**Supplementary Table 1**. Adverse drug reactions categorized by System Organ Class (SOC) and three most reported preferred terms recognized in ICSRs reporting statins as suspected drugs.

|  |  |
| --- | --- |
| **SOC and ADRs** | **Number of cases (%)** |
| **Musculoskeletal and connective tissue disorders** | **418** (43.7) |
| *Myalgia* | 260 (27.2) |
| *Muscle spasms* | 93 (9.7) |
| *Rhabdomyolysis* | 11 (1.1) |
| **Investigations** | **250** (26.1) |
| *Creatine phosphokinase increased* | 161 (16.8) |
| *Transaminases increased* | 37 (3.9) |
| *High cholesterol blood levels* | 13 (1.4) |
| **General disorders and administration site conditions** | **56** (5.9) |
| *Asthenia* | 16 (1.7) |
| *Therapeutic failure* | 11 (1.1) |
| *Pain* | 5 (0.5) |
| **Gastrointestinal disorders** | **54** (5.6) |
| *Upper abdominal pain* | 9 (0.9) |
| *Nausea* | 4 (0.4) |
| *Vomit* | 4 (0.4) |
| **Skin and subcutaneous tissue disorders** | **45** (4.7) |
| *Itch* | 17 (1.8) |
| *Hives* | 8 (0.8) |
| *Erythema* | 6 (0.6) |
| **Nervous system disorders** | **27** (2.8) |
| *Headache* | 13 (1.4) |
| *Paraesthesia* | 3 (0.3) |
| *Dizziness* | 2 (0.2) |
| **Hepatobiliary disorders** | **26** (2.7) |
| *Hypertransaminasemia* | 20 (2.1) |
| *Hyperbilirubinemia* | 2 (0.2) |
| *Jaundice* | 1 (0.1) |
| **Product issues** | **22** (2.3) |
| *Product measured potency issue* | 22 (2.3) |
| **Metabolism and nutrition disorders** | **13** (1.4) |
| *Hypercholesterolemia* | 3 (0.3) |
| *Hypertriglyceridemia* | 2 (0.2) |
| *Hyperglycaemia* | 2 (0.2) |
| **Respiratory, thoracic and mediastinal disorders** | **8** (0.8) |
| *Cough* | 3 (0.3) |
| *Dyspnoea* | 3 (0.3) |
| *Epistaxis* | 1 (0.1) |
| **Injury, poisoning and procedural complications** | **5** (0.5) |
| *Tendon lesion* | 1 (0.1) |
| *Traumatic coma* | 1 (0.1) |
| *Use not registered* | 1 (0.1) |
| **Renal and urinary disorders** | **4** (0.4) |
| *Acute renal lesion* | 2 (0.2) |
| *Renal failure* | 1 (0.1) |
| *Hyperazotemia* | 1 (0.1) |
| **Ear and labyrinth disorders** | **4** (0.4) |
| *Vertigo* | 4 (0.4) |
| **Vascular disorders** | **4** (0.4) |
| *Hypertensive crisis* | 1 (0.1) |
| *Flushing* | 1 (0.1) |
| *Hypotension* | 1 (0.1) |
| **Psychiatric disorders** | **4** (0.4) |
| *Nightmares* | 1 (0.1) |
| *Insomnia* | 1 (0.1) |
| *Depression* | 1 (0.1) |
| **Eye disorders** | **4** (0.4) |
| *Visual compromise* | 1 (0.1) |
| *Miosis* | 1 (0.1) |
| *Blurred vision* | 1 (0.1) |
| **Blood and lymphatic system disorders** | **4** (0.4) |
| *Anaemia* | 2 (0.2) |
| *Thrombocytopenia* | 1 (0.1) |
| *Neutropenia* | 1 (0.1) |
| **Immune system disorders** | **3** (0.3) |
| *Hypersensitivity* | 3 (0.3) |
| **Reproductive system and breast disorders** | **3** (0.3) |
| *Erectile dysfunction* | 1 (0.1) |
| *Gynecomastia* | 1 (0.1) |
| *Breast pain* | 1 (0.1) |
| **Cardiac disorders** | **2** (0.2) |
| *Palpitations* | 2 (0.2) |
| **Total** | **956** (100.0) |

**Supplementary Table 2**. Case series of preventable ICSRs involving HMG-CoA reductase inhibitors (statins) as suspected drugs.

|  |  |  |  |
| --- | --- | --- | --- |
| **Case characteristics:**  **Patient’ Gender, Age, Ethnicity ADR Seriousness**  **ADR Outcome  ADR Mechanism** | **Critical criteria as cause of preventability (related to HPP or PB)** | **Case description** | **Adverse drug reaction/s** |
| **Case 1**  Female, 57 years old, European  Not serious  Not available  Dose-related | Therapeutic duplication (HPP)  Labeled drug-drug interaction (simvastatin + atorvastatin) (HPP) | A case in treatment with two different statins (simvastatin + atorvastatin) | Myalgia |
| **Case 2**  Female, 69 years old, European  Not serious  Recovered  Unknown | Therapeutic duplication (HPP)  Labeled drug-drug interaction (simvastatin\ezetimibe + rosuvastatin) (HPP) | A case in treatment with two different statins (simvastatin\ezetimibe + rosuvastatin) | Swollen abdomen |
| **Case 3**  Male, 53 years old, European  Not serious  Not available  Dose-related | Therapeutic duplication (HPP)  Labeled drug-drug interaction (simvastatin + atorvastatin) (HPP) | A case in treatment with two different statins (simvastatin + atorvastatin) | Myalgia, increased blood levels of creatine phosphokinase |
| **Case 4**  Male, 67 years old, European  Not serious  Not available  Dose-related | Labeled drug-drug interaction (rosuvastatin + clopidogrel) (HPP) | A case in treatment with rosuvastatin and clopidogrel  According to SmPC of medical products containing rosuvastatin, clopidogrel could determine a 2-fold increase of rosuvastatin area under the curve (AUC†). | Myalgia |
| **Case 5**  Male, 67 years old, European  Not serious  Improvement  Dose-related | Inappropriate prescription for patient’s underlying medical condition (hepatitis C virus, *HCV*) or underlying pathology (HPP) | A case with HCV in treatment with simvastatin/ezetimibe  According to SmPC of medical products containing the combination simvastatin + ezetimibe, these drugs are contraindicated in patients with active liver disease | Increased blood levels of creatine phosphokinase |
| **Case 6**  Male, 62 years old, European  Not serious  Recovered  Dose-related | Labeled drug-drug interaction (simvastatin/ezetimibe + ciclosporin) (HPP) | A case in treatment with simvastatin/ezetimibe and ciclosporin  According to SmPC of medical products containing the combination simvastatin + ezetimibe, the risk of myopathy and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as ciclosporin). | Myositis |
| **Case 7**  Male, 45 years old, European  Not serious  Recovered  Dose-related | Labeled drug-drug interaction (fluvastatin + ciclosporin) (HPP) | A case in treatment with fluvastatin and ciclosporin  According to SmPC of medical products containing fluvastatin, the risk of myopathy and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as ciclosporin). | Myalgia, increased blood levels of creatine phosphokinase |
| **Case 8**  Female, 45 years old, European  Serious – hospitalization  Recovered  Dose-related | Labeled drug-drug interaction (rosuvastatin + ciclosporin) (HPP) | A case in treatment with rosuvastatin and ciclosporin  According to SmPC of medical products containing rosuvastatin, the risk of myopathy and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as ciclosporin). | Rhabdomyolysis, hepatitis, acute renal failure, diarrhea |
| **Case 9**  Male, 56 years old, European  Serious –other clinical condition  Improvement  Dose-related | Labelled drug-drug interaction (atorvastatin + ezetimibe) (HPP) | A case in treatment with atorvastatin and ezetimibe  According to SmPC of medical products containing atorvastatin, the risk of myopathy may be increased with the concomitant use of ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products. | Myasthenia gravis (worsening), CPK increased |
| **Case 10**  Female, 60 years old, European  Not serious  Not available  Unknown | Wrong indication (HPP) | A case in treatment with simvastatin for hypertension.  According to SmPC of medical products containing simvastatin, hypertension is not an authorized indication for simvastatin. | Dyspepsia, palpitation |
| **Case 11**  Male, 54 years old, European  Not serious  Improvement  Dose-related | Labeled drug-drug interaction (rosuvastatin + clopidogrel) (HPP) | A case in treatment with rosuvastatin and clopidogrel  According to SmPC of medical products containing rosuvastatin, clopidogrel could determine a 2-fold increase of rosuvastatin area under the curve (AUC†). | Myalgia |
| **Case 12**  Male, 81 years old, European  Not serious  Not available  Dose-related | Labeled drug-drug interaction (rosuvastatin + clopidogrel) (HPP) | A case in treatment with rosuvastatin and clopidogrel  According to SmPC of medical products containing rosuvastatin, clopidogrel could determine a 2-fold increase of rosuvastatin area under the curve (AUC†). | Increased blood levels of creatine phosphokinase |
| **Case 13**  Male, 74 years old, European  Not serious  Recovered  Dose-related | Labeled drug-drug interaction (atorvastatin + verapamil) (HPP) | A case in treatment with atorvastatin and verapamil  According to SmPC of medical products containing atorvastatin, the risk of adverse drug reaction is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as verapamil). | Nightmare |
| **Case 14**  Male, 76 years old, European  Not serious  Not available  Dose-related | Labeled drug-drug interaction (atorvastatin + amiodarone) (HPP) | A case in treatment with atorvastatin and amiodarone  According to SmPC of medical products containing atorvastatin, the risk of myopathy, liver injury and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as amiodarone). | Myalgia, increased blood levels of creatine phosphokinase, alanine and aspartate transaminases |
| **Case 15**  Female, 73 years old, European  Not serious  Improvement  Dose-related | Inappropriate prescription for patient’s underlying medical condition (hepatitis C virus, *HCV*) or underlying pathology (HPP) | A case with HCV in treatment with simvastatin  According to SmPC of medical products containing simvastatin, this drug is contraindicated in patients with active liver disease. | Myalgia |
| **Case 16**  Male, 73 years old, European  Not serious  Recovered  Dose-related | Labeled drug-drug interaction (simvastatin/ezetimibe + fenofibrate) (HPP) | A case in treatment with simvastatin/ezetimibe and fenofibrate  According to SmPC of medical products containing the combination simvastatin + ezetimibe, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. Therefore, co-administration of simvastatin + ezetimibe with fibrates is not recommended. | Increased blood levels of creatine phosphokinase |
| **Case 17**  Female, 60 years old, European  Not serious  Recovered  Dose - related | Wrong indication (HPP) | A case in treatment with rosuvastatin arrhythmia.  According to SmPC of medical products containing rosuvastatin, arrhythmia is not an authorized indication for rosuvastatin. | Upper abdominal pain |
| **Case 18**  Male, 76 years old, European  Not serious  Not recovered yet  Dose-related | Labeled drug-drug interaction (atorvastatin + amiodarone) (HPP) | A case in treatment with atorvastatin and amiodarone  According to SmPC of medical products containing atorvastatin, the risk of myopathy, liver injury and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as amiodarone). | Muscle cramps |
| **Case 19**  Female, 76 years old, European  Serious–life threatening  Improvement  Dose-related | Self-medication with non-over-the-counter drug (PB) | A case attempted suicide by using a non-therapeutic dosage of atorvastatin, lamotrigine, nebivolol, nortriptyline, fluoxetine and trimipramine | Hypotension, miosis, traumatic coma |
| **Case 20**  Male, 77 years old, European  Not serious  Not available  Dose-related | Labeled drug-drug interaction (atorvastatin + amiodarone) (HPP) | A case in treatment with atorvastatin and amiodarone  According to SmPC of medical products containing atorvastatin, the risk of myopathy, liver injury and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as amiodarone). | Increased blood level of alanine and aspartate transaminases |
| **Case 21**  Male, 81 years old, European Not serious  Recovered  Dose-related | Labeled drug-drug interaction (rosuvastatin + clopidogrel) (HPP) | A case in treatment with rosuvastatin and clopidogrel  According to SmPC of medical products containing rosuvastatin, clopidogrel could determine a 2-fold increase of rosuvastatin area under the curve (AUC†). | Myalgia, increased blood levels of creatine phosphokinase |
| **Case 22**  Male, 94 years old, European  Not serious  Recovered  Dose-related | Labeled drug-drug interaction (atorvastatin + amiodarone) (HPP) | A case in treatment with atorvastatin and amiodarone  According to SmPC of medical products containing atorvastatin, the risk of myopathy, liver injury and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as amiodarone). | Myalgia |
| **Case 23**  Male, 69 years old, European Serious–other clinically significant condition  Not available  Dose-related | Inappropriate prescription for patient’s underlying medical condition (hepatitis C virus, *HCV*) or underlying pathology (HPP) | A case with HCV in treatment with rosuvastatin  According to SmPC of medical products containing rosuvastatin, this drug is contraindicated in patients with active liver disease. | Increased blood level of alanine and aspartate transaminases |
| **Case 24**  Female, 72 years old, European  Not serious  Recovered  Dose-related | Labeled drug-drug interaction (rosuvastatin + clopidogrel) (HPP) | A case in treatment with rosuvastatin and clopidogrel  According to SmPC of medical products containing rosuvastatin, clopidogrel could determine a 2-fold increase of rosuvastatin area under the curve (AUC†). | Increased blood levels of creatine phosphokinase |
| **Case 25**  Female, 74 years old, European  Not serious  Recovered  Dose-related | Labeled drug-drug interaction (atorvastatin + verapamil) (HPP) | A case in treatment with atorvastatin and amiodarone  According to SmPC of medical products containing atorvastatin, the risk of adverse drug reaction is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as verapamil). | Epigastralgy |
| **Case 26**  Female, 49 years old, European  Not serious  Improvement  Dose-related | Labelled drug-drug interaction (atorvastatin + ezetimibe) (HPP) | A case in treatment with atorvastatin and ezetimibe  According to SmPC of medical products containing atorvastatin, the risk of myopathy may be increased with the concomitant use of ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products. | Myalgia |
| **Case 27**  Female, 51 years old, European  Not serious  Improvement  Dose-related | Self-medication with non-over-the-counter drug (PB) | A case attempted autolesionism by using a non-therapeutic dosage of with atorvastatin and canrenone. | Psychomotor agitation |
| **Case 28**  Male, 59 years old, European  Serious–other clinically significant condition  Not available  Dose-related | Labeled drug-drug interaction (rosuvastatin + clopidogrel) (HPP) | A case in treatment with rosuvastatin and clopidogrel  According to SmPC of medical products containing rosuvastatin, clopidogrel could determine a 2-fold increase of rosuvastatin area under the curve (AUC†). | Muscular injury, increased blood levels of creatine phosphokinase |
| **Case 29**  Female, 55 years old, European  Not serious  Improvement  Dose-related | Labelled drug-drug interaction (lovastatin + omeprazole) (HPP) | A case in treatment with lovastatin and omeprazole  According to SmPC of medical products containing lovastatin, the risk of myopathy may be increased with the concomitant use of omeprazole. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products. | Myalgia |
| **Case 30**  Male, 70 years old, European  Serious–other clinically significant condition  Not available  Dose-related | Inappropriate prescription for patient’s underlying medical condition (hepatitis C virus, *HCV*) or underlying pathology (HPP) | A case with HCV in treatment with atorvastatin  According to SmPC of medical products containing atorvastatin, this drug is contraindicated in patients with active liver disease. | Increased blood levels of creatine phosphokinase, alanine and aspartate transaminases |
| **Case 31**  Female, 67 years old, European  Not serious  Improvement  Dose-related | Therapeutic duplication (HPP) | A case in treatment with three different statins (atorvastatin, rosuvastatin, and simvastatin) | Myalgia |
| **Case 32**  Female, 65 years old, European  Not serious  Improvement  Dose-related | Labelled drug-drug interaction (atorvastatin + ezetimibe) (HPP) | A case in treatment with atorvastatin and ezetimibe  According to SmPC of medical products containing atorvastatin, the risk of myopathy may be increased with the concomitant use of ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products. | Joint pain |
| **Case 33**  Male, 38 years old, European  Not serious  Improvement  Dose-related | Therapeutic duplication (HPP)  Labeled drug-drug interaction (simvastatin + atorvastatin) (HPP) | A case in treatment with two different statins (atorvastatin and simvastatin) | Increased blood levels of creatine phosphokinase |
| **Case 34**  Female, 73 years old, European  Not serious  Recovered  Susceptibility | Documented hypersensitivity to administered drug or drug class (HPP)  Self-medication with non-over-the-counter drug (PB)  Non-compliance (PB) | A case with medical history of hypersensitivity to an un-specified excipient was treated with a medical product having pravastatin as active ingredient with that specific excipient.  Moreover, the patient arbitrarily self-treat herself with multiple medical product, against the recommendations of the general practitioner (not reported). | Lips oedema, paraesthesia |

HPP= Healthcare Professional’ Practice; PB=Patient Behaviour

†In the field of pharmacokinetics, the AUC is the area under the curve in a plot of drug concentration in blood plasma versus time.

**Supplementary Table 3**. Demographic and clinical characteristics of cases that discontinued and not-discontinued statins.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Level** | **Not Discontinued (n=122)** | **Discontinued (n=533)** | **Total (n=655)** |
| Year | 2012 | 6 (4.9) | 76 (14.3) | 82 (12.5) |
|  | 2013 | 13 (10.7) | 99 (18.6) | 112 (17.1) |
|  | 2014 | 23 (18.9) | 114 (21.4) | 137 (20.9) |
|  | 2015 | 36 (29.5) | 139 (26.1) | 175 (26.7) |
|  | 2016 | 32 (26.2) | 77 (14.4) | 109 (16.6) |
|  | 2017 | 12 (9.8) | 28 (5.3) | 40 (6.1) |
| Age | mean (SD) | 60.3 (11.0) | 62.5 (10.7) | 62.1 (10.8) |
| Gender | Female | 42 (34.7) | 263 (50.3) | 305 (47.4) |
|  | Male | 79 (65.3) | 260 (49.7) | 339 (52.6) |
|  | missing | 1 | 10 | 11 |
| Seriousness | Death | 0 (0.0) | 1 (0.2) | 1 (0.2) |
|  | Not defined | 1 (0.8) | 12 (2.3) | 13 (2.0) |
|  | Not serious | 116 (95.1) | 487 (91.4) | 603 (92.1) |
|  | Serious– hospitalization | 0 (0.0) | 11 (2.1) | 11 (1.7) |
|  | Serious–life threatening | 0 (0.0) | 2 (0.4) | 2 (0.3) |
|  | Serious–other clinically significant condition | 5 (4.1) | 20 (3.8) | 25 (3.8) |
| Outcome | Death | 0 (0.0) | 1 (0.2) | 1 (0.2) |
|  | Improvement | 36 (29.5) | 185 (34.7) | 221 (33.7) |
|  | Not available | 47 (38.5) | 136 (25.5) | 183 (27.9) |
|  | Not recovered yet | 29 (23.8) | 8 (1.5) | 37 (5.6) |
|  | Recovered | 10 (8.2) | 197 (37.0) | 207 (31.6) |
|  | Resolution with sequelae | 0 (0.0) | 6 (1.1) | 6 (0.9) |
| Reporter | General practitioner | 8 (6.6) | 169 (31.7) | 177 (27.0) |
|  | Hospital physician | 29 (23.8) | 129 (24.2) | 158 (24.1) |
|  | Not defined | 1 (0.8) | 3 (0.6) | 4 (0.6) |
|  | Nurse | 6 (4.9) | 2 (0.4) | 8 (1.2) |
|  | Other healthcare professions | 1 (0.8) | 4 (0.8) | 5 (0.8) |
|  | Patient | 3 (2.5) | 8 (1.5) | 11 (1.7) |
|  | Pharmaceutical company | 1 (0.8) | 0 (0.0) | 1 (0.2) |
|  | Pharmacist | 3 (2.5) | 10 (1.9) | 13 (2.0) |
|  | Specialist | 70 (57.4) | 208 (39.0) | 278 (42.4) |
| Action taken | Yes | 78 (63.9) | 478 (89.7) | 556 (84.9) |
| Causality | Possible | 113 (92.6) | 396 (74.3) | 509 (77.7) |
|  | Probable | 9 (7.4) | 137 (25.7) | 146 (22.3) |
| Medical products | >1 | 111 (91.0) | 365 (68.5) | 476 (72.7) |
|  | 1 | 11 (9.0) | 168 (31.5) | 179 (27.3) |
| Statin | atorvastatin | 80 (65.6) | 251 (47.1) | 331 (50.5) |
|  | fluvastatin | 1 (0.8) | 6 (1.1) | 7 (1.1) |
|  | lovastatin | 0 (0.0) | 27 (5.1) | 27 (4.1) |
|  | pravastatin | 3 (2.5) | 29 (5.4) | 32 (4.9) |
|  | rosuvastatin | 15 (12.3) | 69 (12.9) | 84 (12.8) |
|  | simvastatin | 14 (11.5) | 115 (21.6) | 129 (19.7) |
|  | simvastatin and ezetimibe | 9 (7.4) | 36 (6.8) | 45 (6.9) |
| Preventability | Not preventable | 114 (93.4) | 507 (95.1) | 621 (94.8) |
|  | Preventable | 8 (6.6) | 26 (4.9) | 34 (5.2) |

**Supplementary Table 4**. Demographic and clinical characteristics of patients enrolled during the active surveillance at Caserta Local Health Unit from May 28th 2014 to May 12th 2016.

|  |  |  |
| --- | --- | --- |
| **Variable** | **Level** | **Total** |
| Age | Mean (SD) | 62.6 (11.3) |
| Gender | Female | 78 (50.6) |
|  | Male | 76 (49.4) |
| Ethnicity | Balkan | 1 (0.6) |
|  | Caucasoid | 153 (99.4) |
| Weight | Mean (SD) | 75.5 (11.5) |
|  | Missing | 8 |
| Height | Mean (SD) | 166.5 (8.9) |
|  | Missing | 8 |
| Body Mass Index | Mean (SD) | 27.2 (3.4) |
|  | Missing | 8 |
| Condition of abuse | Alcohol | 2 (1.3) |
|  | Smoking | 26 (16.9) |
| History to drugs hypersensitivity reaction | Yes | 7 (4.5) |
| Increased blood levels of creatine phosphokinase  at baseline | Yes | 2 (1.3) |
| Hypertension | Yes | 97 (63.0) |
| Diabetes | Yes | 9 (5.8) |
| Arrhythmia | Yes | 7 (4.5) |
| COPD | Yes | 10 (6.5) |
| Thyroid disorder | Yes | 11 (7.1) |
| Liver disorder | Yes | 3 (1.9) |
| Concurrent medicines | Yes | 22 (14.3) |
| Statin - indication of use | Dyslipidaemia | 9 (5.8) |
|  | Mixed dyslipidaemia | 1 (0.6) |
|  | Hypercholesterolemia | 137 (89.0) |
|  | Mixed Iperlipidemia | 2 (1.3) |
|  | Hypertriglyceridemia | 1 (0.6) |
|  | Primary cardiovascular prevention | 3 (1.9) |
|  | Secondary cardiovascular prevention | 1 (0.6) |
| Statin | Atorvastatin | 83 (53.9) |
|  | Fluvastatin | 1 (0.6) |
|  | Lovastatin | 10 (6.5) |
|  | Pravastatin | 12 (7.8) |
|  | Rosuvastatin | 11 (7.1) |
|  | Simvastatin | 37 (24.0) |

SD= standard deviation; COPD= Chronic obstructive pulmonary disease.