

3) Dehydration
CORE UnLabeled
IB UnLabeled

4) Diarrhea
CORE Labeled
IB Labeled

5) Weakness when walking
CORE Labeled
IB Labeled

6) Could not urinate due to infection
CORE UnLabeled
IB UnLabeled

7) Obstructed urethra
CORE UnLabeled
IB UnLabeled

2) Drug : Eligard (LEUPRORELIN)
Active Substance : 1) LEUPRORELIN
Drug Characterization : Suspect
Form Strength : 1) 45 Milligram
Form of Admin : 1) Injection
Lot Number : 1) L15276CUY
Daily Dose : 1) 0.25 milligram(s) (45 milligram(s), 1 in 6 Month)
Route of Admin : 1) Subcutaneous
Indications : 1) Prostate cancer [10060862 - Prostate cancer]
Therapy Dates : 1) From : 13/Oct/2022 To :Continuing
Action(s) Taken With Drug : Dose not changed

Causality

1) Loss of muscle tone (Muscle tone decreased - 10028344, Hypotonia - 10021118)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable

Continuation Sheet for CIOMS report

ReChallenge : Not Applicable

2) Urinary tract infection/ This infection became complicated (Complicated urinary tract infection - 10080628, Urinary tract infection - 10046571)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

3) Dehydration (Dehydration - 10012174, Dehydration - 10012174)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

4) Diarrhea (Diarrhea - 10012727, Diarrhoea - 10012735)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

5) Weakness when walking (Weakness - 10047862, Asthenia - 10003549)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

6) Could not urinate due to infection (Unable to urinate - 10076880, Urinary retention - 10046555)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

7) Obstructed urethra (Urethral obstruction - 10046459, Urethral obstruction - 10046459)
Causality as per reporter : Not assessed
Causality as per Mfr : Not Related
DeChallenge : Not applicable
ReChallenge : Not Applicable

Labeling :

1) Loss of muscle tone
CORE UnLabeled
IB UnLabeled

2) Urinary tract infection/ This infection became complicated
CORE Labeled
IB Labeled

3) Dehydration
CORE UnLabeled
IB UnLabeled

4) Diarrhea
CORE Labeled
IB Labeled

5) Weakness when walking
CORE Labeled
IB Labeled

6) Could not urinate due to infection
CORE Labeled
IB Labeled

7) Obstructed urethra
CORE UnLabeled
IB UnLabeled

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

Dosage Text :

Drug 1 :Enzalutamide

1) 160 mg, once daily

Drug 2 :Leuprorelin

1) 45 mg, other (every 6 months, lyophilized, for suspension)

24a. NAME AND ADDRESS OF MANUFACTURER (Continuation...)

Continuation Sheet for CIOMS report

Study # :Enzalutamide_Astellas PSP