SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	SPAIN		Unk		41 Years	Male	Unk		FEB	2009

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

Other Serious Criteria: Medically Significant, IMPORTANT MEDICAL EVENT
INSOMNIA [Insomnia]
PARAESTHESIA [Paraesthesia]
THERAPY PARTIAL RESPONDER [Therapy partial responder]
OFF LABEL USE [Off label use]
PRODUCT USE IN UNAPPROVED INDICATION [Product use in unapproved indication]
INTENTIONAL PRODUCT MISUSE [Intentional product misuse]
DRUG ABUSE [Drug abuse]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

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

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) UNSPECIFIED CAFFEINE (CAFFEINE) Unknown
#2) Xeomin (Botulinum toxin type a) Powder for solution for injection **(Continued on Additional Information Page)**

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

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) UNK	#1) Unknown
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) MIGRAINE (Migraine)
#2) MIGRAINE (Migraine)

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

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) Unknown	#1) Unknown
#2) FEB-2009 / FEB-2009	#2) 1 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, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	Migraine (Migraine)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Chiesi Farmaceutici SpA
via Palermo, 26/A
Parma, 43122 ITALY

26. REMARKS
Medically Confirmed: Yes
World Wide #: ES-CHIESI-2025CHF04136

24b. MFR CONTROL NO.
2025CHF04136

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

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

DATE OF THIS REPORT
17-JUN-2025

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER

UNKNOWN
SPAIN

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Description: Case reference no. 2025CHF04136 is a report sent by other health professional and received through Eudravigilance (E2B authority number: ES-MRZWEB-2025060000032) which refers to a male patient aged 41 years.

Concomitant medication and past drug history have not been provided.

The patient had a past medical history of migraine.

On an unspecified date, the patient started taking Unspecified Caffeine for migraine.

On an unspecified date in Feb-2009, the patient started taking Xeomin [botulinum toxin type a] (powder for solution for injection) for migraine till Feb-2009. On an unspecified date, the patient started taking Ergotamine, Zomig [zolmitriptan], Voltaren 24H [diclofenac sodium], Botox [botulinum toxin type a] for 1 day, Tryptizol [amitriptyline hydrochloride], Maxalt [rizatriptan benzoate], Relpax [eletriptan hydrobromide], Homeopathics nos, metamizole sodium, prednisone, paroxetine, Acetaminophen [paracetamol], valproate sodium, metamizole magnesium, lamotrigine, ibuprofen, flunarizine dihydrochloride, bromazepam, Topamax [topiramate], paroxetine hydrochloride and atropa bella-donna all for migraine. These were considered as co-suspect drugs.

On an unspecified date in Feb-2009, the patient experienced significant medical events of insomnia, paraesthesia and therapy partial responder.

On an unspecified date in Feb-2009, the patient had off label use, product use in unapproved indication, intentional product misuse and drug abuse.

The patient’s outcome was unknown for the events of insomnia, paraesthesia, therapy partial responder, off label use, product use in unapproved indication, intentional product misuse and drug abuse.

The reporter did not assess the causal relationship between the events and Unspecified Caffeine.

No further information is expected as the case was received from regulatory authority.

Case comments:
This 41 year-old male patient experienced insomnia, paraesthesia, therapy partial responder, off label use, product use in unapproved indication, intentional product misuse and drug abuse while being treated with Unspecified Caffeine for migraine.
The events insomnia, therapy partial responder and paraesthesia were assessed as serious (Seriousness criterion: important medical event).
The event drug abuse was assessed as non-serious.
The events off label use, product use in unapproved indication and intentional product misuse were considered as non-serious by convention.
The insomnia, paraesthesia and therapy partial responder are not listed adverse reactions for Caffeine according to reference safety information. The product use in unapproved indication, drug abuse and intentional product misuse were considered as unlisted by convention. According to the local RSI, the off label use was considered as unlisted.
The adverse reactions of insomnia, paraesthesia and therapy partial responder are unexpected as per Canadian product monograph.
The product use in unapproved indication, drug abuse and intentional product misuse were considered as unexpected by convention.
The off label use was considered as unexpected as per Canadian product monograph.
Regarding events of insomnia and paraesthesia, multiple co-suspect drugs could provide possible explanation. Insufficient information regarding start date of Caffeine precludes assessment of causal role of suspect drug.
The company has assessed the causality between Unspecified Caffeine and insomnia, paraesthesia as unassessable in accordance with the WHO-UMC causality assessment method.
Regarding an event of therapy partial responder, event seems related to co-suspect drug Xeomin [botulinum toxin type A] with no causal role of suspect drug.
The company has assessed the causality between Unspecified Caffeine and therapy partial responder as not related in accordance with the WHO-UMC causality assessment method.
Regarding off label use it was reported that, co-suspect drug Xeomin [botulinum toxin type A] was used for migraine which is not in accordance with label. As off label is related with co-suspect drug, there is no attribution with suspect drug.
The company has assessed the causality between Unspecified Caffeine and off label use as not related in accordance with the WHO-UMC causality assessment method.
Causality was assessed as not applicable for product use in unapproved indication, intentional product misuse and drug abuse as these were not events per se.
The single individual case report does not modify the benefit/risk balance of this product. Therefore, no changes in the label or other measures are recommended at this point. However, the company will continue to monitor all respective reports received and, based on cumulative experience, will re-evaluate the available evidence on an ongoing basis.

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

ADDITIONAL INFORMATION

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
#3) Ergotamine (Ergotamine) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#4) Zomig (Zolmitriptan) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#5) Voltaren 24H (Diclofenac sodium) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#6) Botox (Botulinum toxin type a) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	duration 1 day; 1 day
#7) Tryptizol (Amitriptyline hydrochloride) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#8) Maxalt (Rizatriptan benzoate) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#9) Relpax (Eletriptan hydrobromide) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#10) Homeopathics nos (Homeopathics nos) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#11) Metamizole sodium (Metamizole sodium) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#12) Prednisone (Prednisone) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#13) Paroxetine (Paroxetine) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#14) Acetaminophen (Paracetamol) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#15) Valproate sodium (Valproate sodium) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#16) Metamizole magnesium (Metamizole magnesium) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#17) Lamotrigine (Lamotrigine) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#18) Ibuprofen (Ibuprofen) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#19) Flunarizine hydrochloride (Flunarizine	UNK; Unknown	MIGRAINE (Migraine)	Unknown;

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ADDITIONAL INFORMATION

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dihydrochloride) ; Regimen #1			Unknown
#20) Bromazepam (Bromazepam) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#21) Topamax (Topiramate) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#22) Paroxetine hydrochloride (Paroxetine hydrochloride) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown
#23) Atropa bella-donna (Atropa bella-donna) ; Regimen #1	UNK; Unknown	MIGRAINE (Migraine)	Unknown; Unknown