SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
	Russian Federation				70 Years	Female	11	Apr	2025	☐ PATIENT DIED

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

#1| Complaints of severe general weakness [Asthenia] |

#2| Body tremors [Tremor] |

#3| Nausea [Nausea] |

Initial spontaneous report received on 04-Jun-2025 from TAKEDA (ID TAP-13140/RU- RZN -2984734), and forwarded to Ferrer on 09-Jun-2025, originally reported by a Russian toxicologist physician.

This case concerns a 70-year-old female chinese patient (Height: 150 CM // Weight: 60 KG) on treatment with ACTOVEGIN(deproteinized hemoderivative of calf blood), MILDRONATE(meldonium) and CITICOLINE (citicoline).
/...continued

☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
☐ LIFE THREATENING
☐ CONGENITAL ANOMALY
☐ OTHER

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1| Actovegin | Blood, calf, deprot., lmw portion, Blood, calf, deprot., lmw portion | Unknown (NOS) | Unknown
#2| Mildronate | Meldonium dihydrate, Meldonium dihydrate | Solution (NOS) | Unknown {Lot#: Unknown}
/..continued

20 DID REACTION ABATE AFTER STOPPING DRUG?
#1| ☒ YES ☐ NO ☐ NA
#2| ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1| Dosing frequency 1 day (Duration of MP administration: 5 days)	#1| IV drip
#2| Dosing frequency 1 day (Duration of MP administration: 5 days)	#2| IV drip

17. INDICATION(S) FOR USE
#1| Atherosclerosis [Arteriosclerosis]
#2| Ischemic heart disease [Myocardial ischaemia]
/...continued

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1| ☐ YES ☐ NO ☒ NA
#2| ☐ YES ☐ NO ☒ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
#1| 07-Apr-2025 to 11-Apr-2025	#1| 5.0 [Day]
#2| 07-Apr-2025 to 11-Apr-2025	#2| 5.0 [Day]

III. CONCOMITANT DRUG(S) AND HISTORY

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

23. OTHER RELEVANT HISTORY (e.g diagnostics, allergics, pregnancy with last month of period, etc.)
Medical History Sub Section:

#1| Current Condition | Atherosclerosis [Arteriosclerosis] |
#2| Current Condition | Ischemic heart disease [Myocardial ischaemia] |

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

26. REMARKS
Company Comments: ID: 20-25-RUS-FER-0000338
Nausea is expected according to the reference safety document of Citicoline while asthenia and tremor are unexpected. This adverse reaction was involved in a serious case due to hospitalization reported. The action taken with the drug was withdrawn and the outcome of the events were recovered. In this particular case, the temporal relationship and the well-known pharmaco-toxicologic profile of the product could enhance the causal relationship. Further information should be needed to make a clear medical assessment and to investigate other ethiologies. Based on the information provided, the Company assessed as Probable the causal relationship between the drug and the event according to the Karch Lasagna modified method.

24b. MFR CONTROL NO.
20-25-RUS-FER-0000338

25b. NAME AND ADDRESS OF REPORTER
Russian Federation
Other or unknown Physician
Physician

24c. DATE RECEIVED BY MANUFACTURER
04-Jun-2025

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

DATE OF THIS REPORT

25a. REPORT TYPE

16-Jun-2025	☒ INITIAL	☐ FOLLOWUP:	

ADDITIONAL INFORMATION

7+13 DESCRIBE REACTION(S) continued

According to the patient, this morning, during outpatient treatment, the above-mentioned complaints appeared. Intravenous infusions of the following medicinal products were administered: Actovegin, Meldonium, and Citicoline. Toward the end of the infusion, the patient experienced a sensation of “malaise.” She was referred to [REDACTED]. Blood pressure was within the normal range.

In the emergency department, she was examined by a neurologist and a cardiologist; no acute disorder was identified. She was hospitalized in [REDACTED]. The patient is unable to specify the doses of the medicinal products.

Drug treatment: Inpatient regimen.

Diet: Standard therapeutic diet.

IV infusions: Potassium chloride solution + calcium chloride + magnesium chloride + sodium acetate + sodium chloride + malic acid, 1000 mL once daily.

MEDICAL HISTORY

No medical history reported, no allergy reported.

LABORATORY TESTS

BP was within the normal range.

SUSPECTS PRODUCTS

-ACTOVEGIN (deproteinized hemoderivative of calf blood), solution for injections, unknown dose, QD, intravenous route, from 07-Apr-2025 to 11-Apr-2025, for Atherosclerosis. The product was discontinued on 11-Apr-2025.

-MELDONIUM (meldonium), solution for intravenous, intramuscular and parabulbar administration, unknown dose, QD, intravenous route, from 07-Apr-2025 to 11-Apr-2025, for Ischemic heart disease. The product was discontinued on 11-Apr-2025.

-CITICOLINE (citicoline), solution for injections, unknown dose, QD, intravenous route, from 07-Apr-2025 to 11-Apr-2025, for Atherosclerosis. The product was discontinued on 11-Apr-2025.

CONCOMITANT PRODUCTS

No concomitant treatment reported.

ADVERSE REACTIONS/SPECIAL SITUATIONS

-Complaints of severe general weakness (LLT: Weakness generalized) on 11-Apr-2025 to 13-Apr-2025. The outcome of the event was Recovered.

- Body Tremors (LLT: Tremor) on 11-Apr-2025 to 11-Apr-2025. The outcome of the event was Recovered.

- Nausea (LLT: Nausea) on 11-Apr-2025 to 11-Apr-2025. The outcome of the event was Recovered.

REPORTER COMMENTS

Seriousness was reported serious (Hospitalization) by the reporter.

SERIOUSNESS

-LLT: Generalized weakness has been considered serious due to hospitalization.

-LLT: Tremor has been considered serious due to hospitalization.

-LLT: Nausea has been considered serious due to hospitalization.

This case has been assessed as Serious.

Lab Data:

#1| Unknown | BP was within the normal range [Blood pressure normal] | Unknown(L) | Unknown(H) | BP was within the normal range

14-21. 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	20 DID REACTION ABATE AFTER STOPPING DRUG?

				21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1| Actovegin | Blood, calf, deprot., lmw portion, Blood, calf, deprot., lmw portion | Unknown (NOS) | Unknown {Lot#: Unknown} Regimen #1	Dosing frequency 1 day (Duration of MP administration: 5 days); IV drip	Atherosclerosis [Arteriosclerosis]	07-Apr-2025 to 11-Apr-2025; 5.0 [Day]	Yes; NA
#3| Citicoline | Citicoline | Solution for injection | Unknown {Lot#: Unknown} Regimen #1	Dosing frequency 1 day (Duration of MP administration: 5 days); IV drip	Atherosclerosis [Arteriosclerosis]	07-Apr-2025 to 11-Apr-2025; 5.0 [Day]	Yes; NA