1.1. An overview of reports on sitagliptin

Introduction

Sitagliptin (Januvia®) was registered for the European marked on March 21st 2007 with the Netherlands as rapporteur. It is indicated as *treatment of for patients with type 2 diabetes mellitus. It can be used as monotherapy in patients who are inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance or as dual oral therapy in combination with metformin or a sulphonylureum derivate or a peroxisome proliferator-activated receptor gamma (PPARγ) agonist or as triple oral therapy in combination with a sulphonylurea and metformin or a PPARγ agonist and* metformin. It is also indicated *as add-on to insulin (with or without metformin)* [1].

The improvement in glycaemic control observed with sitagliptin may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells.

In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. GLP-1 does not impair the normal glucagon response to hypoglycaemia.

The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP [2].
Since its introduction in the Netherlands, sitagliptin is used by only a small proportion of the patients with diabetes mellitus [3].

Table 1. Number of sitagliptin users in the Netherlands between 2007 and 2009

Drug	2007	2008	2008
sitagliptin	1,292	5,389	7,837

In this overview the reports received by Lareb through both the spontaneous reporting system as well as the Lareb Intensive Monitoring system will be discussed.

Reports of ADRs

On November 19, 2010 the Netherlands Pharmacovigilance Centre Lareb had received 44 reports of drugs containing sitagliptin. 40 of these concerned sitagliptin and four reports the combination drug sitagliptin/metformin.
These reports contained a total of 92 suspect adverse drug reactions.
Of these reports nine were reported as serious according to the CIOMS criteria which includes reaction leading to (prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events, congenital abnormalities and other medically significant reactions. Four of these reports were received through the marketing authorisation holder (MAH). The serious reports concerned the following ADRs; pneumonia, pancreatitis, respiratory tract infections,

allergic reaction, hypoglycaemia, meningioma, mastitis and extrinsic allergic alveolitis. In one report the ADR was not specified, only that the patient had died.

Since August 1st 2009 Lareb is monitoring the safety of sitagliptin via its Lareb Intensive Monitoring system. On November 9, 2010 179 patients had signed up for the sitagliptin study with Lareb Intensive Monitoring and 21 for the sitagliptin/metformin study. Of these patients, 42 reported adverse drug reactions, which means that 21% of all patients in the cohort reported and ADR. A total of 94 suspect adverse drug reactions were reported. None of these ADRs were considered to be serious according to the criteria by the CIOMS committee.

Table 2. reported adverse events on sitagliptin, grouped by system organ class received through spontaneous reporting and Lareb Intensive Monitoring

System Organ Class	ADRs Lareb	ADRs LIM	≥ 2 reports in Lareb database and/or >2 reports in LIM*	common and very common adverse drug reactions according to SPC
Blood and lymphatic system	0			
Cardiac disorders	1	1		
Ear and labyrinth disorders				
Eye disorders	2	2		
Gastrointestinal disorders	22	28	nausea, abdominal pain, dyspepsia, constipation, diarrhoea, abnormal faeces, gastro-intestinal motility disorder, upper abdominal pain	diarrhoea, dry mouth, nausea, flatulence, constipation, upper abdominal pain, vomiting
General disorders and administration site conditions	10	11	fatigue, oedema	peripheral oedema
Hepatobiliary disorders	0			
Immune system disorders	0			
Infections and infestations	4	2		influenza
Injury, poisoning and procedural complications	0			
Investigations	1	5		
Metabolism and nutrition disorders	5	6	decreased appetite, hypoglycaemia	hypoglycaemia
Musculoskeletal and connective tissue disorders	9	5	myalgia, arthralgia	
Neoplasm, benign, malignant and unspecified	1			
Nervous system disorders	11	16	headache, somnolence, dizziness	headache and somnolence
Psychiatric disorders	2	3		
Renal and urinary disorders	1	2		
Reproductive	1	2	erectile dysfunction	

System Organ Class	ADRs Lareb	ADRs LIM	≥ 2 reports in Lareb database and/or >2 reports in LIM*	common and very common adverse drug reactions according to SPC
disorders				
Respiratory disorders	10	2	dyspnoea,	
Skin and subcutaneous tissue disorders	12	5	hyperhidrosis, pruritus, urticaria, rash	
Vascular disorders	0	4	peripheral coldness	

* ADRs grouped by PT reported two or more times via the spontaneous reporting system or via the intensive monitoring system.

The adverse drug reactions reported via the spontaneous reporting system as well as through intensive monitoring are in general consistent with the ADR profile of sitagliptin as reported in the SmPC. However two cluster of reports, one concerning effects on the respiratory tract and one concerning arthralgia and myalgia might be worth further investigation since this kind of reactions are not mentioned in the SmPC but they constitute a relatively large portion of the reports received by Lareb. These reports will be described in more detail below.

Table 3. Reports concerning the respiratory tract associated with the use of sitagliptin

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 110243 F, 66	sitagliptin diabetes		upper respiratory tract infection, dyspnoea, suffocating feeling	3 years, discontinued, not yet recovered
B 108192 F, 62	sitagliptin diabetes	hydrochlorthiazide, tolbutamide, metformin, metorpolol	respiratory tract infection, feeling cold, pain of extremities	6 months, drug withdrawn, not yet recovered
C 106636 M, 71	sitagliptin/metformin diabetes	pantoprazole, lisinopril/hydrochlorthiazide, simvastatin, carbasalate calcium	pneumonia	6 weeks, no changed, recovered
D 91540 F,	sitagliptin diabetes	acetylsalicylic acid oxazepam	extrinsic allergic alveolitis	not reported, not reported, unknown
E 86616 M, 64	sitagliptin diabetes	sotalol, cabergolin, acetylsalicylic acid, hydrocortisone, simvastatin, metformin, losartan, levothyroxine	dyspepsia, dyspnoea	2 weeks, discontinued, recovered

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
F 102368 F, 52	sitagliptin/metformin diabetes	amlodipine, glimepiride, salbutamol inhalation, baclofen, simvastatin, irbesartan	arthralgia, dyspnoea	3 days, discontinued, not yet recovered
G 83895 F, 58	sitagliptin/metformin diabetes	metformin, pravastatin	oedema, dissiness, fatigue, myalgia, dyspnoea, renal insufficiency	2 months, discontinued, recovered
H 81243 M, 64	sitagliptin diabetes	glimepriride, quinalapril, simvastatin	nipple disorder, urticaria, dyspepsia, dyspnoea	week discontinued recovered
I 104416 M, 59	sitagliptin diabetes	glimepiride, metformin	bronchial hyperreactivity, malaise, urticaria, blood glucose fluctuation	18 hour discontinued not yet recovered
J 108686 M, 47	sitagliptin diabetes	metformin, glicazide, simvastatin, perindopril	oedema, epigastric pain, dyspnoea	6 weeks discontinued, recovered
K, LIM M, 50	sitagliptin diabetes	paroxetin	respiratory tract infection, sinusitis	5 weeks, drug withdrawn, recovering

Lareb received 11 reports of negative effects on the respiratory tract associated with the use of sitagliptin. The reported reactions were dyspnoea (6 times) upper respiratory tract infection (3 times). A suffocating feeling, pneumonia, extrinsic allergic alveolitis and bronchial hyper reactivity were all reported once. Sometimes these symptoms were reported together with other ADRs. The reports concerns 5 females and 6 males. The age ranges from 47 to 71 years. The latency varies from days to three years. In 9 cases the drug was withdrawn, recovery was reported in 5 of these recovery was reported.

Table 4. Reports concerning musculoskeletal disorders associated with the use of sitagliptin.

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 81535 M, 61 – 70 years	sitagliptin diabetes		muscle disorder, concentration impaired	4 weeks, drug withdrawn, recovered with sequelae
B 83190 F, 70 years and older	sitagliptin diabetes		arthralgia	4 days, discontinued, not recovered
C 81787 F, 51 – 60 years	sitagliptin diabetes		arthralgia	4 weeks, drug withdrawn, recovered

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
D 79965 M, 61 – 70 years	sitagliptin metformin diabetes		myalgia, fatigue, hyperhidrosis, abdominal discomfort	30 days, not reported, not recovered
E 103673 F, 41 – 50 years	sitagliptin diabetes	thyroid hormones, levothyroxine	hyperglycaemia, decreased appetite, abdominal pain, myalgia, depressed mood	7 days, drug withdrawn, recovered
F 102368 F, 51 – 60 years	sitagliptin/metformin diabetes	amlodipine, glimepiride, salbutamol inhalation, baclofen, simvastatin, irbesartan	arthralgia, dyspnoea	3 days, discontinued, not yet recovered
G 83895 F, 51 – 60 years	sitagliptin/metformin diabetes	metformin, pravastatin	oedema, dizziness, fatigue, myalgia, dyspnoea, renal insufficiency	2 months, discontinued, recovered
H 108192 F, 61 – 70 years	sitagliptin 100 mg diabetes	hydrochlorthiazid, tolbutamide, metformin, metorpolol	respiratory tract infection, feeling cold, pain of extremities	6 months, drug withdrawn, not yet recovered
I, LIM 1 F, 51 – 60 years	sitagliptin 100 mg diabetes	metformin, enalapril, omega 3 fish oil, polycosanol	diarrhoea, nausea and pain in extremity	weeks, drug withdrawn, recovering from the two first events, not recovered from the third event
J, LIM 2 M, 51 – 60 years	sitagliptin 100 mg diabetes	metformin, simvastatin	diarrhoea, myalgia, photosensitivity	8 months, no change, recovering (these data are applicable to the myalgia)
K, LIM 3 M, 51 – 60 years	sitagliptin 100 mg diabetes	atorvastatin, acetylsalicylic acid, pioglitazone	arthralgia, muscle tightness	3 months, no change, not recovered
L, LIM 4 F, 70 years and older	sitagliptin 100 mg diabetes	glicazide, bisoprolol	arthritis	18 days, drug withdrawn, recovered

Lareb received 12 reports on musculoskeletal effects associated with the use of sitagliptin. Muscle disorder, muscle tightness and arthritis were all reported once. Arthralgia (4 times), myalgia (4 times) and pain of extremities (2 times) were also reported. Sometimes these symptoms were reported in conjunction with other ADRs. These reports concerned 4 males and 8 females. The age ranges from 45-82 years. The latency varies from 3 days to 8 months. In 9 cases the drug was discontinued, of these 5 had recovered.

Discussion and conclusion

The aim of this report was to give an overview of the ADRs associated with the use of sitagliptin using information from both the spontaneous reporting system as well as from the Lareb Intensive Monitoring system.

The chance of receiving reports with rare and serious ADRs through spontaneous reporting is high.
Lareb Intensive Monitoring is a prospective observational cohort study. It follows first time users of a certain drug during a certain time period. By collecting data with this method it is possible to gather information about the frequency of certain ADRs.
In this report the differences between the two systems is visible. All the serious reports were received by spontaneous reporting. Via the intensive monitoring system we can calculate the frequency of ADRs. For example of all patients in the sitagliptin cohort, 21% had reported an adverse drug reaction.

The overall safety profile presented in this report is quite consistent with the information provided in the SmPC of sitagliptin. When analyzing the data, there were two associations that were not labelled in the SmPC but where we have received a number of reports on, namely reactions affecting the respiratory tract and reports on myalgia and arthralgia. These two associations will be analysed further by Lareb in order to see if these might be potential signal. .

References

1. SmPC Januvia®. (version date: 26-8-2010, access date: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000722/WC500039054.pdf.
2. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368(9548):1696-705.
3. College voor Zorgverzekeringen. GIP databank. (version date: 15-10-2009, access date: http://www.gipdatabank.nl/index.asp?scherm=homepage&infoType=a.

This signal has been raised on April 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).