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| SUSPECT ADVERSE REACTION REPORT |  |  |  |  |  |  |  |  |  |  |
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## 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                                                                                                                                                                                                                                                                                                                 |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Spain       | Day              | Month | Year | 81 Years | Male   | Day                | Month | Year |                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |             |                  |       |      |          |        | 24                 | Jan   | 2024 |                                                                                                                                                                                                                                                                                                                                                                |
| <b>7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)</b><br><b>Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)</b><br>#1  Hepatitis tóxica [Hepatitis toxic]  <br><br>This case has been downloaded from the EudraVigilance database without narrative (L2A). (WWID: ES-AEMPS-1500548)<br><br>New version is created due to there is information not extracted (mapped) from database to the fields in the CIOMS:<br><br>Patient's weight and height: 72kg, 162cm<br>ALZIL PLUS 20 MG/10 MG COMPRIMIDOS RECUBIERTOS CON PELICULA, action taken: withdrawn<br>LEVADURA ROJA ARROZ, action taken: withdrawn<br>FOSTER NEXTHALER 200 MICROGRAMOS/6 MICROGRAMOS POR INHALACION POLVO /...continued |             |                  |       |      |          |        |                    |       |      | <input checked="" type="checkbox"/> PATIENT DIED<br><input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION<br><input type="checkbox"/> INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY<br><input type="checkbox"/> LIFE THREATENING<br><input type="checkbox"/> CONGENITAL ANOMALY<br><input type="checkbox"/> OTHER |

## II. SUSPECT DRUG(S) INFORMATION

|                                                                                                                                                                                                                              |                                                                   |                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>14. SUSPECT DRUG(S) (include generic name)</b><br>#1  ALZIL PLUS   Rosuvastatin + Ezetimibe   Film-coated tablet   Unknown {Lot#: Unknown}<br>#2  Levadura   Saccharomyces cerevisiae   Unknown   Unknown {Lot#: Unknown} |                                                                   | <b>20 DID REACTION ABATE AFTER STOPPING DRUG?</b><br>#1  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA<br>#2  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA      |
| <b>15. DAILY DOSE(S)</b><br>#1  Unknown<br>#2  10 mg/dia                                                                                                                                                                     | <b>16. ROUTE(S) OF ADMINISTRATION</b><br>#1  Unknown<br>#2  Oral  |                                                                                                                                                                                                                                                |
| <b>17. INDICATION(S) FOR USE</b><br>#1  Unknown<br>#2  Hipercolesterolemia (autoprescripcion) [Hypercholesterolaemia]                                                                                                        |                                                                   | <b>21. DID REACTION REAPPEAR AFTER REINTRODUCTION?</b><br>#1  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA<br>#2  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA |
| <b>18. THERAPY DATES (from/to)</b><br>#1  16-Mar-2023 to 29-Jan-2024<br>#2  16-Jun-2023 to 18-Jan-2024                                                                                                                       | <b>19. THERAPY DURATION</b><br>#1  320.0 [Day]<br>#2  217.0 [Day] |                                                                                                                                                                                                                                                |

## III. CONCOMITANT DRUG(S) AND HISTORY

|                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
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| <b>22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)</b><br>#3  Foster nexthaler   Beclometasone dipropionate, Formoterol fumarate   Inhalation use   2020 to Unknown<br>#4  Febuxostat   Febuxostat   80 mg   Unknown   2017 to Unknown /...continued                                                                                                                            |  |
| <b>23. OTHER RELEVANT HISTORY (e.g diagnostics, allergics, pregnancy with last month of period, etc.)</b><br>Medical History Sub Section:<br>#1  COPD [Chronic obstructive pulmonary disease]  <br>#2  Valvular heart disease NOS [Cardiac valve disease]  <br>#3  Hypertension arterial [Hypertension]  <br>#4  Single functional kidney [Single functional kidney]  <br>#5  Hepatopathy [Liver disorder]   /...continued |  |

## IV. MANUFACTURER INFORMATION

|                                                                                                                                                    |                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>24a. NAME AND ADDRESS OF MANUFACTURER</b><br>FERRER INTERNACIONAL, S.A.<br>Diagonal Avenue 549, 08029, Barcelona, Spain<br>Phone: +34936003700, |                                                                                                                                                                                               | <b>26. REMARKS</b><br>Company Comments: ID: 20-24-ESP-FER-0000125<br>Hepatitis toxic is expected according to the reference safety document of Rosuvastatin/Ezetimibe. This adverse reaction was involved in serious case due to caused/prolonged hospitalization. The suspected drug was withdrawn and the event resulted in death. Statin side effects can vary between different statins, but common side effects include headache, dizziness, gastrointestinal disorders or myalgia. Toxic hepatitis can be caused by alcohol, chemicals, drugs or nutritional supplements. In some cases, toxic hepatitis develops within hours or days of exposure to a toxin. In other cases, it may take months of regular use before signs and symptoms appear. In this particular case the temporal association and the well-known pharmacologic profile of the product could enhance the causal relationship. It is noteworthy to point that other suspected drug (saccharomyces cerevisiae) could be also involved in the onset of the event. Further information should be needed to make a clear medical assessment and to investigate other etiologies. In summary, based on the information provided, the Company assessed as conditional the causal relationship between the drug and the event according to the Karch- Lasagna method. |
|                                                                                                                                                    | <b>24b. MFR CONTROL NO.</b><br>20-24-ESP-FER-0000125                                                                                                                                          | <b>25b. NAME AND ADDRESS OF REPORTER</b><br>Spain<br>Physician                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>24c. DATE RECEIVED BY MANUFACTURER</b><br>02-Apr-2024                                                                                           | <b>24d. REPORT SOURCE</b><br><input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE<br><input checked="" type="checkbox"/> HEALTH <input type="checkbox"/> OTHER:<br>PROFESSIONAL |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>DATE OF THIS REPORT</b><br>14-May-2025                                                                                                          | <b>25a. REPORT TYPE</b><br><input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

## ADDITIONAL INFORMATION

**7+13 DESCRIBE REACTION(S) continued**

PARA INHALACION, action taken: not changed

FEBUXOSTAT 80 mg 28 comprimidos, action taken: not changed

LORAZEPAM 1 mg 50 comprimidos, action taken: not changed

OMEPRAZOL 20 mg 28 cápsulas, action taken: not changed

ESCITALOPRAM 10 mg 28 comprimidos, action taken: not changed

Action of the reaction is fatal, end date of the reaction: 14Mar2024

## Lab Data:

#1| 07-Mar-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 8.4, Hcto 24.4%, leucocitos 12230 (N 11240, L 530), plaquetas 47000.

- Coagulación: act. protrombina 50%, TP 19s, INR 1.63.

- GV: pH 7.331, pCO2 51.2, pO2 75.4, bicarbonato 26.4.

- Bioquímica: glucosa 176, urea 294, creatinina 4.42, FG 12, prot. totales 4.4, potasio 2.5, calcio 8.1, LDH 324, GOT 88, GPT 223, Bi total 36.6, osmolalidad 345, osmolalidad calculada 337.5, osmol gap 7.

- PCR 75.6

#2| 05-Mar-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 8.4, Hcto 23.4%, leucocitos 5970 (N 5250, L 380), plaquetas 43000.

- GV: pH 7.357, pCO2 47.4, pO2 49.9, bicarbonato 26

- Bioquímica: glucosa 176, urea 239, creatinina 4.32, FG 12, prot. totales 4.3, sodio 147, potasio 2.3, calcio 8.5, LDH 298, GOT 201, GPT 374, Bi total 36.7, Bi directa 31.1.

- NT-proBNP 35000

- PCR 84.2

#3| 04-Mar-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 8.3, leucocitos 3850 (N 3170, L 320), plaquetas 50000.

- Coagulación: act. protrombina 50%, TP 19s, INR 1.62, TTPA ratio 1.22, fibrinógeno 115.

- Bioquímica: glucosa 151, urea 238, creatinina 4.41, FG 12, urato 12.5, prot. totales 4.4, potasio 3.1, calcio 8, fosfato 6.8, LDH 354, GOT 268, GPT 429, GGT 238, Bi total 33.8, Bi directa 29.4.

- Orina 24 horas: volumen 2200, sodio 134, potasio 72.9.

#4| 03-Mar-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 8.6, Hc 23.4%, leucocitos 3.700, neutrófilos normales, linfocitos 480, plaquetas 66.000.

- Bioquímica: glucosa 192, urea 239, Cr 4.17, FGE 12, proteínas totales 4.8, K 3.3, Na y Cl normales, Ca 7.6 (Ca corregido 7.7), LDH 314, GOT 347, GPT 497. PCR 3.9. NT-proBNP 33.362.

- Gasometría venosa: pH 7.339/pCO2 38.4/pO2 122.5/bicarbonato 20.2.

#5| 02-Mar-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 8.8, Hc 23.4%, leucocitos y neutrófilos normales, linfocitos 440, plaquetas 65.000.

- Coagulación: actividad de protrombina 54%, tiempo de protrombina 18seg, INE 1.53, TTPA Ratio 1.26, fibrinógeno 116.

- Bioquímica: glucosa 199, urea 235, Cr 4.4. FGE 12, Cl 98, GOT 465, GPT 551. NT proBNP 23.113.

- Gasometría venosa: pH 7.302/pCO2 39.4/pO2 41.7/bicarbonato 19.

- Orina: proteínas 25, Bi 3, hematíes 250. Resto normal.

- PCR virus respiratorios: PCR Coronavirus oc43 positivo, resto negativo.

#6| 01-Mar-2024 | Ultrasound abdomen [Ultrasound abdomen] | Unknown(L) | Unknown(H) | Hígado con datos de hepatopatía crónica avanzada con datos directos e indirectos de HTPo. Gran quiste hidatídico calcificado. Vesícula hepatizada.

#7| 01-Mar-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 9.2, Hcto 24.3%, leucocitos 6450 (N 5390, L 560), plaquetas 73000.

- Coagulación: TP ratio 1.49, act. protrombina 55%, TP 17s, INR 1.49, TTPA 43s, TTPA ratio 1.38, fibrinógeno 132.

- Bioquímica: urea 218, creatinina 4.41, FG 12, urato 11.4, prot. totales 4.3, albúmina 3.2, sodio 132, cloro 96, calcio 8.1, fosfato 6.3, LDH 352, GOT 574, GPT 601, Bi total 31.4, Bi directa 29.9, GGT 252, FA 90.

#8| 29-Feb-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | -Hemograma: Hb 9.20, Hto 24.50%, VCM 84.50, ADE 21.50%, linfocitos 560, plaquetas 65000.

-Coagulación: TP ratio 1.49, Act protrombina 55%, TP 17, INR 1.49, TTPA 45, TTPA ratio 1.44, fibrinógeno 141.

-Bioquímica: urea 199, Cr 4.26, FG 12, urato 11, prot totales 4.4, alb 3, bi total 31.7, bi directa 28.5, sodio 131, calcio 7.5, calcio corregido 8.3, fosfato 6.3, LDH 324, GOT 623, GPT 595, GGT 212, FA 95.

-PCR 5.5

#9| 28-Feb-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | -Hemograma: Hb 9.90, Hto 26.60%, VCM 83.60, ADE 21.40%, linfocitos 830, plaquetas 65000.

-Coagulación: TP ratio 1.50, Act protrombina 55%, TP 17, INR 1.50, TTPA 47, TTPA ratio 1.53, fibrinógeno 176.

-Bioquímica: urea 181, Cr 4.22, FG 12, urato 11.6, prot totales 4.6, albúmina 2.9, bi total 31.6, bi directa 28.8, sodio 128, cloro 97, magnesio 2.6, calcio 7.9, calcio corregido 8.8, fosfato 6.8, LDH 331, GOT 836, GPT 665, GGT 181, FA 101.

#10| 27-Feb-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 10.10, Hto 27.40%, VCM 83.80, ADE 21.30%, plaquetas 69000.

-Coagulación: TP ratio 1.66, Act Protrombina 48%, TP 19, INR 1.66, TTPA ratio 1.61, fibrinógeno 194.

-Bioquímica: urea 148, Cr 3.73, FG 14, urato 11.1, prot totales 4.4, alb 2.8, bi total 29.6, bi directa 25.5, sodio 126, potasio 4.2, cloro 95, calcio 7.8, calcio corregido 8.7, LDH 339, GOT 1064, GPT 689, GGT 133, FA 96.

#11| 26-Feb-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: hb 10.6, hcto 28%, vcm 84, leu 7.85 (N5.23, L1.45) plt 69

- Coagulación: AP 56%, TP 17s, INR 1.48, TTPA 48

- Bioquímica: glu 72, urea 129, crea 3.27 (empeoramiento), urato 10.7, prot 4.7, bil 2.8, bil 30 (empeoramiento), Na 127, K 3.7, CaCo9.2, P 4.6, LDH 471, GOT 1538, GPT 771, GGT 138. Colesterol 78, triglicéridos 163.

- Orina 24 horas: volumen 600 ml, sodio 6, potasio 36.9.

-Autoinmunidad: Ac anti nucleares negativo, anti gp210 negativo, anti sp100 negativo, anti ms liso negativo, anti F actina negativo, anti SLA negativo (1.5).

-PCR VEB: negativo.

#12| 23-Feb-2024 | COLANGIO RM [Cholangiogram] | Unknown(L) | Unknown(H) | Liquido libre intraabdominal localizado periesplenico, peri y subhepatico y en ambas goteras

paracolicas. Sin dilatación de vía biliar. Quiste hidatídico hepático sin otras alteraciones parenquimatosas.

#13| 21-Feb-2024 | Ultrasound abdomen [Ultrasound abdomen] | Unknown(L) | Unknown(H) | Hígado con datos de hepatopatía crónica avanzada. Gran quiste hidatídico calcificado. Ligera esplenomegalia. Vesícula contraída y paredes engrosadas sin signos de colecistitis. Hidronefrosis RD grado IV. Quistes en RI uno de ellos con protuberancia (probable Bosniak IIF.) Area pancreática mal valorada por neummatización. No dilatación de vía biliar

#14| 21-Feb-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hb 10.50, Hto 30.50%, VCM 87.10, ADE 22.50%, plaquetas 77000.

-Coagulación: TP ratio 1.59, Act protrombina 51%, TP 18, INR 1.59, TTPA 44, TTPA ratio 1.43, fibrinógeno 285.

-Bioquímica: urea 125, Cr 1.91, FG 32, urato 14.2, prot totales 5.3, alb 2.9, bi total 20.1, bi directa 16.7, calcio 8.7, resto de iones en rango, LDH 579, GOT 1500, GPT 671, GGT 238, FA 110.

-Colesterol 78, TG 163.

-Ferrocinética: hierro 139, ferritina 1424, B12 915, á fólico 7.2, transferrina 146, IST 75%.

-Proteínas especiales: PCR 18.7, IgG 1405, IgA 891, IgM 130.

-Proteinograma: Fracción beta 2 elevada debido a IgA alta.

Fraccion gamma de aspecto dudoso.

-Autoinmunidad: Ac anti nucleares (ANA), mitocondriales, músculo liso, LKM y ANCA negativos.

-Serología: positivo para VHE-IgG, CMV IgG, VEB IgG e IgM. Resto negativo.

#15| 19-Feb-2024 | Digestive tract X-ray [X-ray gastrointestinal tract] | Unknown(L) | Unknown(H) | Líneas renopsoas conservadas. Quiste hidatídico.

#16| 19-Feb-2024 | Thorax X-ray [Chest X-ray] | Unknown(L) | Unknown(H) | SCF libres. ICT normal. No signos de condensación

#17| 19-Feb-2024 | Blood test [Blood test] | Unknown(L) | Unknown(H) | Hemograma: Hto 33.30% Hb 12.10 VCM 86.50 Leucocitos 7120 con formula leucocitaria (N4340 L1530 M1190)

Plaquetas 102000

- Bioquímica: Glucosa 114 Urea 131 Creatinina 1.99 FG 31 Bi total 19.2 (previa 3.7) Bi directa 16.7 (previa 3.5) Sodio 136 potasio 4.3 LDH 654 CK 27 GOT 1384 (Prevía 1058) GPT 652 Amilasa 122 FA 137 pcr 25.4

- Orina: Nitritos negativos. Sto: No procede.

## 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#5| Lorazepam | Lorazepam | Tablet | 1 g | Unknown | 2019 to Unknown

#6| Omeprazol | Omeprazole | 20 mg | Unknown | 2017 to Unknown

#7| Escitalopram | Escitalopram oxalate | Tablet | 10 mg | Unknown | 11-Jan-2024 to Unknown

#8| Furosemide | Furosemide | Tablet | 40 mg | Unknown | Aug-2023 to Unknown

#9| Acido acetil salicilico | Acetylsalicylic acid | Tablet | 100 mg | Unknown | 2017 to Unknown

#10| Acenocumarol | Acenocumarol | Tablet | 4 mg | Unknown | 06-May-2019 to Unknown

#11| Bisoprolol | Bisoprolol | Tablet | 2.5 mg | Unknown | 2017 to Unknown

## 23. OTHER RELEVANT HISTORY continued

Medical History Sub Section:

#6| | Hepatic cyst [Hepatic cyst] |

Drug History Sub Section:

#1| Rosuvastatin | Rosuvastatin calcium | 24-Jan-2023 to 16-Mar-2023 (Historical Drug)