bijwerkingen centrumlareb

Update overview of reports on new antidiabetic drugs

Introduction

In Quarterly report 2015-2, Lareb gave an overview of the reports concerning the new antidiabetic drugs that have been approved for the Dutch market in the recent years [1]. In Quarterly report 2015-2 the reports up till February 4, 2015, were included. This overview from 1 year ago comprised 344 reports, consisting of 739 ADRs, in the national reporting database. Furthermore there were 315 ADRs reported in the LIM system. At that time, the overview showed no signal which required specific additional action.

The new antidiabetic drugs we describe in this update overview concern dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, and in addition these drugs in a fixed combination with metformin. A detailed list of drugs, is shown in table 1.

Table 1. Overview of new antidiabetic drugs currently registered in the Netherlands

DRUG CLASS	ACTIVE SUBSTANCE(S)	BRAND NAME
DPP-4 inhibitors	Alogliptin	Vipidia®
	Alogliptin/metformin	Vipdomet®
	Linagliptin	Trajenta®
	Linagliptin/metformin	Jentadueto®
	Saxagliptin	Onglyza®
	Saxagliptin/metformin	Komboglyze®
	Sitagliptin	Januvia®
	Sitagliptin/metformin	Janumet®
	Vildagliptin	Galvus®
	Vildagliptin/metformin	Eucreas®
SGLT-2 inhibitors	Canagliflozin	Invokana®
	Canagliflozin/metformin	Vokanamet®
	Dapagliflozin	Forxiga®
	Dapagliflozin/metformin	Xigduo®
	Empagliflozin	Jardiance®
	Empagliflozin/metfomin	Synjardy®
GLP-1 agonists	Albiglutide	Eperzan®
	Dulaglutide	Trulicity®
	Lixisenatide	Lyxumia®
	Exenatide	Byetta® / Bydureon®
	Liraglutide	Victoza®

The number of patients using new antidiabetic drugs in the Netherlands is shown in table 2.

Table 2. Number of patients using new antidiabetic drugs in the Netherlands between 2010 and 2014 [2].

Drug	2010	2011	2012	2013	2014
DPP-4 inhibitors					
Linagliptin (+ metformin)	0	0	2.544	4.571	5.254
Saxagliptin (+ metformin)	1.216	2.442	2.898	2.644	2.232
Sitagliptin (+ metformin)	15.895	22.170	29.232	29.904	28.307
Vildagliptin (+ metformin)	8.392	10.009	12.234	12.811	12.120
GLP-1 agonists					
Lixisenatide	0	0	0	0	33
Exenatide	1.269	1.315	1.908	1.708	1.528
Liraglutide	3.878	7.712	10.172	11.061	10.892
SGLT-2 inhibitors					
Dapagliflozin (+ metformin)	0	0	0	458	1.868
	0	0	0	0	95

Canagliflozin					
Empagliflizon	0	0	0	0	1

Reports

We provide an update overview of the reports received both from the national adverse drug reaction (ADR) database, including spontaneous and study reports, and from the Lareb Intensive Monitoring System (LIM). From LIM, data since 2011 were used in this review. It is important to note that one patient can suffer from several ADRs.

On February 2 2016 the database of the Netherlands Pharmacovigilance Centre Lareb contained 410 reports in the national reporting database (spontaneous and study reports), consisting of 845 ADRs. There were 391 serious ADRs reported. In 15 reports a fatal outcome was reported, or it was reported that the patients eventually died. Additional information regarding the number of reports and ADRs is provided in table 3.These cases with a fatal outcome are described in the paragraph “Reports with fatal outcome”.

Table 3. Numbers of reports received by Lareb in the national reporting database

	DPP-4 inhibitors	**GLP-1 agonists**	**SGLT-2 inhibitors**	**Total**
Total number of reports	231	153	26	410
Number of serious reports (%)	71 (31%)	75 (49%)	9 (35%)	155 (38%)
Total number of ADRs[#]	517	278	50	845
Number of serious ADRs	227	141	23	391
Reports with a fatal outcome	12	3	0	15

[#] One report can contain multiple ADRs

There were 234 patients in the LIM system who had reported at least 1 ADR. In total 367 ADRs were reported in LIM for the new antidiabetic drugs. The total number of patients in the study who completed at least one questionnaire was 540. This includes the patients who did not report an ADR. All the serious reports from the LIM system are also transported to the Lareb database. Additional information on the LIM reports are provided in table 4.

Table 4. Number of patients using new antidiabetic drugs who reported at least one ADR in Lareb Intensive Monitoring (LIM)

Drug class	**Number of included patients**	**Number of reports**	**Number of ADRs**	**Reports with a fatal outcome**
DPP-4 inhibitors	361	127	196	0
GLP-1 agonists	104	62	101	0
SGLT-2 inhibitors	75	45	70	0
Total	**540**	**234**	**367**	**0**

Reports with fatal outcome

The reports with a fatal outcome are described in detail below. The cases with the reported reaction death and seriousness death are listed. Furthermore, the cases are listed where death was not coded as a reaction, nor was the CIOMS seriousness category ‘death’ used, but the report mentioned that the patients eventually died. In these reports the circumstances of death were not described, nor if there was any relationship with the drug.

The cases with a fatal outcome were heterogeneous and in most reports there was another cause of death or underlying pathology could not be excluded as cause of death. In some of the cases with fatal outcome causality could not properly be assessed due to poor documentation level of the reports.

Case 82645:
This serious spontaneous report from a physician through the MAH concerns an patient of unknown gender and age who used sitagliptin and experienced an unspecified adverse event with a fatal outcome.

Case 90139:
This serious spontaneous report from a physician through the MAH concerns a 79-year-old female who used vildagliptin for 7 days. Concomitant medications were metformin and loperamide. The patient was known to have a pancreatic tumor prior to the start of vildagliptin. The patient died due to the pancreatic tumor.

Case 110019:
This serious spontaneous report from a specialist doctor concerns a 60-year-old female with lactic acidosis with a latency of 7 years after starting metformin and 5.5 months after starting liraglutide. The patient also had acute renal insufficiency possibly based on dehydration caused by abdominal complaints. Metformin and liraglutide were withdrawn. The patient was treated with kidney replacement therapy and bicarbonate. The patient died. Concomitant medications were simvastatine, digoxine, furosemide, valsartan, enalapril. The medical history indicates atrial fibrillation, COPD, respiratory insufficiency, morbid obesity and nephrosclerosis.

Case 130016:
This serious spontaneous report from a physician through the MAH concerns a patient with unknown gender and age who used vildagliptin. The patient died due to a myocardial infarction.

Case 152110:
This serious spontaneous report from a general practitioner concerns a 63-year-old male who died due to ventricular fibrillation and a myocardial infarction after using liraglutide for one month. The medical history indicated several myocardial infarctions, hypercholesterolemia and hypertriglyceridemia.

Case 153795:
This serious spontaneous report from the investigator of a clinical trial through the MAH concerns a 64-year-old male with pancreatitis and pancreatic adenocarcinoma following administration of saxagliptin / placebo, perindopril and insulin with a latency of 1,3 years. Concomitant medications indicated acetylsalicylic acid, ispaghula (psylla seeds), lipase, amylase, salbutamol, fluticasone, salmeterol and other drugs for obstructive airway diseases, esomeprazole, tiotropium bromide, ezetimibe, tamsulosin. The medical history indicated myocardial infarction, hypertension, dyslipidemia and upper respiratory tract infection.

Case 170370:
This serious spontaneous report from a physician through the MAH concerns a male of unknown age with a history of epilepsy who used vildagliptin. The patient died due to a planned suicide.

Case 115339:
This serious spontaneous report from the investigator of a clinical trial through the MAH concerns a female aged 60 years, with anaphylactic shock following administration of benzathine benzylpenicillin with a latency of less than a day after start. The patient was hospitalized. The patient also used insulin glargine, pioglitazone, saxagliptine and metformin. The patient recovered from the reaction. Concomitant medication was tramadol. The report mentioned that the patient died.

Case 122203:
This serious spontaneous report from the investigator of a clinical trial through the MAH concerns a male aged 62 years, whose hospitalization was prolonged due to hyperglycemia and infection after planned bariatric surgery (post-operative infection) after administration of insulin, saxagliptin/placebo and metformin with a latency of 5,5 months after start. The drug saxagliptin/placebo was withdrawn.

The action taken for metformin is unknown. The patient has not recovered. Concomitant medication was not reported. The patient died.

Case 122857:
This serious spontaneous report from the investigator of a clinical trial through the MAH concerns a male aged 67 years, who was hospitalized for carpal tunnel cleavage while using saxagliptin/placebo, metformin and insulin for type II diabetes mellitus. The carpal tunnel syndrome started 175 days before administration of insulin glargine, insulin aspart, metformin, saxagliptin/placebo. The patient recovered from the reaction. Concomitant medication was not reported. The medical history indicated coronary artery bypass grafting, coronary artery disease, and hypertension. The report mentioned that the patient died.

Case 153793:
This serious spontaneous report from a physician through the MAH concerns a female aged 69 years, with lung disorder following administration of exenatide extended release (Bydureon®) with a latency of 1 year after start. The patient was hospitalized and intubated. The drug exenatide was withdrawn. The patient has not recovered. Concomitant medications were levothyroxine sodium, salbutamol, insulin aspart, rosuvastatin, hydroxocobalamin, exenatide, metformin, fosinopril, amlodipine, paroxetine. Before starting exenatide (Bydureon®) the patient had been using exenatide (Byetta®). The report mentioned that the patient died.

Case 172805:
This serious spontaneous report from a nurse through the MAH concerns a male of unknown age, with blood pressure, angina pain, tiredness and muscle compliant (muscle disorder) while on therapy with saxagliptin for diabetes mellitus. In the hospital amyotrophic lateral sclerosis was diagnosed. The drug saxagliptin was withdrawn. The patient died. Concomitant medications were fluticasone, omeprazole, diclofenac, metformin, naproxen.

Case 200274:
This serious spontaneous report from a physician concerns a female aged 63 years, with sudden, unexpected death following administration of saxagliptin for type II diabetes mellitus with a latency of 9 days after start. The dose for saxagliptin is not changed. The patient died. In the previous weeks (months) there had been several concommitant disorders: dyspnoea possibly in COPD, moderately regulated diabetes mellitus, possible neurological deficits and a newly diagnosed renal function disorder. Concomitant medications were macrogol/electrolytes, salbutamol, levothyroxine sodium, metoprolol, hydrochlorothiazide, simvastatin, telmisartan, oxazepam, omeprazole, glimepiride, metformin. The medical history indicates mental retardation in Williams syndrome, hypothyroidism, gastroesophageal reflux, dyspnoea, hypercholesterolaemia, obstipation, hypertension.

Case 203983:
This serious spontaneous report from a physician through the MAH concerns a male aged 56 years, with pancreatitis following administration of sitagliptin with unknown latency. The action taken for sitagliptin is unknown. The patient died in the same month in which the pancreatitis started.

Case 205511:
This serious spontaneous report from a physician through the MAH concerns a patient of unknown gender and age, with hepatic infection following administration of vildagliptin and another not specified drug with an unknown latency. The action taken for vildagliptin is unknown. The action taken for the non-specified drug is not applicable. The patient died.

Reports in relation to System Organ Class

In order to provide more insight into the spectrum of ADRs reported to Lareb, the ADRs were grouped into MedDRA® System Organ Classes (SOCs). This information is provided in table 5 (national reporting database) and table 6 (LIM database)

Table 5: Overview of reported ADRs in the national reporting database of the new antidiabetic drugs per MedDRA® System Organ Class

SYSTEM ORGAN CLASS (SOC)	DPP-4 INHIBITORS		GLP-1 AGONISTS		SGLT-2 INHIBITORS		TOTAL
	N	%	N	%	N	%	
Blood and lymphatic system disorders	0	0.0	3	1.1	0	0.0	3
Cardiac disorders	13	2.5	7	2.5	5	10.0	25
Congenital, familial and genetic disorders	0	0.0	1	0.4	0	0.0	1
Ear and labyrinth disorders	3	0.6	0	0.0	0	0.0	3
Endocrine disorders	0	0.0	2	0.7	1	2.0	3
Eye disorders	11	2.1	1	0.4	0	0.0	12
Gastrointestinal disorders	112	21.7	75	27.0	7	14.0	194
General disorders and administration site conditions	46	8.9	32	11.5	4	8.0	82
Hepatobiliary disorders	3	0.6	2	0.7	0	0.0	5
Immune system disorders	2	0.4	3	1.1	0	0.0	5
Infections and infestations	20	3.9	6	2.2	6	12.0	32
Injury, poisoning and procedural complications	7	1.4	5	1.8	0	0.0	12
Investigations	42	8.1	16	5.8	2	4.0	60
Metabolism and nutrition disorders	24	4.6	19	6.8	6	12.0	49
Musculoskeletal and connective tissue disorders	34	6.6	7	2.5	2	4.0	43
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	8	1.5	15	5.4	0	0.0	23
Nervous system disorders	52	10.1	11	4.0	3	6.0	66
Pregnancy, puerperium and perinatal conditions	0	0.0	2	0.7	0	0.0	2
Psychiatric disorders	20	3.9	7	2.5	2	4.0	29
Renal and urinary disorders	20	3.9	10	3.6	2	4.0	32
Reproductive system and breast disorders	4	0.8	2	0.7	6	12.0	12
Respiratory, thoracic and mediastinal disorders	41	7.9	5	1.8	2	4.0	48
Skin and subcutaneous tissue disorders	53	10.3	32	11.5	0	0.0	85
Social circumstances	0	0.0	0	0.0	0	0.0	0
Surgical and medical procedures	0	0.0	2	0.7	0	0.0	2
Vascular disorders	2	0.4	5	1.8	2	4.0	9
Unspecified	0	0.0	8	2.9	0	0.0	8
Total	**517**	**100**	**278**	**100**	**50**	**100**	**845**

Table 6: Overview of ADRs of the new antidiabetic drugs per MedDRA® System Organ Class in the LIM database*

System Organ Class (SOC)	**DPP-4 INHIBITORS**		**GLP-1 AGONISTS**		**SGLT-2 INHIBITORS**	
	N	%	N	%	N	%
Blood and lymphatic system disorders	1	0.5	0	0	0	0
Cardiac disorders	1	0.5	0	0	0	0
Congenital, familial and genetic disorders	0	0	0	0	0	0
Ear and labyrinth disorders	0	0	0	0	0	0
Endocrine disorders	0	0	0	0	0	0
Eye disorders	4	2.0	1	1.0	2	2.9
Gastrointestinal disorders	62	31.6	71	70.3	16	22.9
General disorders and administration site disorders	20	10.2	8	7.9	12	17.1

Hepatobiliary disorders	0	0	0	0	0	0
Immune system disorders	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0
Infections and infestations	6	3.1	0	0	6	8.6
Investigations	14	7.1	4	4.0	6	8.6
Metabolism and nutrition disorders	14	7.1	3	3.0	2	2.9
Musculoskeletal and connective tissue disorders	15	7.7	2	2.0	1	1.4
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	0	0	0	0
Nervous system disorders	33	16.8	7	6.9	7	10.0
Pregnancy, puerperium and perinatal conditions	0	0	0	0	0	0
Psychiatric disorders	1	0.5	1	1.0	0	0
Renal and urinary tracts disorders	5	2.6	0	0.0	15	21.4
Reproductive system and breasts disorders	0	0.0	0	0.0	2	2.9
Respiratory and thoracic disorders	7	3.6	1	1.0	0	0
Skin and subcutaneous tissue disorders	11	5.6	3	3.0	0	0
Social circumstances	0	0	0	0	0	0
Surgical and medical procedures	0	0	0	0	0	0
Vascular disorders	2	1.0	0	0	1	1.4
Total	**196**	**100**	**101**	**100**	**70**	**100**

* If the same patient reported the same ADR in multiple questionnaires, the ADR was only counted once

Reports concerning diabetic ketoacidosis

In a communication from June 13, 2015 the Medicines Evaluation Board (MEB) of the Netherlands, is warning for diabetic ketoacidosis in patients with diabetes type 2 who are being treated with SGLT-2 inhibitors, and provides advices for health care professionals and patients. This was based on an European Medicines Agency (EMA) decision, after assessment by the Pharmacovigilance Risk Assessment Committee (PRAC). Furthermore a Direct Health Care Professional Communication (DHPC) was sent out by the marketing authorization holders [3].

In the Lareb database, there were 2 reports of ketoacidosis and GLP-1 agonists and 3 reports of ketoacidosis and SGLT-2 inhibitors.
For the patients using GLP-1 agonists, no concomitant medication was reported. Both cases report the withdrawal of insulin prior to the start of the suspect drug. The development of ketoacidosis may be explained by the inability of GLP-1 mono therapy to meet the patients' insulin requirement. This is supported by the fact that hyperglycemia was reported for one patient. For the other patient no additional information was provided. Based on the described cases, the development of ketoacidosis in relation to the use of GLP-1 agonists could be seen as a suboptimal treatment compared to the previous use of insulin instead of a classical ADR.
In the 3 reports concerning the SGLT-2 inhibitor and diabetic ketoacidosis, one patient had additional risk factors, that is inflammation of unknown cause and vomiting. Another patient had myocardial infarction as risk factor, but the myocardial infarction also might have been luxated by the ketoacidosis. In one report (201024) no possible risk factors for the diabetic ketoacidosis were described. In this case the latency after start of the SGLT-2 inhibitor dapagliflozine was 7 days.

The cases of diabetic ketoacidosis and SGLT-2 inhibitors are described here in detail:

Case 165573:

This serious (hospitalisation for 6 days, lifethreatening) spontaneous report from a specialist doctor concerns a male aged 40 years, with diabetic ketoacidosis following administration of dapagliflozine for type 2 diabetes mellitus with a latency of 8 days after start. The drug dapagliflozine was withdrawn. The patient was treated with insulin (i.v.), hydration and potassium supplementation. The patient recovered. Concomitant medications were exenatide, ramipril, metformin, simvastatin and glimepiride. According to the reporter other factors that could have caused or aggravated ketoacidosis were an inflammation e.c.i., and vomiting during treatment with tramadol for back pain.

Case 201024:
This serious (hospitalisation for 5 days) spontaneous report from a health care professional concerns a female aged 41 years, with ketoacidosis following administration of dapagliflozine for type 2 diabetes mellitus with a latency of 7 days after start. Laboratory tests included: metabolic acidosis pH 7.06 partly respiratory compensation, blood glucosis 26.5 mml, sodium: 139, potassium: 5.5, urine: Ketons: strongly positive. The drug dapagliflozine was withdrawn. The patient was treated with infusion therapy and insulin. The patient recovered 1 day after the onset of the reaction. Concomitant medications were omeprazole, triamcinoloneacetonide (nasal spray), methyldopa (levorotatory) and metformin.
The medical history indicates laparoscopic cholecystectomy.

Case 213758:
This serious (Hospitalisation) spontaneous report from a specialist doctor concerns a male aged 72 years, with ketoacidosis following administration of dapagliflozine for type 2 diabetes mellitus with a latency of 1 year after start. The patient had experienced complaints of chest pain, dyspnoea, nausea, vomiting and malaise. A respiratory tract infection was suspected and antibiotics were started. During the following week the complaints starting to get more severe and more frequent. He was referred to the hospital and an acute myocardial infarction was diagnosed. He underwent PCI of the RAD en LAD. After this procedure, the patient still experienced dyspnoea and vomiting. Physical examination revealed a pulse of 100 b.p.m. and a rapid, deepened breathing. Blood test showed high blood ketone bodies and high glucose. The drug dapagliflozine was withdrawn, the patient was hospitalized for three days and the ketoacidosis was treated. At the time of reporting, one day after onset of the ketoacidosis, the patient is recovering. Concomitant medication was insulin glargine. The reporter mentioned that it is possible that the myocardial infarction was luxated by the ketoacidosis.

Reports concerning pancreatic disorders

In the literature, the use of DPP-4 inhibitors and GLP-1 agonists has been associated with pancreatic disorders, including pancreatitis and pancreatic carcinoma [4-10,10-12]. Therefore, we performed an analysis of all reports describing pancreatic events associated with these drugs (see table 7 and detailed information below).

Table 7. Number of reports considering pancreatic events

DRUG CLASS	REPORTS CONSIDERING PANCREATIC EVENTS	% OF TOTAL NUMBER OF ADRS	TOTAL NUMBER OF REPORTS
DPP-4 inhibitors	25*	10.1%	248
GLP-1 agonists	15*	9.1%	165
SGLT-2 inhibitors	0	0.0%	28

* A pancreatic carcinoma was reported for 3 patient using a DPP-4 inhibitor and five patients using a GLP-1 agonists.

The 40 reports retrieved concern 30 reports of pancreatitis which is a labeled ADR of the DPP-4 inhibitors and GLP-1 agonists. There were 7 reports of pancreatic carcinoma, and 1 of suspicion of pancreatic carcinoma. The other 2 reports concerned a benigne intraductal papillary mucinous neoplasm, and a report of pancreas infection.
The reports concerning pancreatic carcinoma are described in detail below.
In summary, the cases should be interpreted with caution, since they could be confounded by several factors, including concomitantly used drugs and pre-existing conditions. Furthermore, a meta-analysis

of 88 studies reports a pooled relative risk (RR) for pancreatic cancer in patients with diabetes compared with patients without diabetes of 2.08 (95% CI 1.87-2.32) [13]. Therefore confounding by indication should be considered for this association. Although the use of GLP-1 agonists has been linked to pancreatic carcinoma in the scientific literature [4,5,12], EMA concluded that "*…. the results of the study by Butler et al are not considered to constitute a new safety signal for the GLP 1 based therapies with respect to pancreatic safety. This is further supported by the review of available preclinical and clinical data.*" [11].

Case 128706:
This serious spontaneous report from a physician through the MAH concerns a a 65-year-old female with a history of iron deficiency anemia and polyps of the small intestine. After the start of liraglutide the polyps had grown up to the pancreas. Treatment with liraglutide was ceased after a treatment duration of four months. The patient underwent a Whipple procedure due to a duodenal adenoma and pancreatic carcinoma. At the time of reporting the patient had not yet recovered. The polyps and anemia had been present prior to the start of liraglutide.

Case 153795:
This report is described in detail in the section 'Reports with fatal outcome'

Case 156072:
This serious spontaneous report from a specialist doctor concerns a 64-year-old male with a history of several pancreatic disorders, including necrotizing pancreatitis (later chronic pancreatitis) and pancreatic cysts. Approximately 1 year after starting liraglutide the pancreatitis aggravated and the patient was diagnosed with a pancreas carcinoma. Liraglutide was withdrawn and a pancreatectomy was performed, after which the patient recovered. Additionally the medical history reports surgery for a rectal adenoma, obesity, smoking and alcohol abuse.

Case 156699:
This serious (Hospitalisation, Lifethreatening) spontaneous report from a general practitioner concerns a female aged 69 years, with pancreas carcinoma following administration of liraglutide for type 2 diabetes mellitus with a latency of 23 months after start. The patient was treated with chemotherapy, surgical resection was no longer possible. According to the reporter other causes of the pancreatic carcinoma could be the previous use of methotrexate or spontaneous development of the tumor. The medical history indicated rheumatoid arthritis and pancytopenia after using methotrexate.

Case 158890:
This serious (Lifethreatening) spontaneous report from a specialist doctor concerns a 74-year-old female. Approximately 10 months after starting liraglutide, metastatic pancreatic carcinoma was diagnosed. It was not reported whether liraglutide was withdrawn. At the time of reporting the patient had not recovered. No additional information regarding treatment was provided. The medical history indicated hypertension.

Case 176665:
This serious spontaneous report from a specialist doctor concerns a 68-year-old male with an advanced stage of pancreas carcinoma following administration of liraglutide for diabetes mellitus with a latency of 4 years after start. At the time of diagnosis liraglutide had already been withdrawn for 6 months. The patient was treated with chemotherapy and had not recovered at the time of reporting. According to the reporter it was unknown if other risk factors for the carcinoma were present.

Case 196167:
This serious (Lifethreatening) spontaneous report from a general practitioner concerns a male aged 47 years, with suspicion of a pancreas carcinoma following administration of sitagliptine for type 2 diabetes mellitus with a latency of 3 years after start. The drug sitagliptine was withdrawn. The patient outcome is unknown. Concomitant medication was metformin. The medical history indicates proteinuria.

Case 205632:
This well documented serious (lifethreatening) spontaneous report from a general practitioner concerns a male aged 69 years, with pancreas carcinoma following administration of saxagliptine for diabetes mellitus with a latency of 5 years after start. The drug saxagliptine had already been

withdrawn 5 months before the diagnosis of pancreas carcinoma, because of increasing blood glucose values. The patient outcome is unknown. Concomitant medications were triamcinolone and metformin.

Saxagliptin and heart failure

On November 2 2014 the Food and Drug Administration (FDA) released a Safety Announcement concerning heart failure and saxagliptin, because of the SAVOR study showing increased rate of hospitalization for heart failure with the use of saxagliptin [14]. Lareb received no reports concerning cardiac failure. Lareb received 1 report of edema of the ankles in a 70-year old female, with a latency of 1 week. The patient was recovering despite continuation of sixagliptin. No other indications for cardiac failure were described in this case.

Other especially notable reports

All the associations were manually screened. Reports that were especially noticed because of their potential seriousness, exceptionality or remarkable number of PT's are reported here. In parentheses the numbers of the reports are mentioned. For each association relevant information concerning the SmPC was added.

Lareb received 1 MAH study report of saxagliptin and acute kidney failure (157574).
The SmPC pf saxagliptin reports decreased renal function and acute renal failure as adverse drug reaction with unknown frequency [15].

Lareb received 1 MAH reports of sitagliptin and extrinsic allergic alveolitis in a female with unknown age, with unknown latency (104937). No further information was provided.
Because of the poor documentation causality is not assessable.
The SmPC of sitagliptin does not report alveolitis as an adverse drug reaction. Interstitial pulmonary disease is reported as adverse drug reaction with unknown frequency [16]

Lareb received 3 reports of throat pain and sitagliptin (112073, 117981, 173287). In two of these reports the patients experienced other complaints as well (abdominal pain and diarrhea, and amongst others headache). One patient had no other complaints. In this patient, the latency was 12 days and there was a positive dechallenge 2 days after withdrawal.
The SmPC of sitagliptin does not report oropharyngeal pain as an adverse drug reaction [16].

Lareb received 3 reports of sitagliptin and angio-oedema (200154, 139775, 149486). One patient experienced swollen mouth and lip and another patient dyspnoea and throat tightness. The other patient had enalapril as other suspect drug.
The SmPC of sitagliptin reports angio-oedema as an adverse drug reaction with unknown frequency [16].

Lareb received 2 reports of sitagliptin and bullous pemphigoid (163118, 212546). The patients were both female, the ages were 71 and 76 years. Latencies were 44 days and 2.8 months. Both patients recovered after withdrawal. Both patients had been treated with clobetasol cream and one patient also with doxycycline.
The SmPC of sitagliptin reports bullous pemphigoid as an adverse drug reaction with unknown frequency [16].

Lareb received 1 reports of vildagliptin and renal failure (84193). This report concerned a 75 year old female, the latency was 13 days. Renal biopsy showed clear tubulopathy with vacuolization and swelling of the tubular epithelium. The patient was temporarily dialysed and recovered.
The SmPC of vildagliptin does not report renal failure as adverse drug reaction [6].

Lareb received 1 report of urosepsis and cangliflozine (210942). The report concerned a 67-year old female, latency was 20 days. The patient was hospitalized for 13 days. Urine culture showed proteus mirabilis. The reaction was treated with cefuroxim and the patient was recovering.
The SmPC of canagliflozin reports that urosepsis as an adverse drug reaction that was reported post-marketing [17].

Lareb received 1 report of dapagliflozin and acute renal injury (180149). This concerned a 72-year old female. The reaction had a latency of 2 moths for dapagliflozin, and 1 year for the concomitant suspect drug candesartan. The patient was hospitalized for 5 hours. After withdrawal of only the dapagliflozin, the patient recovered.
The SmPC of dapagliflozin reports renal function disorder as a sometimes occurring adverse drug reaction [18].

Lareb received 3 reports of exenatide and carcinoma's (161363, 180536, 141216). One report concerned a 58 year old male with renal cell carcinoma with a latency of 3.2 years. Surgery was performed. The outcome is unknown. Another report concerns a 73-year old male with oesophageal carcinoma, with a latency of 3 years. The outcome is unknown. The patient reported that another cause of the reaction might have been reflux, whether or not related to exenatide.
The third report was a MAH report with very limited information, concerning a male of unknown age with lung cancer with an unknown latency. In this case the information is too limited for causality assessment.
The SmPC of exenatide does not report malignancies as adverse drug reaction [7].

Lareb received 1 report of haemolytic anaemia and liraglutide (149448). Glimepiride was concomitant suspect drug though, started at the same date as liraglutide, of which haemolytic anaemia is a labeled adverse drug reaction [19]. The report concerned a 49 year old male, latency was 5 days. Liraglutide and glimepiride were withdrawn. The reaction was treated with prednisolone and erythrocytes concentrate and the patient recovered.
The SmPC of liraglutide does not report haemolytic anaemia as adverse drug reaction [9].

Lareb received 1 report of liraglutide and chronic discoid lupus erythematosus (147135). The report concerned a 53 year old male, the latency was 4 months. Histopathology was performed and was most compatible with lupus erythematosus, with at serology investigations weakly positive ANA, and positive SSA. The reaction was treated with local mometasone, and liraglutide was withdrawn. The patient is recovering. As far as known by the reporter patient had no (excessive) exposure to UV radiation or sunlight.
The SmPC of liraglutide does not report chronic discoid lupus erythematosus as adverse drug reaction [9].

Lareb received 1 report of liraglutide and panniculits (142162). The report concerned a 51 year old male, with a latency of 14 days. a CT scan showed panniculitis of intra-abdominal fat surrounding the pancreas, there was no pancreatitis. Liraglutide was withdrawn and the patient recovered.
The SmPC of liraglutide does not report panniculitis as adverse drug reaction [9].

Lareb received 1 report of liraglutide and a neuroendocrine tumor (not further specified) (134093). The report concerned a 68 year old male, with a latency of 9 months. The neuroendocrine tumor was treated with octreotide. The medical history indicated diabetes type 2 and prostate carcinoma treated with 125-Jodium.
The SmPC of liraglutide does not report a neuroendocrine tumor as adverse drug reaction [9]. In the literature neuroendocrine tumors were linked to incretin therapy [5].

Lareb received 2 reports of liraglutide and acute renal failure (117518, 156948). The first patient also experienced lactic acidosis and dehydration. In the other patient vomiting and diarrhoea might have played a role in the reaction.
The SmPC of liraglutide reports acute renal failure as a sometimes occurring adverse drug reaction [9].

Discussion and conclusion

The aim of this report was to provide an update overview of the ADRs received for three classes of new antidiabetic drugs. Both data from the national reporting database and LIM database were analyzed.
Cases with a fatal outcome were reported. The cases with fatal outcome were heterogeneous and in most reports there was another cause of death, or underlying pathology could not be excluded or was

likely as cause of death. In some of the cases with fatal outcome causality could not properly be assessed due to poor documentation level of the reports.
Lareb received 3 reports of (diabetic) ketoacidosis and SGLT-2 inhibitor. This association was already described in the previous Quarterly Report and last year the Dutch MEB sent out a communication on this topic after PRAC assessment at the EMA, warning for diabetic ketoacidosis in patients with diabetes type 2 who are being treated with SGLT-2 inhibitors [3].
The causality between the use of antidiabetic drugs and pancreatic carcinoma of which Lareb received several reports, is challenging since it may be confounded by several factors, including the patients' diabetes mellitus.
In 2014 2014 a Safety Announcement by the FDA was released concerning heart failure and saxsagliptin [14]. Lareb received no reports of this association.
All the associations in the Lareb database were reported per System Organ classes in table 4 and 5. All the associations were manually screened and reports that were especially noticed because of their potential seriousness, exceptionality of remarkable number, were further analyzed. These associations were all reported in the SmPC, or there were yet too few reports for advices on regulatory actions (e.g. sitagliptin and oropharyngeal pain, vildagliptin and renal failure, liraglutide and chronic discoid lupus erythematosus, liraglutide and panniculits, and liraglutide and neuroendocrine tumor).
In the future Lareb will continue to monitor this group of new antidiabetic drugs for new signals.

References

1. Overview of reports on new antidiabetic drugs. Lareb Quarterly Report 2015(2):32-39. (version date: 3-7-2015, access date: 2-3-2016) http://www.lareb.nl/Signalen/KWB_2015_2_diabet.aspx.
2. College voor Zorgverzekeringen. GIP Databank. (version date: 4-1-2016, access date: 5-3-2016) http://www.gipdatabank.nl/.
3. College ter Beoordeling van Geneesmiddelen. Nieuwbericht [Communication]. (version date: 13-7-2015, access date: 5-3-2016) http://www.cbg-meb.nl/actueel/nieuws/2015/07/13/meldingen-diabetische-ketoacidose-bij-gebruik-sglt2-remmers.
4. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 2011;141(1):150-6.
5. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013;62(7):2595-604.
6. European SPC Galvus® (vildagliptin). (version date: 18-12-2014, access date: 4-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000771/WC500020327.pdf.
7. European SPC Byetta® (exenatide). (version date: 5-12-2014, access date: 4-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf.
8. European SPC Bydureon® (exenatide). (version date: 6-2-2015, access date: 4-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/002020/WC500108241.pdf.
9. European SPC Victoza® (liraglutide). (version date: 6-2-2015, access date: 4-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf.
10. Batabyal P, Van der Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg.Oncol. 2014;21(7):2453-62.
11. EMA Assessment report for GLP-1 based therapies. (version date: 25-7-2013, access date: 4-3-2016) http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/08/WC500147026.pdf.
12. Labuzek K, Kozlowski M, Szkudlapske D, Sirkorska P, Koslowska M, Okopien B. Incretin-based therapies in the treatment of type 2 diabetes--more than meets the eye? Eur J Intern Med 2013;24(3):207-12.
13. Batabyal P, Van der Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg.Oncol. 2014;21(7):2453-62.
14. FDA Drug Safety COmmunication: FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR). (version date: 2-11-2014, access date: 7-3-2016) http://www.fda.gov/Drugs/DrugSafety/ucm385287.htm.
15. Dutch SmPC Onglyza (saxagliptine)® 2.5 mg tablets. (version date: 18-7-2014, access date: 7-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/001039/WC500044316.pdf.
16. European SPC Januvia® (sitagliptin). (version date: 19-11-2014, access date: 4-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000722/WC500039054.pdf.
17. European SPC Invokana® (canagliflozine). (version date: 15-11-2013, access date: 7-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/002649/WC500156456.pdf.
18. European SPC Forxiga® (dapagliflozine). (version date: 12-11-2012, access date: 7-3-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/002322/WC500136026.pdf.
19. Dutch SmPC Amaryl® (glimepiride). (version date: 7-4-2015, access date: 7-3-2016) http://db.cbg-meb.nl/IB-teksten/h17843.pdf.