bijwerkingen centrumlareb

## PCSK9 inhibitors and myalgia

### Introduction

Evolocumab and alirocumab are selective proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors that stop the enzyme PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the hepatic cell. This results in increased hepatic LDLR expression and decreases LDL-cholesterol in serum. PCSK9 inhibitors are indicated for *primary hypercholesterolemia* and *familial hypercholesterolemia*. PCSK9 inhibitors are indicated for patients that cannot tolerate statins or as additional therapy when other lipid lowering treatment is not sufficient (1;2). Evolocumab was granted marketing authorization in the Netherlands in July 2015 (1). Alirocumab was granted marketing authorization in the Netherlands in September 2015 (2). Both drugs are on the European Medicines Agency's list of medicinal products under additional monitoring for adverse reactions (3).

Myalgia is a common complaint and can have various causes. Common causes are excessive exercise, trauma and several drugs (including statins, bisphosphonates, ciprofloxacin). Various metabolic, inflammatory, endocrine, psychiatric and rheumatic disorders are also associated with myalgia. Medication-induced myalgia is usually generalised myalgia (4).

### Reports

From 24 July 2016 to 4 March 2018 the Netherlands Pharmacovigilance Centre Lareb received twenty-nine reports of myalgia associated with the use of evolocumab and nine reports of myalgia associated with the use of alirocumab. The reports of evolocumab are listed in table 1 and the reports of alirocumab are listed in table 2.

*Evolocumab*

Sixteen reports involved men and thirteen reports involved women. The ages varied from 44 to 82 years with an average of 63 and median of 64 years. In five cases, ezetimibe and/or a statin were also reported as suspect drugs (cases C, G, L, T and V). Ezetimibe was a concomitant drug in six cases (cases A, F, O, U, AA and AC) and a bisphosphonate was a concomitant drug in one case (case A). Previous statin or ezetimibe related muscular symptoms or intolerance was mentioned in twelve cases. Positive dechallenge was reported in nineteen cases (cases B, D, E, F, J, L, M, N, O, Q, S, T, U, W, Y, Z, AA, AB, AC). In six positive dechallenges the patient also used ezetimibe. In case T ezetimibe and rosuvastatin were additional suspect drugs which were not withdrawn. In this case evolocumab was administered as intramuscular injection. Five positive rechallenges were reported (cases D, E, F, Q and U). A negative dechallenge was reported in two cases (cases G and H). In case G the patient had not recovered from myalgia 10 days after evolocumab was withdrawn and 13 days after ezetimibe was withdrawn. The timeframe is unknown for case H. The latency varied from one day in five cases, up to one month in seven cases, up to six months in ten cases and the latency was one year or more in four cases. Latency was unknown in three cases. Aggravation of myalgia with every next administration of evolocumab was reported in three cases (cases W, Y and Z). Location of myalgia varied and was reported from generalised to localised in legs, hips, knees, extremities, shoulders, neck, back and breast. In case F, myalgia was localised in the back, at the injection site and occurred five days after every administration. Arthralgia was reported as additional adverse drug reaction in eight cases, muscle spasms were reported in three cases, musculoskeletal stiffness was reported in two cases and muscular weakness was reported in one case. Influenza like illness was reported as additional adverse reaction in four cases. Medical history of possibly confounding disorders was reported in three cases, including chronic myalgia, Tietze syndrome and fibromyalgia (cases R, S and Z). Treatment of myalgia was not reported.

Table 1. Reports of myalgia associated with the use of evolocumab in the Lareb database.

| **Patient, Sex, Age (years), Source** | **Drug Indication for use** | **Concomitant medication** | **Suspected adverse drug reaction*** | **Time to onset, Action with drug, Outcome** |
|---|---|---|---|---|
| A, NL-AMGEN-NLDSL2016 125809, F, 71 years | Evolocumab 140 mg/ml – Hypercholesterolaemia | Alendronic acid<br>Colecalciferol<br>Irbesartan<br>Ezetimibe | Rhinorrhoea<br>Headache<br>Muscle spasms<br>Nausea | 3.5 months<br>Drug withdrawn<br>Outcome unknown |

| | | | | |
|---|---|---|---|---|
| and older, MAH | | | Myalgia<br>Off label use | |
| B, NL-AMGEN-NLDSP2016163423, M, 51-60, MAH | Evolocumab 140 mg/ml – Unknown indication | | Myalgia<br>Malaise<br>Arthralgia<br>Muscle spasms | < 1 month<br>Drug temporarily withdrawn<br>Recovered |
| C, NL-AMGEN-NLDSL2017015290, F, 61-70 MAH | Evolocumab 140 mg/ml – Unknown indication<br>Metformine 850 mg – Diabetes mellitus<br>Vildagliptine 50 mg – Diabetes mellitus<br>Atorvastatine 40 mg – Angina pectoris | | Myalgia<br>Headache | Unknown<br>Unknown<br>Not recovered |
| D, NL-AMGEN-NLDSL2017044044, M, 61-70, MAH | Evolocumab 140 mg/ml – Hypercholesterolaemia, dyslipidemia | | Myalgia<br>Arthralgia<br>Nasal congestion<br>Secretion discharge | 7 weeks<br>Drug withdrawn<br>Recovered |
| E, NL-AMGEN-NLDSL2017066095, M, 61-70, MAH | Evolocumab 140 mg/ml – Hypercholestrolaemia | Lercanidipine<br>Acetylsalycylic acid | Myalgia | 7 weeks<br>Drug withdrawn<br>Recovered |
| F, NL-AMGEN-NLDSL2017071888, F, 51-60, MAH | Evolocumab 140 mg/ml – Hypercholesterolaemia | Ezetimibe<br>Acetylsalicylic acid | Abdominal pain<br>Myalgia<br>Influenza like illness | 1.1 year<br>Dose reduced<br>Recovered |
| G, NL-AMGEN-NLDSL2017082937, F, 61-70, MAH | Ezetimibe 10 mg – Hypercholesterolemia<br>Evolocumab 140 mg/ml – Hypercholesterolemia | | Bone pain<br>Drug intolerance<br>Fatigue<br>Myalgia<br>Pain in extremity<br>Somnolence | 4 months<br>Drug withdrawn<br>Not recovered |
| H, NL-AMGEN-NLDSL2017083703, F, 71 years and older, MAH | Evolocumab 140 mg/ml – Hypercholesterolemia | | Dizziness<br>Myalgia<br>Dry mouth | Unknown<br>Drug withdrawn<br>Not recovered |
| I, NL-AMGEN-NLDSL2017087526, F, 61-70, MAH | Evolocumab 140 mg/ml – Hypercholesterolaemia | | Arthralgia<br>Back pain<br>Influenza like illness<br>Limb discomfort<br>Mobility decreased<br>Myalgia<br>Pruritus | Unknown<br>Action unknown<br>Outcome unknown |
| J, NL-AMGEN-NLDSL2017092053, M, 41-50. MAH | Evolocumab 140 mg/ml – Hypercholesterolaemia | TIicagrelor<br>Acetylsalicylic acid | Depressed mood<br>Fatigue<br>Musculoskeletal stiffness<br>Myalgia | 1.5 month<br>Drug withdrawn<br>Recovered |
| K, NL-AMGEN-NLDSL2017100613, F, 61-70, MAH | Evolocumab 140 mg/ml – Hypercholesterolaemia | Fenrpocoumon<br>Tadalafil | Bone pain<br>Headache<br>Myalgia<br>Pain in extremity | 4 months<br>Drug withdrawn<br>Outcome unknown |
| L, NL-AMGEN-NLDSL2017103722, M, 71 years and older, MAH | Evolocumab 140 mg/ml – Hypercholesterolemia<br>Ezetimibe 10 mg – Hypercholesterolemia | Insulin aspart<br>Insulin glargine | Adverse reaction<br>Myalgia | 6 months<br>Drug withdrawn<br>Recovered |
| M, NL-AMGEN-NLDSL2017108018, M, 71 years | Evolocumab 140 mg/ml – Hypercholesterolaemia | Acetylsalicylic acid<br>Ranitidine<br>Diazepam | Myalgia | < 1 day<br>Drug withdrawn<br>Recovered |

| | | | | |
|---|---|---|---|---|
| and older, MAH | | | | |
| N, 223012, M, 51-60, Specialist doctor | Evolocumab 140 mg/ml – Hypercholesterolaemia | Acetylsalicylic acid<br>Ticagrelor<br>Fosinopril<br>Metoprolol | Arthralgia<br>Eye swelling<br>Malaise<br>Myalgia | 9 days<br>Drug withdrawn<br>Recovered |
| O, 231403, M, 41-50, Specialist doctor | Evolocumab 140 mg/ml – Hypercholesterolaemia | Ezetimibe | Myalgia | 4 weeks<br>Drug withdrawn<br>Recovered |
| P, 244845, M, 41-50, Other healthcare professional | Evolocumab 140 mg/ml – Hypercholesterolaemia | | Myalgia | 1 day<br>Dose not changed<br>Recovered |
| Q, 246817, M, 51-60, Other healthcare professional | Evolocumab 140 mg/ml – Hypercholesterolaemia | Paracetamol<br>Insulin glargine<br>Carbasalate calcium<br>Isosorbide mononitrate<br>Tolbutamide<br>Nitroglycerin<br>Metoprolol | Arthralgia<br>Fatigue<br>Myalgia | 1 week<br>Drug withdrawn<br>Recovering |
| R, 247355, F, 61-70, Pharmacist | Evolocumab 140 mg/ml – Hypercholesterolaemia | Losartan/ Hydrocholorthiazide<br>Nebivolol<br>Acetylsalicylic acid<br>Omeprazole | Hyperhidrosis<br>Musculoskeletal stiffness<br>Myalgia<br>Oedema<br>Palpitations | 1 day<br>Drug withdrawn<br>Outcome unknown |
| S, 248289, F, 71 years and older, General practitioner | Evolocumab 140 mg/ml – Hypercholesterolemia | Candesartan<br>Hydrochlorothiazide<br>Dabigatran<br>Macrogol<br>Spironolactone<br>Levocetirizine<br>Calcium/ vitamin d<br>Tramadol<br>Temazepam<br>Lactulose | Back pain<br>Myalgia | 3 months<br>Drug withdrawn<br>Recovering |
| T, NL-AMGEN-NLDSL2017 129644, M, 61-70, MAH | Evolocumab 140 mg/ml – Hypercholesterolaemia<br>Ezetimibe 10 mg – Hypercholesterolemia<br>Rosuvastatine 5 mg – Hypercholesterolemia | | Incorrect route of drug administration<br>Myalgia | Unknown<br>Drug withdrawn<br>Recovering |
| U, NL-LRB-00251347, M, 61-70, General practitioner | Evolocumab 140 mg/ml – Hypercholesteraemia | Metformine<br>Acetylsalicylic acid<br>Doxazosin<br>Olmesartan/ amlodipine<br>Formoterol/ beclometasone<br>Tiotropium<br>Pantoprazole<br>Ezetimibe<br>Isosorbide dinitrate | Myalgia | 1 day<br>Drug withdrawn<br>Recovered |
| V, NL-LRB-00251852, M, 61-70, Consumer | Ezetimibe 10 mg – Cholesterol<br>Evolocumab 140 mg/ml – Cholesterol | | Arthralgia<br>Myalgia | 1 year<br>Dose not changed<br>Not recovered |
| W, NL-LRB-00254241, M, 71 years and older, Consumer | Evolocumab 140 mg/ml – Hypercholesterolaemia | Acetylsalicylic acid<br>Losartan<br>Tamsulosine<br>Pantoprazole | Muscle spasms<br>Myalgia | 5 weeks<br>Drug withdrawn<br>Recovered |
| X, NL-LRB-00255730, M, 61-70, Consumer | Evolocumab 140 mg/ml – Hypercholesteraemia | | Myalgia | 4 weeks<br>Not applicable<br>Not recovered |
| Y, NL-LRB-00261184, F, 61-70, Consumer | Evolocumab 140 mg/ml – Hypercholesterolaemia | | Myalgia | 1 day<br>Drug withdrawn<br>Recovered |

| | | | | |
|---|---|---|---|---|
| Z, NL-LRB-00264856, F, 41-50, Consumer | Evolocumab 140 mg/ml – Hypercholesteraemia | Ethinylestradiol/ levonorgestrel | Arthralgia<br>Dizziness<br>Fatigue<br>Influenza like illness<br>Malaise<br>Myalgia<br>Nausea | 2 weeks<br>Drug withdrawn<br>Recovering |
| AA, NL-LRB-00266536, F, 51-60, specialist doctor | Evolocumab 140 mg/ml – Familial hypercholesterolaemia | Ezetimibe<br>Metformine<br>Colecalciferol<br>Esomeprazole<br>Salmeterol/ fluticasone | Muscular weakness<br>Myalgia<br>Nausea | 3 months<br>Drug withdrawn<br>Recovered |
| AB, NL-LRB-00270162, F, 51-60, Consumer | Evolocumab 140 mg/ml – Hypercholesterolaemia | | Influenza like illness<br>Myalgia | 1 year<br>Drug withdrawn<br>Recovering |
| AC, NL-LRB-249489, M, 71 years and older, Consumer | Evolocumab 140 mg/ml – Hypercholesterolaemia | Metformine<br>Carbamazepine<br>Isosorbide mononitrate<br>Losartan<br>Ezetimibe<br>Insulin aspart<br>Insulin human<br>Metoprolol<br>Carbasalate calcium | Arthralgia<br>Blood pressure decreased<br>Chills<br>Cough<br>Myalgia<br>Oropharyngeal pain<br>Sneezing | 6 weeks<br>Drug withdrawn<br>Recovering |

*Alirocumab*

Six reports involved women and three reports involved men. The ages varied from 58 to 69 years with an average of 63 and median of 64 years. In four cases ezetimibe was reported as concomitant drug (cases A, F, G and H). Previous statin or ezetimibe related muscular symptoms or intolerance was mentioned in seven cases (cases A, B, D, E, F, G and I). Statin-induced myopathy was reported as medical history in case E. Increased blood creatine phosphokinase was reported in case G. This patient was examined by a neurologist and no underlying muscular disorder was found. A positive dechallenge was reported in cases D, E, F and G. In cases F and G, the patient also used ezetimibe. In case A the patient was recovering after dose reduction. This patient also used ezetimibe. A negative dechallenge was reported in case C. This patient had not recovered several days after withdrawal. Latency varied from one day in three cases, up to one month in two cases, up to six months in two cases and in one case a latency of 11 months was reported. Latency was unknown in case B. Location of myalgia was reported in two cases and varied from lower back, neck, hip and legs. Muscular weakness and limb discomfort were reported as additional adverse drug reaction in one case. Arthralgia, musculoskeletal chest pain and musculoskeletal pain were reported as additional adverse reactions in one case and muscle spasms were reported in one case. In case E baclofen was used as concomitant drug for chronic muscle spasms. Polyneuropathy as medical history was reported in case I. This patient also experienced akathisia and formication. Treatment of myalgia was not reported.

Table 2. Reports of myalgia associated with the use of alirocumab in the Lareb database.

| **Patient, Sex, Age (years), Source** | **Drug<br>Indication for use** | **Concomitant medication** | **Suspected adverse drug reaction*** | **Time to onset, Action with drug, Outcome** |
|---|---|---|---|---|
| A, NL-LRB-00264975, M, 61-70, Other healthcare professional | Alirocumab 150 mg/ml – Hypercholesterolaemia | Ezetimibe | Myalgia | 4 weeks<br>Dose reduced<br>Recovering |
| B, NL-LRB-00266331, F, 61-70, Consumer | Alirocumab 75 mg/ml – Drug use for unknown indication | Perindopril<br>Metoprolol<br>Clopidogrel<br>Omeprazole | Fatigue<br>Limb discomfort,<br>Muscular weakness<br>Myalgia | Unknown<br>Dose not changed<br>Outcome unknown |
| C, NL-LRB-00269947, F, 61-70, Consumer | Alirocumab 75 mg/ml – Hypercholesterolaemia | Omeprazole<br>Fosinopril<br>Levothyroxine<br>Calcium/ vitamin d | Arthralgia<br>Back pain<br>Chest pain<br>Cough | 3 months<br>Drug withdrawn<br>Not recovered |

| | | | | |
|---|---|---|---|---|
| | | | Headache<br>Musculoskeletal chest pain<br>Musculoskeletal pain,<br>Myalgia | |
| D, NL-LRB-00273789, F, 61-70, Consumer | Alirocumab 75 mg/ml – Drug use for unknown indication | Diclofenac<br>Paracetamol<br>Paroxetine<br>Ranitidine<br>Magnesium | Cough<br>Diarrhoea<br>Dyspnoea<br>Headache<br>Listless<br>Mood altered<br>Myalgia<br>Nausea<br>Oropharyngeal pain<br>Sneezing | 1 day<br>Drug withdrawn<br>Recovered |
| E, NL-LRB-234047, M, 51-60, Specialist doctor | Alirocumab 150 mg/ml – Cardiovascular disorder NOS | Metoprolol<br>Perindopril<br>Indapamide<br>Acenocoumarol<br>Baclofen | Fatigue<br>Mobility decreased<br>Myalgia | 11 months<br>Drug withdrawn<br>Recovered |
| F, NL-LRB-244585, F, 61-70, Specialist doctor | Alirocumab 150 mg/ml – Hypercholesterolaemia | Omeprazole<br>Bisoprolol<br>Ticagrelor<br>Ezetimibe<br>Oxazepam<br>Macrogol<br>Insulin glulisine<br>Insulin glargine<br>Tramadol<br>Acetylsalicylic acid<br>Amitriptyline | Breast pain<br>Dizziness<br>Dyspnoea<br>Fatigue<br>Myalgia<br>Pain | 10 weeks<br>Drug withdrawn<br>Recovering |
| G, NL-LRB-247322, M, 51-60, Specialist doctor | Alirocumab 75 mg/ml – Hypercholesterolaemia | Ketotifen<br>Pantoprazole<br>Sildenafil<br>Nitroglycerin<br>Ezetimibe<br>Magnesium<br>Barnidipine<br>Clopidogrel | Blood creatine phosphokinase increased<br>Myalgia | 1 month<br>Drug withdrawn<br>Recovering |
| H, NL-LRB-249286, F, 61-70, Consumer | Alirocumab 75mg/ml – Hypercholesterolaemia | Ezetimibe | Constipation<br>Diarrhoea<br>Myalgia<br>Nausea | 2 hours<br>Dose not changed<br>Not recovered |
| I, NL-LRB-00264129, F, 51-60, Consumer | Alirocumab 75 mg/ml – Hyper LDL cholesterolaemia | Pramipexole<br>Levocetirizine<br>Escitalopram<br>Omeprazole<br>Levothyroxine | Akathisia<br>Eye disorder<br>Formication<br>Muscle spasms<br>Myalgia<br>Pruritus<br>Restlessness<br>Thirst | 12 hours<br>Action unknown<br>Not recovered |

**Other possibly muscle-related symptoms**

*Evolocumab*

The Netherlands pharmacovigilance centre Lareb received sixteen reports of muscle-related symptoms associated with evolocumab. Five reports include pain in extremity, four reports include muscle spasms, four reports include muscular weakness and one report includes musculoskeletal discomfort. Five positive dechallenges were reported in these cases and two negative dechallenges were reported.

*Alirocumab*

The Netherlands pharmacovigilance centre Lareb received eleven reports of muscle-related symptoms associated with alirocumab. Five reports include muscle spasms, three reports include pain in extremities, two reports include muscular weakness and one report includes musculoskeletal pain. Five positive dechallenges were reported in these cases and one negative dechallenge was reported.

**Other sources of information**

*SmPC*

Myalgia is not mentioned in the Dutch SmPCs of alirocumab and evolocumab. Back pain and arthralgia are mentioned in the Dutch SmPC of evolocumab. The SmPC of alirocumab does not contain reactions in the System Organ Class (SOC) musculoskeletal and connective tissue disorders (1;2).

Myalgia is described as adverse drug reaction of evolocumab in the SmPC of the FDA. The incidence of myalgia was 4.0% of patients on evolocumab (n=599) compared to 3.0% of patients on placebo (n=302). Increase of creatine kinase levels to more than five times the upper limit of the normal range occurred in 7 patients (1.2%) on evolocumab and in 1 patient on placebo (0.3%). Myalgia is also mentioned among adverse reactions that led to treatment discontinuation with an incidence (2 patients, 0.3%) higher than placebo (0 patients, 0%) (5;6).

Myalgia is also described as adverse drug reaction of alirocumab in the SmPC of the FDA. An incidence of myalgia was reported for 4.2% of patients on alirocumab (n=2476) compared to 3.4% of patients on placebo (n=1276) (7).

*Literature*

In a meta-analysis of 35 randomized controlled trials comparing treatment with and without PCSK9 inhibitors in 45,539 patients with hypercholesterolemia, the incidence of myalgia was not significantly higher (OR: 0.95, 95% CI: 0.75-1.20, p=0.65) in PCSK9 inhibitor use (400 events in n=9,033) compared to no PCSK9 inhibitor treatment (233 events in n=5252). No PCSK9 inhibitor treatment varied and consisted of placebo, ezetimibe or statin therapy. PCSK9 inhibitor treatment was also associated with fewer increases of creatine kinase (279 events in n=24,407) (OR: 0.84, 95% CI: 0.70-1.01, p=0.06) compared to no PCSK9 inhibitor treatment (227 events in n=20,284). In most of the included controlled trials patients were on background statin therapy (8).

*Databases*

Table 3. Reports of the PT ‘myalgia’ associated with evolocumab and alirocumab in the Lareb, Eudravigilance (9) and WHO database (10).

| Database | Drug | MedDRA PT | Number of reports | ROR (95% CI) |
|---|---|---|---|---|
| Lareb | Evolocumab | Myalgia | 31* | 8.5 [5.7 – 12.6] |
| | Alirocumab | Myalgia | 9 | 5.1 [2.5 – 10.3] |
| Eudravigilance | Evolocumab | Myalgia | 236 | 9.3 [8.1 – 10.6] |
| | Alirocumab | Myalgia | 147 | 8.8 [7.4 – 10.4] |
| WHO | Evolocumab | Myalgia | 1355 | 5.8 [5.5 – 6.1] |
| | Alirocumab | Myalgia | 532 | 8.6 [7.9 – 9.4] |

* The number of reports is not equal to the number of reports described because at the time of assessing, the Lareb database contained two duplicate reports that were not combined yet.

*Prescription data*

Table 4. Number of patients using alirocumab and evolocumab in the Netherlands in 2016 (11).

| Drug | 2016 |
|---|---|
| Evolocumab | 2,061 |
| Alirocumab | 884 |

*Mechanism*

The mechanism for myalgia or muscle related symptoms as adverse drug reaction of PCSK9 inhibitors is not known. Several possible mechanisms have been proposed for statin-related muscle symptoms

(12). Some of these mechanisms are related to cholesterol decrease rather than statin treatment and can possibly also explain PCSK9 inhibitor-induced myalgia.
One of the proposed mechanisms is damage to the sarcolemma due to decreased cholesterol since cholesterol is an important component of the sarcolemma. Damaged sarcolemma can contribute to myalgia and can result in creatine kinase release. Cholesterol is also a component of the sarcoplasmic reticulum in the myocyte, which stores and releases calcium for regulation of muscular contraction and relaxation. The sarcoplasmic reticulum could also possibly contribute to myalgia due to decreased cholesterol.
Another proposed mechanism that could possibly contribute to PCSK9 inhibitor-induced myalgia is myopathy caused by increased lipid in myocytes. PCSK9 inhibition leads to an increase of LDL receptors on the hepatic cell. An increase of LDL receptors on the myocyte can result in increased lipid in myocytes (12).

**Discussion and conclusion**

The Netherlands Pharmacovigilance Centre Lareb received 38 cases of myalgia and 27 cases of other muscle-related symptoms associated with the use of PCSK9 inhibitors over a period of almost two years. Myalgia is not described in the Dutch SmPCs of evolocumab and alirocumab but it is described in the SmPCs of these drugs of the FDA. Myalgia can have various causes. Besides, most PCSK9 inhibitor users have previously experienced myalgia while using a statin since statin intolerance is included in one of the indications of PCSK9 inhibitors. The possibility of channeling bias is present because prescribing PCSK9 inhibitors could be channelled to patients with possible pre-existing factors for developing muscular symptoms. Therefore, muscular symptoms could be incorrectly attributed to the use of PCSK9 inhibitors (13).
However, positive dechallenges were reported in 23 cases of myalgia, positive rechallenges were reported in nine cases of myalgia and ten positive dechallenges were reported in other cases of muscle-related symptoms. Because of these reports received by Lareb, further attention to myalgia and muscle-related symptoms associated with PCSK9 inhibitors is warranted.

References


(1) SmPC Repatha. (Version date: 17-7-2015, access date: 24-4-2018) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/003766/WC500191398.pdf
(2) SmPC Praluent. (Version date: 23-9-2015, access date: 24-4-2018) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/003882/WC500194521.pdf
(3) Website EMA. List of medicinal product under additional monitoring. (Version date: 26-4-2018, access date: 2-5-2018) http://www.ema.europa.eu/docs/en_GB/document_library/Medicines_under_additional_monitoring/2013/04/WC500142453.pdf.
(4) UptoDate: Approach to the patient with myalgia. (Version date: 25-4-2016, access date: 2-5-2018) https://www.uptodate.com/contents/approach-to-the-patient-with-myalgia.
(5) FDA SmPC Repatha, Amgen. (Version date: 2017, access date: 30-4-2018) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125522s013lbl.pdf.
(6) Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014 May 8;370(19):1809-19.
(7) FDA SmPC Praluent, Sanofi-Aventis. (Version date: 2017, access date: 30-4-2018) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125559s002lbl.pdf.
(8) Karatasakis A, Danek BA, Karacsonyi J, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: A meta-analysis of 35 randomized controlled trials. J Am Heart Assoc 2017 Dec 9;6(12).
(9) Eudravigilance database. (Version date: 2018, access date: 1-5-2018) http://bi.eudra.org.(access restricted).
(10) WHO Global Individual Case Safety Reports database (Vigilyze). (Version date: 2018, access date: 13-3-2018) http://www.vigiaccess.org/.
(11) GIP database - Drug information System of the Dutch Health Care Insurance Board. (Version date: 27-2-2018, access date: 24-4-2018) http://www.gipdatabank.nl/.
(12) Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy - European aetherosclerosis society consensus panel statement on assessment, aetiology and management. Eur Heart J 2015 May 1;36(17):1012-22.
(13) Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. Stat Med 1991 Apr;10(4):577-81.


*This signal has been raised on July 5, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl*