

## 1.1. Overview of reports of adverse drug reactions associated with oxaliplatin in 2014 and 2015

### Introduction

Oxaliplatin (Eloxatin<sup>®</sup>, Oxalisin<sup>®</sup> and generic) is a platinum-based drug with antineoplastic properties which was granted marketing authorisation in the Netherlands in 2005. Oxaliplatin is in combination with 5-fluorouracil and folinic acid indicated for use for *adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor and treatment of advanced colorectal cancer*.

The most common adverse reactions of oxaliplatin are gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (peripheral sensory neuropathy). Peripheral sensory neuropathy presents itself as dysesthesia and/or paraesthesia in extremities sometimes combined with cramps. These symptoms can be triggered or exacerbated by exposure to cold temperature or cold objects. An acute syndrome of pharyngolaryngeal dysesthesia is seen in 1-2% of the patients and is characterized by subjective sensations of dysphagia or dyspnoea, without any objective evidence of laryngospasm or bronchospasm (no stridor or wheezing).

Hypersensitivity, including anaphylactic or anaphylactoid reactions, usually occurs during infusion and can be fatal. The symptoms associated with these hypersensitivity reactions are rash, urticaria, conjunctivitis, rhinitis, bronchospasm, angioedema, hypotension, chest pain and anaphylactic shock [1,2].

In November 2014 a hospital pharmacist mentioned in a report that she saw an increase in the occurrence of known adverse drug reactions after administration of oxaliplatin of multiple marketing authorisation holders (MAHs). The adverse drug reactions seemed to be more serious than they used to be, which resulted in an increased use of antihistaminic drugs and in some cases termination of the treatment. She suggested there might be a problem with the raw material of oxaliplatin.

### Reports

From 1 January 2014 until 20 March 2015 the Netherlands Pharmacovigilance Centre Lareb received 42 reports considering possible adverse drug reactions associated with the use of oxaliplatin [3]. Three reporters, all hospital pharmacists, mention in their initial report that they see an increase of adverse drug reactions related to administration of oxaliplatin. An overview of all reports can be found in table 1 in the appendix.

Reports over time

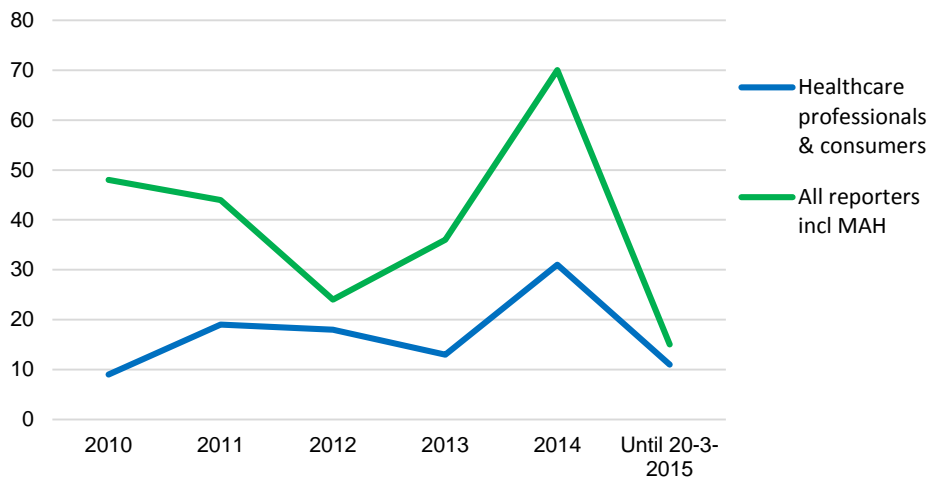


Figure 1. Overview of number reports of ADRs related to oxaliplatin received by the Netherlands Pharmacovigilance Centre Lareb between 1 January 2010 and 20 March 2015.

Figure 1 shows that the number of reports in 2014 of ADRs related to oxaliplatin use increased compared to the four years before. In 2014 the Netherlands Pharmacovigilance Centre Lareb received 31 reports from reporters based in 14 different hospitals. Four hospitals submitted more than one case-report. Until 20 March 2015 four reporters submitted 11 case-reports in total. Three reporters worked in hospitals that also reported similar reactions in 2014.

The Lareb database also contains reports from MAHs where oxaliplatin is mentioned as suspect drug. In 2014 these reports were based in a study (30 reports – Roche), literature (4 cases – multiple MAHs) and spontaneous reporting (5 reports – 2 by Roche, 2 by Sun, 1 by Accord). MAH reports in 2015 were based on a study (1 report – Roche) and literature (3 cases – multiple MAHs).

**Discussion**

The Netherlands Pharmacovigilance Centre Lareb sees an increase in the number of reports of adverse drug reactions associated with the use of oxaliplatin. From 1 January 2014 until 20 March 2015 42 reports have been received from healthcare professionals and consumers. The reported reactions include hypersensitivity reactions, paraesthesia, muscle spasm, bronchospasm and laryngospasm. In 17 cases the reactions occurred while using oxaliplatin of Accord, in 7 cases while using oxaliplatin of Sun and in the other 18 cases the brand/manufacturer of oxaliplatin is unknown. Four reporters from different hospitals reported 29 of the 42 cases and in 23 cases they mentioned the brand of the product used/manufacturer. Three of these reporters mention that there had been no recent changes in the protocol for preparation of the oxaliplatin infusion solution. They also mention there has been an increase in dose reductions because of the adverse drug reactions compared to the years before and these take place earlier in the treatment. For example, in the past dose reductions were often applied after the 6<sup>th</sup> course of an 8-course treatment. But now the dose reduction are already necessary during the 2<sup>nd</sup> – 4<sup>th</sup> course. The reporters mention that they are concerned about this development, because this means the patients don't get the optimal treatment.

In the 2014 spontaneous case-report received from MAH Accord it is also mentioned that the doctor believed that there had been a change, because she saw the adverse events she reported with more patients, which she hadn't seen before. A possible explanation could be due to the preparation or supplier of oxaliplatin.

The Netherlands Pharmacovigilance Centre Lareb has been monitoring this issue since November 2014. Since then, new reports were received. The Netherlands Pharmacovigilance Centre Lareb also actively contacted a number of hospital pharmacists from their Board and Scientific Committee, but this did not lead to new information. Apparently not all hospitals in the Netherlands experience similar problems with oxaliplatin.

Because new cases on the same issue with oxaliplatin continue to be reported, the Netherlands Pharmacovigilance Centre Lareb wants to bring these reports and concerns to the attention of the Dutch Medicines Evaluation Board.

#### References

1. Dutch SmPC Eloxatin. (version date: 23-5-2014, access date: 17-4-2015) <http://db.cbg-meb.nl/IB-teksten/h32774.pdf>.
2. Dutch SmPC Oxalisin. (version date: 1-2-2013, access date: 17-4-2015) <http://db.cbg-meb.nl/IB-teksten/h34033.pdf>.
3. Database of Netherlands Pharmacovigilance Centre Lareb. (version date: 2015, access date: 16-4-2015) [www.lareb.nl](http://www.lareb.nl).

## Appendix

Table 1 Reports reports of adverse drug reactions associated with the use of oxaliplatin received by the Netherlands Pharmacovigilance Centre Lareb from Healthcare Professionals and Consumers from 1 January 2014 until 20 March 2015.

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
A, 167737 F, 61-70 years, Hospital Pharmacist	oxaliplatin, every 3 weeks 235 mg, colon carcinoma	bevacizumab, capecitabine, metoprolol, macrogol	dizziness, paraesthesia, erythema	30 minutes, drug withdrawn, recovered	Since 1st course these reactions. Due to pre-medication, the reactions were less severe during the following courses.
B, 167738 F, 51-60 years, Hospital Pharmacist	oxaliplatin, colon carcinoma	capecitabine, metoclopramide,g ranisetron, macrogol/electrolytes, insulin glargine, metformin, glimepiride, acetylsalicylic acid, lisinopril, atorvastatin, acetaminophen, salbutamol, fluticasone, bimatoprost	blepharospasm, rhinorrhoea, paraesthesia	1 hour, dose not changed, recovered	
C, 167739 M, 61-70 years, Hospital Pharmacist	oxaliplatin, colon carcinoma	granisetron, macrogol/electrolytes, nadroparin, capecitabine, tramadol, acetaminophen	erythema, hyperhidrosis, pruritus, dyspepsia	1 hour, unknown, recovered	Reactions after 7th course.

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
D, 167740 M, 61-70 years, Hospital Pharmacist	oxaliplatin, oedophageal carcinoma	metoclopramide, macrogol/electrolytes,  capecitabine,  temazepam	balance disorder,  tremor	4 months,  dose reduced, recovering	
E, 167741 F, 71 years or older, Hospital Pharmacist	oxaliplatin, every 3-4 weeks, colon carcinoma	metoclopramide, ranisetron,  macrogol/electrolytes,  amlodipine,  valsartan,  acetaminophen,  oxazepam,  latanoprost	dizziness,  erythema,  stridor,  gait disturbance,  pruritus	1 month,  dose reduced, recovered PRURITUS, ERYTHEMA  2 months,  dose reduced, recovered	Reactions occurred during 2nd and 3th course.
F, 169189 F, 61-70 years, Hospital Pharmacist	oxaliplatin, every 3 weeks 250 mg,  colon carcinoma	capecitabine,  ferrous sulfate,  pantoprazole,  carbasalate calcium,  loperamide,  dexamethasone,  ondansetron	hypersensitivity,  pharyngeal oedema,  rash	30 minutes,  unknown,  recovered	Reaction during 3th course. Already had less severe reaction during 2nd course.
G, 169589 M, 51-60 years, Hospital Pharmacist	folinic acid, every 2 weeks 400 mg,  colon carcinoma,  oxaliplatin, every 2 weeks 170mg, colon carcinoma		dyspnoea,  drug interaction	FOLINIC ACID unspecified minutes,  dose not changed, recovered with sequel  OXALIPLATIN unspecified minutes,  dose not changed, recovered with sequel	

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
H, 170428 F, 61-70 years, Hospital Pharmacist	oxaliplatin, rectum carcinoma	capecitabine, granisetron, dexamethasone, metoclopramide, loperamide, macrogol/electrolytes	drug hypersensitivity	2 hours, unknown, recovered	Reaction occurred during 1st course.
I, 171351 M, 61-70 years, Pharmacist	capecitabine 2dd 1000 mg, colon carcinoma oxaliplatin, colon carcinoma		sepsis, intestinal ischaemia, drug interaction	CAPECITABINE 13 days, drug withdrawn, fatal OXALIPLATIN 13 days, unknown, fatal	
J, 173202 F, 51-60 years, Specialist doctor	oxaliplatin, colon carcinoma capecitabine, colon carcinoma		ventricular fibrillation, drug interaction	CAPECITABINE 2 months, drug withdrawn, recovering OXALIPLATIN 2 months, drug withdrawn, recovering	Received CPR/defibrillation.
K, 175612 M, 41-50 years, Hospital Pharmacist	oxaliplatin Accord, every 2 weeks 170 mg, colon carcinoma	fluorouracil, bevacizumab	hypersensitivity	10 minutes, drug withdrawn, recovered	Had been treated with oxaliplatin Fresenius and Teva before and had no complaints.
L, 175799 M, 61-70 years, Other health professional	oxaliplatin Accord, every 3 weeks, unknown indication	fluorouracil	hepatotoxicity	21 days, dose reduced, unknown	Had been treated with oxaliplatin Fresenius before and had no complaints.

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
M, 175800 M, 51-60 years, Hospital Pharmacist	oxaliplatin Accord, every 2 weeks 90 mg, colon cancer metastatic	fluorouracil, bevacizumab	rash pruritic	3 weeks, drug withdrawn, recovered	Reactions occurred 10 minutes after infusion start. The patient had received premedication (prednisolone and clemastin).
N, 176127 M, 71 years and older, Specialist doctor	oxaliplatin, every 3 weeks, colon carcinoma	capecitabine	Interstitial pneumonia, Lung fibrosis interstitial	6 months, drug withdrawn, fatal	Reactions occurred 8 weeks after the last course (had 8 courses in total). Received antibiotics, steroids and mechanical ventilation.
O, 182581 M, 31-40 years, Specialist doctor	oxaliplatin, every 3 weeks 208mg, gastric carcinoma	capecitabine, fosinopril, alfuzosin, sotalol, pyridoxine, pantoprazole, calcium/vitamin D3, tinzaparin, acetaminophen, metoclopramide	syncope, vomiting	4 months, drug withdrawn, recovering	EEG, brain CT-scan, ECG showed no abnormalities.
P, 182937 M, 51-60 years, Hospital Pharmacist	oxaliplatin, once a month, unknown indication	fentanyl, oxycodon, acetaminophen, metoclopramide, pantoprazole, magnesium oxide	erythema, eye swelling, swelling face, palpitations	15 minutes, dose reduced, unknown	First course 8 months earlier during which there was no reaction. Had the same course in 2012 during which the patient developed hand-foot syndrome.

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
Q, 182938 F, 61-70 years, Hospital Pharmacist	oxaliplatin, once a month, unknown indication		erythema, erythema facial, peripheral swelling, palpitations, swelling face	15 minutes, drug withdrawn, unknown	
R, 183931 F, 60-70 years, Specialist doctor	oxaliplatin, every 3 weeks, colon carcinoma	lorazepam	ataxia	2 hour, dose reduced, recovered	Reactions occurred during 2nd course. A MRI and examination by an ophthalmologist showed no abnormalities.
S, 184104 F, 51-60 years, Other health professional	oxaliplatin, every 3 weeks, colon carcinoma	capecitabine, dexamethasone	sensation of foreign body, feeling abnormal, hyperhidrosis	3 hour, dose reduced, recovered	Reactions occurred during 2nd course. During the 1st course the reactions were less severe
T*, 184106 F, 61-70 years, Hospital Pharmacist	oxaliplatin, colon carcinoma		phlebitis, pain, blister	3 hours, unknown, recovering	First reporter to mention a possible raw material issue.
U*, 186167 F, 61-70 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks, colorectal carcinoma	capecitabine, oxazepam, metoprolol, plantago ovata, salmeterol/fluticasone, mirtazapine, salbutamol	laryngospasm	1 hour, dose reduced, recovered	Reactions occurred during 3th course. The following courses the infusion rate was decreased, but the reaction reoccurred.



Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
V*, 186168 F, 71 years or older, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks, colorectal carcinoma	capecitabine, budesonide/formoterol, amlodipine, nicomorphine, magnesium hydroxide, fentanyl, acetaminophen, omeprazole, plantago ovata, macrogol/electrolytes, acetylsalicylic acid, simvastatin, ranitidine, triamterene/epitizide, bisacodyl	dyspnoea	2 hours, unknown, recovered	
W*, 186169 F, 61-70 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks, colorectal carcinoma	capecitabine, metoprolol, irbesartan, oxazepam, zopiclon	dizziness, dyspnoea	unspecified hours, dose reduced, recovered	Reactions occurred during 2nd course. During the 1st course the patient only experienced dizziness.
X*, 186580 F, 51-60 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks, colorectal carcinoma	capecitabine, hydrochlorothiazide	laryngeal disorder, dizziness	3 weeks, dose reduced, recovered	Reactions occurred during 2nd course.
Y, 186581 F, 61-70 years, Hospital Pharmacist	oxaliplatin Sun, every 3 weeks, colorectal carcinoma	dexamethasone, ondansetron	laryngospasm, hypoaesthesia, paraesthesia	2 hours, unknown, recovered	Reactions occurred during 1st course. ranitidine. During 2nd and 3th less severe reactions occurred.

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
Z*, 186583 M, 41-50 years, Hospital Pharmacist	oxaliplatin Accord, seminoma	gemcitabine, carbasalate calcium	salivary hypersecretion, vomiting	unspecified minutes, unknown, recovered	Had BEP and TIP courses before.
AA, 186584 M, 61-70 years, Hospital Pharmacist	oxaliplatin Sun, every 3 weeks 200 mg, oesophageal carcinoma, capecitabine, oesophageal carcinoma	dexamethasone, ondansetron	laryngospasm, muscle spasms	CAPECITABINE 3 weeks, unknown, recovered OXALIPLATIN 3 weeks, unknown, recovered	Reactions occurred during 2nd course. Patient received a lower dose than during the first course, because of the blood count.
AB*, 186585 M, 51-60 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks, colorectal carcinoma	oxazepam, capecitabine, bevacizumab	laryngospasm, dyspnoea	1 hour, unknown, recovered	
AC, 186587 M, 70 years or older, Hospital Pharmacist	oxaliplatin Sun, every 3 weeks 250 mg, colorectal carcinoma capecitabine, every 3 weeks, colorectal carcinoma	dexamethasone, ondansetron	muscle spasms, dysphonia, gait disturbance	CAPECITABINE 2 hours, unknown, recovered OXALIPLATIN 2 hours, unknown, recovered	Reactions occurred during 3th course. No complaints during the first two courses.
AD*, 186588 M, 61-70 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks, colorectal carcinoma	metoclopramide,g ranisetron, magnesium hydroxide, mebeverine, valerian extract, acetaminophen, capecitabine, bevacizumab	laryngospasm, dyspnoea	3 weeks, dose reduced, recovered	During 1st course no complaints, but reactions occurred during 2nd, 3th and 4th course.

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
AE, 186589 F, 51-60 years, Hospital Pharmacist	oxaliplatin Sun, every 3 weeks 220 mg, colorectal carcinoma	dexamethasone, ondansetron	laryngospasm, speech disorder, dysphagia	4 hours, unknown, recovered	Reactions occurred during 2nd course.
AF, 188271, F, 71 years or older, Pharmacist	oxaliplatin, colon carcinoma		erythema, abdominal discomfort, hypertension	unknown, dose reduced, recovered	Reactions occurred during the 3th cycle 5th course Folfox.
AG*, 189687 F, 61-70 years, Hospital Pharmacist	oxaliplatin Sun, 250 mg, colorectal carcinoma	capecitabine, magnesium hydroxide, oxazepam, oxycodon	laryngospasm	1 day, unknown, recovering	Reaction occurred during 2nd course. During 1st course only abnormal feeling in knee.
AH*, 192099, F, 61-70 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks, colon carcinoma		bronchospasm	Unspecified minutes, drug withdrawn, recovered	
AI*, 192199, M, 61-70 years, Hospital Pharmacist	capecitabine 2dd 150mg during 2 weeks every 3 weeks, colon carcinoma  oxaliplatin Accord, every 3 weeks, colon carcinoma	losartan, simvastatin, temazepam, thiamine, tramadol, dexamethasone, metoclopramide, magnesium hydroxide, granisetron, capecitabine	polyneuropathy, temperature intolerance, paraesthesia, drug interaction	CAPECITABINE Unspecified hours, dose not changed, not recovered OXALIPLATIN Unspecified hours, dose reduced, not recovered	

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
AJ*, 192275, M, 61-70 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks 290 mg, colorectal carcinoma	broohexine, noscapine, metoprolol, atorvastatin, acetylsalicylic acid, macrogol/electrolytes, metoclopramide, multivitamins and minerals	infusion related pain, polyneuropathy, temperature intolerance, muscle spasms	5 Minutes, drug withdrawn, recovering	Reaction occurred during 1st course. Dose reduction and lower infusion rate were applied during the 2nd course, but the reaction occurred again.
AK, 192523, F, 61-70 years, Hospital Pharmacist	capecitabine, 2dd 1500mg during 2 weeks every 3 weeks, colorectal carcinoma  oxaliplatin Sun, every 3 weeks 200 mg, colorectal carcinoma	dexamethasone ondansetron	muscle spasms, dyspnoea, drug interaction	CAPECITABINE 3 hours,  drug withdrawn, recovered OXALIPLATIN 3 hours,  drug withdrawn, recovered	The patient had used premedication (dexamethasone and ondansetron).
AL, 192524, M, 61-70 years, Hospital Pharmacist	oxaliplatin Sun, every 3 weeks 250 mg, colorectal carcinoma	capecitabine	swollen tongue, rash, lip swelling, ocular hyperaemia	RASH, OCULAR HYPERAEMIA 30 minutes,  unknown,  recovered  SWOLLEN TONGUE, LIP SWELLING  30 minutes,  unknown,  recovered with sequel	Patient had no complaints during earlier oxaliplatin administration.
AM*, 193079, F, 61-70 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks 200 mg, Colorectal carcinoma	granisetron, dexamethasone, metoclopramide, capecitabine, sodium lauryl sulfate t/sorbitol, macrogol/electrolytes	trismus, infusion related pain	1 hour, dose reduced, recovered	The patient recovered from trismus 1 week after administration.

Patient, Number, Sex, Age, Source	Drug, daily dose, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome	Extra information
AN*, 193082, F, 51-60 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks 130 mg/m <sup>2</sup> , metastatic colorectal cancer	capecitabine, granisetron, dexamethasone, metoclopramide, magnesium hydroxide	bronchospasm	30 minutes, dose reduced, recovered	
AO*, 193085, M, 41-50 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks 130 mg/m <sup>2</sup> , colorectal carcinoma	capecitabine	infusion related pain, temperature intolerance	3 weeks, dose reduced, recovered	Reactions occurred during 2nd course.
AP*, 193086, F, 61-70 years, Hospital Pharmacist	oxaliplatin Accord, every 3 weeks 130 mg/m <sup>2</sup> , colorectal carcinoma	capecitabine, levothyroxine, simvastatin, tramadol, macrogol/electrolyt es, granisetron, dexamethasone, metoclopramide,de xtran 70/ hypromellose	muscle spasms, trismus, temperature intolerance	1 hour, dose reduced, recovered	

*Italic* = Serious case-report

\* = Reporter mentions seeing an increase in adverse drug reactions

Case-reports reported by the same hospital:

Hospital 1: Patients A – E

Hospital 2: Patients K – M, T

Hospital 3: Patients P & Q

Hospital 4: Patients S & AG

Hospital 5: Patients U – X, Z, AB, AD, AH – AJ, AM – AP

Hospital 6: Patients Y, AA, AC, AE, AK, AL

Table 2. Number of reports of adverse drug reactions associated with the use of oxaliplatin received by the Netherlands Pharmacovigilance Centre Lareb between 1 January 2010 and 20 March 2015

Year	Reports from consumers & Healthcare Professionals	Total number of reports received from all reporters incl. MAH
2010	9	48
2011	19	44

Year	Reports from consumers & Healthcare Professionals	Total number of reports received from all reporters incl. MAH
2012	18	24
2013	13	36
2014	31	70
Until 20-3-2015	11	15

*This signal was raised on July 2015. 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](http://www.cbg-meb.nl)*