CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
UNKNOWN	COSTA RICA	19	OCT	1977	47 Years	Female	46.00 kg		MAY	2025

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [LOWER LEVEL TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Multisystem failure; multi-systemic failure [Multiorgan failure]
Distributive shock [Distributive shock]
Abdominal ascites [Ascites]

Case Description: This Costa Rica case is a solicited report received on 05 Jun 2025, from a nurse from a patient support program via Ferrer. This 47-year-old, 46 kg, female patient began therapy with Remodulin (treprostinil sodium, concentration 5 mg/ml), on 13 Jun 2024 for an unknown indication.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☒ PATIENT DIED Date: 26-MAY-2025
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☒ OTHER

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Treprostinil sodium (SQ) (TREPROSTINIL SODIUM) Injection, 5.0 mg/ml
(Continued on Additional Information Page)

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) UNK [0.060 mg/ml], continuing	#1) Subcutaneous use

17. INDICATION(S) FOR USE
#1) Primary pulmonary arterial hypertension
(Continued on Additional Information Page)

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) Unknown	#1) Unknown

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

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) Tadalafilo (Tadalafilo) ; Unknown
#2) Ambrisentan (Ambrisentan) ; Unknown
#3) Prednisona (Prednisona) 5 mg; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Current Condition	
Unknown to Ongoing	Current Condition	Cardiac failure (Cardiac failure)
	Heart failure	

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
United Therapeutics
55 T W Alexander Drive, P.O. Box 14186
Research Triangle Park, NC 27709 UNITED STATES
Phone: 1 (919) 485-8350

26. REMARKS
World Wide #: CR-UNITED THERAPEUTICS-UNT-2025-019720
Study ID: PSP_Remodulin_043

24b. MFR CONTROL NO.
UNT-2025-019720

24c. DATE RECEIVED BY MANUFACTURER
30-JUN-2025

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
10-JUL-2025

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP: 2

25b. NAME AND ADDRESS OF REPORTER
COSTA RICA
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
(Continued on Additional Information Page)

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The patient's dose was unknown [0.060 mg/ml], continuous via subcutaneous (SQ) route. On 19 May 2025, 11 months and 7 days after initiating SQ Remodulin, the patient was admitted to the hospital for abdominal ascites (hospitalized and medically significant). Further, on an unreported date in May 2025, during hospitalization, her health deteriorated, causing multisystem failure (multiple organ dysfunction syndrome, hospitalization prolonged and medically significant) and distributive shock (hospitalization prolonged and medically significant). On 26 May 2025, 11 months and 14 days after initiating SQ Remodulin, she died (death and medically significant) at 1:30 AM and the cause of death was not provided. It was also unknown if an autopsy was performed.

Action taken with SQ Remodulin was not reported for the events of ascites, multiple organ dysfunction syndrome and distributive shock. Action taken with SQ Remodulin was not applicable for the event of death. The outcome of ascites, multiple organ dysfunction syndrome and distributive shock was not resolved.

The reporter assessed the causal relationship between SQ Remodulin and the events of ascites, multiple organ dysfunction syndrome and distributive shock as not related. The reporter did not provide causality for the event of death with SQ Remodulin.

Follow-up information was received on 12 Jun 2025 as a query response via Ferrer.

Follow up report clarified cause of the death as multiple organ dysfunction syndrome. Thus, the event of death was subsumed under the event of multiple organ dysfunction syndrome. The patient's relevant medical history and indication of SQ Remodulin was added as primary pulmonary arterial hypertension. Relevant medical history included: cardiac failure. On 26 May 2025, the patient died due to multi-systemic failure (previously reported, multiple organ dysfunction syndrome; death). It was further reported that the patient’s death was related to progression of underlying disease [primary pulmonary arterial hypertension]. Action taken with SQ Remodulin was not applicable for the event of multiple organ dysfunction syndrome. The outcome of multiple organ dysfunction syndrome was fatal.

Follow-up information was received on 30 Jun 2025 as a query response via Ferrer.

Event stop date as 26 May 2025 was added to the events of ascites and distributive shock. Additional relevant medical history included: lupus erythematosus [terminal phase]. Additional concomitant medications included: tadalafilo (tadalafil), ambrisentan, and prednisona (prednisone). It was reported that the ascites (previously reported), multiple organ dysfunction syndrome (previously reported) and distributive shock (previously reported) were related to the disease of primary PAH. Action taken with SQ Remodulin was not applicable for the events of ascites and distributive shock. The outcome of ascites and distributive shock was fatal.

Case Comment/Senders Comment: The company has assessed the serious adverse events of multiple organ dysfunction syndrome, distributive shock and ascites as not related to SQ treprostinil. The underlying indication of PAH is known to lead to progressive right heart failure, systemic congestion, impaired organ perfusion including reduced renal perfusion, and maladaptive neurohormonal activation. These pathophysiological changes associated with PAH can culminate in the development of ascites, distributive type shock resulting from low cardiac output and compensatory vasodilation, and ultimately multiple organ dysfunction syndrome. Additionally, this patient had a medical history of cardiac failure. The fatal outcome in this case was consistent with the natural progression of advanced PAH and its systemic complications.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Treprostinil sodium (SQ) (TREPROSTINIL SODIUM) Injection, 5.0 mg/ml; Regimen #1	UNK [0.060 mg/ml], continuing; Subcutaneous use	Primary pulmonary arterial hypertension (Pulmonary arterial hypertension)	Unknown; Unknown
#1) Treprostinil sodium (SQ) (TREPROSTINIL SODIUM) Injection, 5.0 mg/ml; Regimen #2	UNK, continuing; Subcutaneous use	Primary pulmonary arterial hypertension (Pulmonary arterial hypertension)	13-JUN-2024 / 26-MAY-2025; 11 months 14 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Current Condition	Pulmonary arterial hypertension (Pulmonary arterial hypertension);
Unknown to Ongoing	Current Condition Terminal phase	Lupus erythematosus (Systemic lupus erythematosus);

Mfr. Control Number: UNT-2025-019720

ADDITIONAL INFORMATION

25b. Name And Address of Reporters continued
COSTA RICA

NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

Ferrer

COSTA RICA

NAME AND ADDRESS WITHHELD.