1.1. An overview of reports on mirabegron

Introduction

Mirabegron (Betmiga®) was registered for the European market on 20 December 2012. It is indicated for the treatment of *symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome*. Mirabegron is a potent and selective β_3-adrenoceptor agonist. It works by binding to and activating β_3-receptors that are found in the muscle cells of the bladder. Experimental studies have shown that, when activated, β_3-receptors cause the bladder muscles to relax. This is thought to lead to an increase in the capacity of the bladder and changes in the way the bladder contracts, resulting in fewer bladder contractions and thus fewer unwanted urinations [1].

Mirabegron is a new chemical entity, which is subject to additional monitoring and which is included in the Dutch drug reimbursement system [2]. Lareb noticed that the number of reports on this new drug, also received through the Marketing Authorization Holder (MAH), was increasing relatively rapidly. Therefore Lareb wished to provide the Medicines Evaluation Board (MEB) with an overview of received reports of possible adverse drug reactions (ADRs) associated with the use of mirabegron.

Reports

Between 15 January 2013 and 7 January 2015 the Netherlands Pharmacovigilance Centre Lareb received 54 reports related to the use of mirabegron [3]. These reports contained a total of 128 possible ADRs. Of these reports, 16 (29.1%) were reported as serious according to the CIOMS criteria [3]. None of the reports had a fatal outcome. 25 reports were received through the Marketing Authorization Holder (MAH), 14 by pharmacists, six by specialist doctors, four by physicians and five by patients. An overview of all reported ADRs is presented in Table 1. The reports of serious ADRs are described in more detail in Table 2.

Table 1. Reported ADRs on mirabegron, grouped by system organ class

System Organ Class	Adverse drug reaction (Preferred Term)	**Common and uncommon/rare* ADRs according to SmPC**
cardiac disorders	arrhythmia (2)	tachycardia
	atrial fibrillation (4)	palpitation*
	cardiovascular disorder (1)	atrial fibrillation*
	chordae tendinae rupture (1)	
	mitral valve incompetence (1)	
	palpitations (11)	
	sinus tachycardia (1)	
	tachycardia (3)	
endocrine disorders	diabetes mellitus inadequate control (1)	
eye disorders	vision blurred (1)	eyelid oedema*
gastrointestinal disorders	abdominal distension (1)	dyspepsia*

System Organ Class	Adverse drug reaction (Preferred Term)	**Common and uncommon/rare* ADRs according to SmPC**
	abdominal pain upper (1)	gastritis*
	constipation (2)	lip oedema*
	dyspepsia (1)	
	nausea (1)	
general disorders and administration site conditions	chest discomfort (1)	
	chest pain (1)	
	drug ineffective (3)	
	drug interaction (3)	
	feeling abnormal (2)	
	malaise (2)	
	oedema peripheral (1)	
	peripheral swelling (2)	
	swelling (1)	
	thirst (1)	
immune system disorders	hypersensitivity (1)	
infections and infestations	cystitis (3)	urinary tract infection
	urosepsis (1)	vaginal infection*
		cystitis*
injury, poisoning and procedural complications	drug prescribing error (1)	
	overdose (3)	
investigations	blood creatine phosphokinase increased (1)	blood pressure increased, GGT increased, ASAT increased, ALAT increased
	blood pressure increased (1)	
	blood urine present (1)	
	international normalised ratio fluctuation (1)	
	weight increased (2)	
metabolism and nutrition disorders	decreased appetite (1)	
	lactic acidosis (1)	
musculoskeletal and connective tissue disorders	arthralgia (1)	joint swelling
	finger deformity (1)	
	muscle disorder (2)	

System Organ Class	Adverse drug reaction (Preferred Term)	**Common and uncommon/rare* ADRs according to SmPC**
nervous system disorders	burning sensation (1)	
	dizziness (2)	
	epilepsy (1)	
	headache (3)	
	polyneuropathy (1)	
psychiatric disorders	anxiety (1)	
	confusional state (1)	
	nightmare (1)	
renal and urinary disorders	incontinence (1)	
	micturition disorder (3)	
	micturition urgency (5)	
	nocturia (3)	
	pollakiuria (4)	
	renal failure (1)	
	terminal dribbling (1)	
	urethral pain (1)	
	urinary hesitation (2)	
	urinary incontinence (4)	
	urine flow decreased (5)	
respiratory, thoracic and mediastinal disorders	oropharyngeal blistering (1)	
skin and subcutaneous tissue disorders	angioedema (1)	urticaria, rash, rash macular, rash popular, pruritus
	pruritus (2)	leukocytoclastic vasculitis*
	rash (2)	purpura* (angioedema seen in post-marketing experience)
	skin discolouration (1)	
	urticaria(1)	
surgical and medical procedures	off label use (7)	
vascular disorders	circulatory collapse (1)	
	flushing (1)	

Table 2. Reports of serious ADRs (according to CIOMS criteria [4]) associated with the use of mirabegron

Number **Gender, age** **Reporter**	**Suspected drug**	**Concomitant medication**	**Adverse drug reaction** **(*Labelled in SmPC)**	**Time to onset** **Action drug** **Outcome**
A 174429 F, - MAH	mirabegron 50 mg		arrhythmia heart racing* feeling anxious	unknown unknown unknown
B 175083 F, 61-70 physician	bisoprolol 2,5 mg sitagliptin 50 mg metformin 850mg valsartan 160 mg hydrochloro thiazide 12.5 mg rosuvastatin 10 mg mirabegron 50 mg barnipidine 10 mg		creatine kinase increased renal insufficiency lactic acidosis urosepsis drug interaction	5 days withdrawal of all drugs recovered
C 177637 F, unknown MAH	mirabegron 50 mg		atrial fibrillation*	unknown unknown unknown
D 178556 F, unknown MAH	mirabegron 50 mg		allergic reaction swelling swelling of feet	unknown unknown unknown
E 178597 Unknown MAH	mirabegron 50 mg		cardiovascular disorder nos	unknown unknown unknown
F 179255 F, 61-70 MAH	mirabegron 50 solifenacin		bladder infection lack of drug effect	1 day unknown recovering
G 182121 F, unknown MAH	mirabegron 50 mg		pruritus rash	Unknown unknown not recovered
H 182194 F, unknown MAH	mirabegron 50 mg	fesoterodin	blood in urine	unknown unknown unknown
I 183372	mirabegron 50 mg		polyneuropathy	unknown

F, unknown MAH				drug withdrawn not recovered
J 183413 F, unknown MAH	mirabegron 50 mg	omeprazole pyridostigmin latanoprost calcium colecalciferol hydroxyzine ibandronic acid	tightness in chest palpitations* nausea feeling unwell	unknown unknown recovered
K 185670 F, unknown MAH	mirabegron 50 mg		palpitations*	unknown drug withdrawn unknown
L 185969 F, 71 or older pharmacist	mirabegron 50 mg	paracetamol pantoprazol isosorbide insulin clopidogrel acetylsalicylic acid bumetanide acenocoumarol amitriptyline levothyroxine metoprolol perindopril mebeverine	chest pain sinus tachycardia*	unknonw drug withdrawn unknown
M 186050 M, 71 or older MAH	mirabegron 50 mg	amlodipine	atrial fibrillation* lack of drug effect drug dose prescribing error	unknown dose not changed recovered
N 186102 M, 61-70 physician	mirabegron 50 mg		tachycardia* rupture of chordae tendinae mitral valve incompetence	5 months drug withdrawn not recovered
O 186147 F, unknown MAH	mirabegron 50 mg		atrial fibrillation*	31 days unknown unknown
P 186640 F, unknown	mirabegron 50 mg	valsartan	palpitations* pain urethral	unknown drug withdrawn

MAH	recovered

The following items deserve special attention and will be further described: cardiac disorders, off-label use and drug interactions.

Cardiac disorders

Possible cardiac disorders are a potential risk of mirabegron [1,5].Tachycardia, palpitations and atrial fibrillation are described in the SmPC of mirabegron [1]. Because of these ADRs, the selectivity of mirabegron may be questioned as these symptoms can be explained by β_1-agonistic effects. Regarding the ADRs reported to Lareb, palpitations are relatively often reported. It is interesting to see that of all serious reports associated with the use of mirabegron, 10 reports include one or more cardiac disorder, see Table 2.

Off-label use

Lareb received seven reports of off-label use of mirabegron. These were all reports through the MAH. For six reports the off-label indication was benign prostate hyperplasia (BPH). These patients experienced renal and urinary disorders after start of mirabegron (for example: urinary incontinence, micturition urgency, slowing of urinary stream).

In one report mirabegron was used by a boy of seven years old. The boy used mirabegron for an overactive bladder. There is no further information available. In the reported ADRs with off-label use, confounding by indication could be present.

Drug interactions

Lareb received three reports where a possible drug interaction associated with mirabegron was described by the reporter. None of the reported interactions are described in the SmPC of mirabegron [1]. The causality of these possible drug interactions has not been established.

The first report concerned a possible interaction between mirabegron, rosuvastatin, metformine/sitagliptine, bisoprolol, valsartan and diuretics. The patient experienced increased creatine kinase and lactic acidosis with a latency of 5 days after start of mirabegron. The other drugs were already used for 2 years. The specialist doctor who reported this case did so because of the time relation with the start of mirabegron. All drugs were withdrawn. The patient was treated with antibiotics and bicarbonate. The patient recovered. Concomitant medication was not reported. The patient suffered from urosepsis which, according to the reporter, could be also the cause of a renal insuffiency leading to lactic acid acidosis in a patient already using metformin. The patients renal function had been decreased for a longer time.

This report is also described in Table 2, patient B (175083).

A possible interaction with acenocoumarol was reported (183141). The patient experienced an international normalised ratio (INR) fluctuation 8 hours after intake of mirabegron. Mirabegron had been started 13 days before the reaction occurred. The dose for mirabegron is not changed. The action taken for acenocoumarol is unknown. The patient has not recovered; prior to mirabegron use the patient had stable INR values.

The SmPC describes that mirabegron is a weak inhibitor of CYP3A [1]. The R(+)-enantiomer of acenocoumarol is mainly by metabolised CYP2C9, CYP2C19, CYP1A2 and CYP3A4. Theoretically, this

could contribute to a possible interaction. However, the SmPC of mirabegron describes that no clinically significant drug interactions are expected if mirabegron is used with drugs that inhibit, induce or are a substrate of *one* of CYP isozymes or transport proteins, with the exception of the inhibitory effect on the metabolism of mirabegron of CYP2D6 substrates [1].

The third report concerns an interaction with clopidogrel (183802). The patient experienced palpitations and dizziness with a latency of 1 day after start of mirabegron, clopidogrel was used for almost 1 year. The action taken for clopidogrel is not known. The drug mirabegron was withdrawn. The patient is recovering.

Clopidogrel is a substrate for CYP2C19, and also CYP3A4, CYP1A2 and CYP2B6. Substances that are inducers of CYP3A or P-gp ,decrease plasma concentrations of mirabegron, although no dosage adjustment is necessary for mirabegron [1]. Based on the above, a drug-interaction seems unlikely. The reactions could however be possible ADRs of mirabegron; Palpitations are described in the SmPC, but dizziness is not [1].

Literature

The focus of this literature overview is on the cardiovascular safety of mirabegron as that is a focus-point for Lareb based on the reports received.

In Australia, the Therapeutic Goods Agency (TGA) published a Public Assessment Report for mirabegron [6]. In this assessment the safety of mirabegron is discussed, including the potential increased risk of cardiovascular events. This assessment states that the selectivity of mirabegron for β3-receptors over β1- and β2-adrenoceptors in humans, as well as in the species used in nonclinical studies, is not as great as is suggested from the in vitro data on recombinant receptor subtypes expressed in single cells. In the risk-benefit analysis, delegate considerations were on systemic off-target β-agonist effects of mirabegron. The assessment report states that “Specifically, minor increases in pulse rate and blood pressure have been observed and their potential effect on long term cardiovascular outcomes will need further evaluation via the planned post-marketing database study [6].” The MAH’s response to this consideration includes their objective to conduct a long-term EU and US observational study on cardiovascular events to gather substantial cardiovascular data with mirabegron in the setting of real-world medical practice [6].

Also a summary of safety and efficacy as basis for an Advisory Committee briefing document for mirabegron from the US Food and Drug Administration (FDA) mentions that the key safety issues for mirabegron include cardiovascular safety (effects on blood pressure, heart rate, and cardiovascular AEs), neoplasms, hepatic safety, urinary tract related adverse events, and hypersensitivity reactions [7,8]. It should be noted that the FDA mentions that there is no known common mechanistic explanation to implicate mirabegron as related to any cancers or growth of existing tumors [7].

In a pooled 12-week analysis, mirabegron 50 mg was associated with placebo-adjusted mean increases of 0.4-0.6 mmHg in blood pressure and approximately one beat per minute in pulse rate, both reversible upon treatment discontinuation. The incidence of major adverse cardiovascular events as adjudicated by an independent cardiovascular committee was low and similar across treatment groups [9].

There was an absence of clinically relevant cardiovascular interaction upon add-on of mirabegron or tamsulosin to an established tamsulosin or mirabegron treatment in a small open-label study in 48 healthy middle-aged to elderly men [10].

The risk and severity of developing symptomatic palpitations when prescribed mirabegron for overactive bladder was studied in a consecutive cohort of patients with OAB between February 2013 and June 2014. Patients were prescribed mirabegron 50 mg daily and outcomes assessed at 6 weeks. Patients with known cardiac arrhythmias were excluded. In patients who developed palpitations, a detailed account of their symptoms and medical history were documented and a 12-lead electrocardiogram (ECG) was performed to assess heart rate, QT interval and the presence of any persisting arrhythmia was conducted. A total of 279 patients were started on mirabegron. Eight patients (2.9%) reported palpitations whilst taking the drug. Two patients with a history of palpitations with no history of prolonged QT interval or arrhythmia on ECG developed worsening palpitations. The QTc was prolonged in two patients at 0.458 and 0.441 s (QTc <420). Three patients developed chest pain or tightness. The palpitations resolved once therapy was stopped and did not result in serious adverse events such as hospitalisation. The authors conclude that palpitations in an unselected population have a similar incidence to that demonstrated in previous drug trials. Palpitations may be associated with a worsening of cardiovascular dysfunction [11].

Based on the pharmacology of mirabegron there are a number of other ADRs that could theoretically occur. One of these is described below.

In common with other β3-adrenoceptor agonists, mirabegron was originally developed as a treatment for obesity and type 2 diabetes [6]. Increasing energy expenditure through activation of endogenous brown adipose tissue (BAT) is a potential approach to treat obesity and diabetes. The class of β3-adrenergic receptor (AR) agonists stimulates rodent BAT [12], but this activity had never been demonstrated in humans. Mirabegron led to higher BAT metabolic activity as measured via (18)F-fluorodeoxyglucose ((18)F-FDG) using positron emission tomography (PET) combined with computed tomography (CT) in twelve healthy male subjects (p = 0.001), and it increased resting metabolic rate (RMR) by 203 ± 40 kcal/day (+13%; p = 0.001) [13]. Against expectations, Lareb received 2 reports of weight gain. For one patients the number of kg weight gain was reported, in the month that patient used mirabegron she gained 5,5 kg in weight. This is most probably due to edema and not to brown adipose tissue.

Conclusion

As shown from this overview, the ADRs reported to the Netherlands Pharmacovigilance Centre Lareb are generally consistent with the information provided in the SmPC of mirabegron [1]. Off all 54 reports, 16 were concerned serious according to CIOMs criteria [4]. None of the reports had a fatal outcome.

One concern of the use of mirabegron is the possible cardiac disorders. Given the fact that mirabegron is known to cause palpitations and tachycardia, it is possible that it also has affinity for the β_1-adrenergic receptor. A possible role for β3-adrenoceptors in human cardiac function remains controversial [14]. The SmPC of mirabegron only describes caution in severe uncontrolled hypertensive patients and in patients with a known history of QT prolongation or taking medicinal products known to prolong QT interval [1]. Caution should also be in place for patients with other cardiac disorders until more information on the cardiac safety profile of this drug becomes available.

The safety of mirabegron during off label use deserves special attention. All patients using mirabegron off-label, and for which the indication was BPH, experienced urinary disorders. These reports may be biased by confounding by indication.

Since mirabegron is market for only 2 years now, possible new ADRs may come to light in the future. Lareb will continue to monitor the safety of this drug and will inform the Medicines Evaluation Board of any new signals related to the use of this drug.

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This overview was published in 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