bijwerkingen centrumlareb

Lack of effect after substitution of methylphenidate prolonged-release

Introduction

Methylphenidate prolonged-release (Concerta®, Equasym® XL, Medikinet® CR, Ritalin® LA, Kinecteen®) is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) for children and adolescents between 6 and 18 years old [1]. The guideline of the Dutch Association for Psychiatry mentions methylphenidate as drug of first choice for treatment of adults with ADHD preferably with long-acting products [2]. Long-acting products, like Concerta®, can be taken once daily minimizing the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily [1].

In the Netherlands, Concerta® was granted market authorization on 21 November 2002 [1]. Since June 2014 two generics of Concerta® have been authorized, namely methylphenidate prolonged-release Sandoz as of October 2013 [3] and methylphenidate prolonged-release Mylan as of June 2014 [4]. In June 2016 Mylan was granted market authorization for an extra strength 27mg [5]. Both the Sandoz and Mylan products are considered to be bioequivalent to the reference product (Concerta) [4-6].

Reports

From 8 April 2014 until 30 April 2017, the Netherlands Pharmacovigilance Centre Lareb received 75 reports of adverse drug reactions (ADRs) that occurred after substitution of methylphenidate prolonged-release. Reporters were both healthcare professionals and consumers with almost a fifty-fifty share. Of these reports, 29 concerned substitution of Concerta® into methylphenidate prolonged-release Sandoz, 36 Concerta® into methylphenidate prolonged-release Mylan and two methylphenidate prolonged-release Sandoz into methylphenidate prolonged-release Mylan. There were also three reports concerning substitution of Concerta® into methylphenidate prolonged-release of an unspecified brand, three reports where the previous used brand is unknown and two reports concerned substitution of Equasm® XL or Medikinet® CR, which are not bioequivalent to Concerta® or its generics, into one of these. In the following sections the reports concerning substitution of Concerta® into methylphenidate prolonged-release Sandoz or Mylan will be discussed in more detail.

Table 1 Overview of the six types of substitution mentioned in the 75 reports concerning substitution of methylphenidate prolonged-release

Substitution of	Into	Number of reports
Concerta®	Methylphenidate prolonged-release Sandoz	29
Concerta®	Methylphenidate prolonged-release Mylan	36
Methylphenidate prolonged-release Sandoz	Methylphenidate prolonged-release Mylan	2
Concerta®	Methylphenidate prolonged-release unknown brand	3
Methylphenidate prolonged-release unknown brand	Methylphenidate prolonged-release unknown brand, Sandoz or Mylan	3
Equasm® XL or Medikinet® CR	Concerta® or Methylphenidate prolonged-release Mylan	2

Substitution of Concerta® into methylphenidate prolonged-release Sandoz

Of the 29 reports concerning substitution of Concerta® into methylphenidate prolonged-release Sandoz, 19 concerned males and ten females. The patients were between 8 – 51 years of age with a median of 18.5 years. Twenty-five reports mention changes in behavior and/or a decreased, shorter or no effect after substitution. These behavioral changes include abnormal behavior, aggression, anger, irritability, altered mood, concentration problems and daydreaming. None of the reports mentioning a shorter or decreased effect specify the shorter effect in time. Four reports mention only general ADRs, like nausea, headache and somnolence. In about half of the reports the reports the reactions started within one day after substitution with eight reports mentioning a time to onset of one hour or less. In 83% of the reports reactions started within one week after substitution. Eighteen reports mention recovery after switching back to Concerta® and in three reports the patients recovered after withdrawal of methylphenidate prolonged-release Sandoz. Time to recovery is mostly unknown, but if mentioned

this was shortly after withdrawal or re-substitution. All 29 reports can be found in Table 1 in the appendix.

Reports concerning substitution of Concerta® into methylphenidate prolonged-release Mylan

Of the 36 reports concerning substitution of Concerta® into methylphenidate prolonged-release Mylan, 19 concerned females and 17 males. The patients were between 8 – 57 years of age with a median of 14 years. Thirty-five reports mention behavioral changes, a suspected irregular or unreliable release and/or a decreased, shorter or no effect after substitution. One report mentions none of these reactions. The behavioral changes include sleeping disorders, abnormal behavior, agitation, aggression, restlessness, concentration problems, mood swings and depressed mood. Five reports co-report a product quality issue, namely the falling apart of tablets when stored in the original container. Only one of the reporters mentions that this is the cause of the previously mentioned unreliable release of methylphenidate from the tablets. In eight reports the shorter effect is specified; the effect of Concerta® is in a range of 7 – 12 hours and the effect of methylphenidate prolonged-release Mylan between 4 – 8 hours. In about half of the reports the reactions started within one day after substitution with seven reports mentioning a time to onset of one hour or less. In 83% of the reports reactions started within one week after substitution. Twenty-three reports mention recovery after switching back to Concerta® and in four reports the patients recovered after withdrawal of methylphenidate prolonged-release Mylan. Time to recovery is mostly unknown, but if mentioned this was shortly after withdrawal and/or switching back to Concerta®. All 36 reports can be found in Table 2 in the appendix.

Literature

Adverse reactions

The Summary of Product Characteristics (SmPC) of methylphenidate prolonged-release products describe various behavioral and psychic reactions as side effects, for example: aggression, agitation, depression, insomnia, restlessness and mood changes. These reactions are mentioned as common (up to 1 in 10 people) or uncommon (up to 1 in 100 people) [1,3-5].

Release systems and effectiveness

Both Concerta® and methylphenidate prolonged-release Sandoz have an osmotic controlled release system [7,8]. The methylphenidate in the outer layer provides the immediate release while the methylphenidate within the membrane is delivered at a first-order rate for a longer period after administration [9]. Methylphenidate prolonged-release Mylan contains an immediate release fraction and a prolonged-release fraction the latter provided by sugar spheres [4,5]. For Concerta® and methylphenidate prolonged-release Sandoz it is advised not to divide the tablets, but the three highest strengths of methylphenidate prolonged-release Mylan are pre-scored, so they can be easily halved [1,3-5].

Both oral intake of Concerta® and methylphenidate prolonged-release Sandoz, results in an initial maximal concentration of methylphenidate after 1-2 hours. The maximum plasma concentration is reached after 6-8 hours after which the concentration methylphenidate slowly decreases [1,3]. For methylphenidate prolonged-release Mylan the immediate-release phase results in a maximum plasma concentration after 1.35 hours and the prolonged-release phase gives a second peak after 5.3 hours [4,5]. The effect of all three products should last for 12 hours after a once daily intake in the morning [1,3-5].

In May 2015, the Danish Pharmacovigilance Centre reported that they had tested methylphenidate prolonged-release Sandoz as a response to many reports of substitution problems and lack of efficacy after switching from Concerta® to Sandoz. The results showed similarity between Concerta® and methylphenidate prolonged-release Sandoz and the Danish Pharmacovigilance Centre concluded that based on the laboratory results there is no difference between both products. But they considered the number of ADR reports to be a signal which was forwarded to the drug regulatory agency responsible for monitoring all methylphenidate-containing products in the EU [10].

Methylphenidate cost, reimbursement and prescription data

In the Netherlands most drugs are reimbursed out of the basic healthcare insurance. For some drugs patients have to pay an own contribution which could be paid for by their insurance if they have an additional insurance package. One of these drugs is methylphenidate prolonged-release [11]. Most Dutch healthcare insurance companies have a preference policy regarding drug brands they reimburse, for example one of the healthcare insurance companies has chosen methylphenidate prolonged-release Mylan as their preference product in 2017 for methylphenidate prolonged-release products [12].

Table 2 Price of Concerta®, methylphenidate prolonged-release Sandoz and methylphenidate prolonged-release Mylan per 30 tablets as of June 2017 [13]

Strenght	**Concerta®**		**Methylphenidate prolonged-release Sandoz**		**Methylphenidate prolonged-release Mylan**	
	Costs	**Own contribution**	**Costs**	**Own contribution**	**Costs**	**Own contribution**
18 mg	€ 34.31	€ 27.38	€ 22.47	€ 15.54	€ 22.47	€ 15.54
27 mg	€ 40.25	€ 29.85	-	-	€ 34.21	€ 23.80
36 mg	€ 41.48	€ 27.61	€ 24.54	€ 10.67	€ 24.54	€ 10.67
54 mg	€ 49.08	€ 28.27	€ 28.30	€ 7.50	€ 28.30	€ 7.50

Table 3 Number of patients using methylphenidate prolonged-release in the Netherlands from 2011 – 2015 [14]

	2011	**2012**	**2013**	**2014**	**2015**
Concerta® 18 mg	17,098	17,121	16,600	16,131	11,072
Concerta® 27 mg	14,557	16,072	16,905	17,635	18,536
Concerta® 36 mg	30,397	31,222	31,761	28,513	20,859
Concerta® 54 mg	20,696	22,086	23,233	21,456	15,948
methylphenidate prolonged-release 18 mg brand unknown	-	-	-	1,881	8,085
methylphenidate prolonged-release 27 mg brand unknown	-	-	-	-	-
methylphenidate prolonged-release 36 mg brand unknown	-	-	-	12,511	17,811
methylphenidate prolonged-release 54 mg brand unknown	-	-	-	10,005	13,427

Discussion and conclusion

In the Netherlands, drug substitution is often the result of the preference policy of healthcare insurance companies or of drug shortages. For methylphenidate prolonged-release products there can be three reasons of substitution, namely: i) the preference policy of healthcare insurance companies, ii) to reduce the own contribution of the patient or iii) pharmacies dispense the for them financially most preferable drug brand depending on the contract they have with the healthcare insurance companies [15].

Drug substitution of brands into generics often leads to complaints as patients have a poor opinion of and mistrust in generics [16]. A review by Håkonsen et al showed that 8-34% of patients having their drugs substituted into a generic reported poorer effects and/or new side effects after substitution [17].

The reports of ADRs after substitution received by Lareb concern mostly changes in behavior and/or a decreased, shorter or no effect after substitution. Behavioral changes are symptoms of ADHD, but in the reports stands out that most patients, often children, recovered after switching back to Concerta®. So the reported behavioral changes, like daydreaming and concentration problems, are likely to be signs of a decreased effect after substitution. The times to onset of the various reactions vary from minutes to a few months after substitution. The short times to onset could be the result of a difference in release of the immediate-release phase, while longer times to onset could be explained that parents and caretakers realized only at a later stage that the child's behavior had changed for a longer period. Although there are seven reports that mention a shorter or decreased effect after switching from Concerta® to methylphenidate prolonged-release Sandoz, none of these specify this shorter effect in

time. But half of the reports of a shorter or decreased effect after substitution of Concerta® to methylphenidate prolonged-release Mylan mentioned that Mylan works 3 – 4 hours less than Concerta®.

During the repeat-use mutual recognition procedure, Germany and the Netherlands expressed their concerns about bioequivalence in a fed-study for the immediate-release phase between Concerta® and Sandoz. They highlighted that the use of partial metrics under fed condition was considered necessary as Concerta®, the reference product, can also be taken with food. Therefore bioequivalence under fed conditions for the two phases of absorption (immediate and prolonged-release phase) should be demonstrated. Sandoz augmented that this was the result of intra-individual differences [6]. The subject of the referral was the design of the fed study, in which a high variability was observed and the confidence intervals for the ratios of Cmax0-2 and AUC0-2 (partial metrics for the first absorption phase) were outside the standard limits of 85-125%. However, according to the MEB, it is known from the innovator dossier that the first absorption phase is characterized by a very high intra-subject variability under fed conditions due to subject-related physiological effects. During the referral procedure, it was concluded however, that since the point estimates for both Cmax and AUC in the first absorption phase were close to 100%, there is no indication towards different plasma concentrations for the generic formulation, and the observed variability was due to subject-related physiological effects and not due to inferior quality of the generic formulation. Therefore, widening of the limits for confidence intervals was agreed upon and bioequivalence under fed conditions between Methylphenidate Sandoz and Concerta has therefore been concluded.

For the reported ADRs after substitution from Concerta® into methylphenidate prolonged-release Mylan, the difference in release system (osmotic controlled release vs delayed release via sugar spheres) could be the explanation for the difference in effect. This is supported by the difference in pharmacokinetic parameters as the initial peak concentration is seen after 2 hours with Concerta® vs 1.35 hours with Mylan and the second peak concentration after 6-8 hours vs 5.3 hours respectively. As Sandoz also has an osmotic controlled release system, two cases Lareb received of substitution problems after switching from Sandoz to Mylan could be seen as supportive (Table 3 in appendix). One of these cases mentions that when the patient switched from Concerta® to Sandoz he experienced no ADRs, but after substitution of Sandoz into Mylan the patient experienced three hour less effect with Mylan compared to Sandoz. However, according to the MEB, the different pharmacokinetic parameters reported in the SPC of Methylphenidate Mylan as compared to Concerta does not imply that Methylphenidate Mylan has a different pharmacokinetic profile or that Methylphenidate Mylan is not bioequivalent to Concerta. This is reflected in section 5.2 the Mylan SmPC [4,5].

This signal focused on reports of ADRs and lack of efficacy following substitution of Concerta® into one of its generics. Taking into account the previous investigation into reports of substitution problems of after switching from Concerta® to Sandoz and the specifics of the reports of substitution of Concerta® to Mylan, the current focus should be on the reports where the difference in release system could be explanatory for the reported ADRs and lack of efficacy.

References

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Appendix 1

Table 1. Reports of ADRs after drug substitution of Concerta® into methylphenidate prolonged-release Sandoz

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug, outcome
A 171606 M, 11-20 years, Specialist doctor	methylphenidate hcl Sandoz retard tablet mva 36mg, Attention deficit-hyperactivity disorder		drug ineffective, nausea, abdominal pain	2 hours, Drug withdrawn, recovered
B 173896 M, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 54mg, Attention deficit-hyperactivity disorder		aggressive behaviour.	48 hours, Drug withdrawn, Recovered
C 175302 F, 8-10 years, Hospital pharmacist	methylphenidate hcl Sandoz retard tablet mva 54mg, Attention deficit-hyperactivity disorder	Atomoxetine, aripiprazol, methylphenidate, melatonine	abnormal behaviour, aggressive behaviour,	0 days, Drug withdrawn, Recovered
D 176421 M, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 54mg, ADHD	Melatonine	therapeutic response decreased, gastrointestinal discomfort	2 days, Drug withdrawn, Recovered
E 176433 F, 41-50 years, General Practitioner	methylphenidate hcl Sandoz retard tablet mva 54mg, Attention deficit-hyperactivity disorder		drug ineffective, tablet in stool	4 days, Drug withdrawn, Recovered
F 176506 F, 41-50 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 54mg, ADHD		therapeutic response decreased	1 hour, Drug withdrawn, Recovered
G 177597 M, 11-20 years, Specialist doctor	methylphenidate hcl Sandoz retard tablet mva 54mg, Concentration impairment		drug ineffective (controlled release differs from Concerta®)	Unknown weeks, Drug withdrawn, not yet recovered
H 177950 F, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36mg, Attention deficit-hyperactivity disorder		drug ineffective	2 days, Dose not changed, not recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug, outcome
I, 178942, M, 11-20 years, Pharmacist	methylphenidate hcl Sandoz retard tablet mva 54mg, ADHD		drug ineffective	1 day, Drug withdrawn, Recovered
J, 182138, M, 11-20 years, Pharmacist	methylphenidate hcl Sandoz retard tablet mva 36mg, ADHD		drug effect decreased	Unknown, Drug withdrawn, Unknown
K, 186759, M, 8-10 years, Physician	methylphenidate hcl Sandoz retard tablet mva 36mg, ADHD		drug effect decreased	< 1 month, Drug withdrawn, Recovered
L, 188308, M, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 18 mg, Autism	oxcarbazepine, levetiracetam	drug ineffective	4 days, Drug withdrawn, Recovered
M, 189877, M, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36 mg, ADHD		nausea, malaise	1 hour, Drug withdrawn, Recovered
N, 193300, F, 31-40 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit disorder	estradiol/norethisteron, fluoxetine	mood altered, dizziness	7 days, Drug withdrawn, Recovered
O, 194842, M, 41-50 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 54mg, Attention deficit-hyperactivity disorder		therapeutic response decreased	1 hour, Dose not changed, Not recovered
P, 197989, M, 51-60 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 54 mg, Attention deficit-hyperactivity disorder	trazodon	somnolence	2 weeks, Dose not changed, Not recovered
Q, 200060, F, 41-50 years, Physician NOS	methylphenidate hcl Sandoz retard tablet mva 18 mg, Pervasive developmental disorder NOS	Melatonine nitrazepam	depressed mood, sleep disorder, suicidal ideation	Within a day, Drug withdrawn, Recovered
R, 201750, M, 8-10 years, Pharmacist	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit-hyperactivity disorder	melatonine	abdominal discomfort, disturbance in attention,	2 days, Drug withdrawn, Recovered
S, 206496, F, 41-50 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit-hyperactivity disorder		drug ineffective	30 minutes, Drug withdrawn, Recovered
T, 206497, M, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit-hyperactivity disorder		drug ineffective	30 minutes, Drug withdrawn, Recovered
U, 206498, M, 8-10 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit-hyperactivity disorder		drug ineffective,	30 minutes, Drug withdrawn, Recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug, outcome
V, 207695, M, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 54mg, Attention deficit/hyperactivity disorder		nausea	15 minutes, Dose not changed, Not recovered
W, 213461, M, 11-20 years, Pharmacist	methylphenidate hcl Sandoz retard tablet mva 54mg, Drug use for unknown indication		nausea, throat irritation, headache	Unknown hours, Unknown, Unknown
X, 213594, M, 11-20 years, Specialist doctor	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit disorder		therapeutic response decreased	2 weeks, Drug withdrawn, Recovered
Y, 214762, F, 21-30 years, Specialist doctor	methylphenidate hcl Sandoz retard tablet mva 54 mg, Attention deficit-hyperactivity disorder	sertraline	therapeutic response decreased, headache, thirst, dry mouth	Unknown days, Unknown, Recovered
Z, 217405, F, 11-20 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit-hyperactivity disorder		daydreaming, irritability, drug ineffective	1 day, Drug withdrawn, Recovered
AA, 217835, M, 11-20 years, Specialist doctor	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit-hyperactivity disorder		headache, chest discomfort, disturbance in attention, agitation	1 day, Drug withdrawn, Recovered
AB, 217913, M, 11-20 years, Specialist doctor	methylphenidate hcl Sandoz retard tablet mva 18mg, Attention deficit-hyperactivity disorder		drug ineffective, anger, disturbance in attention	1 day, Drug withdrawn, Recovering
AC, 220119, F, 41-50 years, Consumer	methylphenidate hcl Sandoz retard tablet mva 36 mg, Attention deficit disorder	colecalciferol	drug ineffective, fatigue, paraesthesia oral, swollen tongue, dizziness	minutes - 3 hours, Drug withdrawn, Recovered

Patient B, C, D, E, F, I, K, L, M, N, Q, R, S, T, U, X, Z, AA: Recovered after withdrawal Sandoz and switching back to Concerta®
Patient A, AB, AC: Recovered after withdrawal of Sandoz, unknown if Concerta® was restarted
Patient G, J: Unknown if patient recovered after withdrawal Sandoz and switching back to Concerta®
Patient H, O, P: No withdrawal of Sandoz.
Patient V, W, Y: Unknown if Sandoz was withdrawn

Table 2. Reports of ADRs after drug substitution of Concerta® into methylphenidate prolonged-release Mylan

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug outcome
A, 186573, F, 21-30 years, Consumer	methylphenidate hcl Mylan retard tablet 36mg, ADHD	ethinylestradiol/ levonorgestrel	headache, panic attack, disturbance in attention, fatigue, mood swings, dizziness, psychomotor hyperactivity, dry throat, muscle tightness, vision blurred	minutes – 3 hours, unknown, not recovered
B, 188651, M, 31-40 years, Consumer	methylphenidate hcl Mylan retard tablet 18 mg, methylphenidate hcl Mylan retard tablet 54 mg, Attention deficit-hyperactivity disorder		drug ineffective	6 hours, unknown, Recovered
C, 188808, M, 11-20 years, Pharmacist	methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit-hyperactivity disorder	insuline aspart	drug ineffective	Within 1 week, Drug withdrawn, Recovered
D, 188829, M, 51-60 years, Consumer	methylphenidate hcl Mylan retard tablet 36 mg, ADHD	desloratadine	feeling hot, dyspnoea, cough, headache, tremor	1 hour, Drug withdrawn, Recovered
E, 189878, M, 8-10 years, Consumer	methylphenidate hcl Mylan retard tablet 36 mg, ADHD		therapeutic response decreased, nausea, gastrooesophageal reflux disease, restlessness, agitation	1 hour, Drug withdrawn, Recovered
F, 192520, M, 21-30 years, General Practitioner	methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit-hyperactivity disorder		depressed mood, decreased appetite, insomnia	Within a few days, Drug withdrawn, Recovered Positive rechallenge
G, 193088, F, 21-30 years, Pharmacist	methylphenidate hcl Mylan retard tablet 54 mg, Attention deficit-hyperactivity disorder		restlessness, visual impairment	2 hours, Drug withdrawn, Recovering
H, 193672, F, 11-20 years, Pharmacist	methylphenidate hcl Mylan retard tablet 36mg, Attention deficit-hyperactivity disorder		aggression, emotional disorder, suicidal ideation	20 days, Drug withdrawn, Recovering
I, 193688, M, 11-20 years, Specialist doctor	methylphenidate hcl Mylan retard tablet 36mg, Attention deficit-hyperactivity disorder		therapeutic response decreased	1 day, Drug withdrawn, Recovered
J, 194264, F, 51-60 years, Consumer	methylphenidate hcl Mylan retard tablet 18mg, Attention deficit-hyperactivity disorder	cetirizine, colecalciferol	therapeutic response decreased	6 hours, Drug withdrawn, Recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug outcome
K, 194628, F, 11-20 years, Consumer	methylphenidate hcl Mylan retard tablet 18mg, Attention deficit disorder	ethinylestradiol/ drospirenon, desloratadine, fluticasone, paracetamol	anxiety, lethargy, disturbance in attention, aggression, mood swings, myalgia, arthralgia pain in extremity, feeling abnormal	7 days, Drug withdrawn, Not recovered 14 days, Drug withdrawn, Not recovered
L, 195990, F, 11-20 years, Consumer	methylphenidate hcl Mylan retard tablet 54mg, Attention deficit disorder	Cetirizine	therapeutic response decreased	5 hours, Drug withdrawn, Recovered
M, 200223, F, 41-50, years, Consumer	methylphenidate hcl Mylan retard tablet 54mg, Attention deficit-hyperactivity disorder	Short-acting methylphenidate	therapeutic response decreased, product quality issue	2 days, Drug withdrawn, Recovered
N, 200239, F, 31-40 years, Consumer	methylphenidate hcl Mylan retard tablet 36mg, methylphenidate hcl Mylan retard tablet 54mg, Attention deficit-hyperactivity disorder		drug ineffective	2 hours, Drug withdrawn, Recovered
O, 202511, M, 11-20 years, Consumer	methylphenidate hcl Mylan retard tablet 18mg, methylphenidate hcl Mylan retard tablet 54mg, Attention deficit-hyperactivity disorder	melatonine	therapeutic response decreased	5 days, Drug withdrawn, Not recovered
P, 202663, M, 41-50 years, Consumer	methylphenidate hcl Mylan retard tablet 54mg, Attention deficit disorder	citalopram	therapeutic response decreased, product quality issue	Within days, Drug withdrawn, Recovered
Q, 202666, M, 21-30 years, Pharmacist	methylphenidate hcl Mylan retard tablet 18mg, Attention deficit-hyperactivity disorder		tremor, sleep disorder, nausea	Within days, Drug withdrawn, Unknown
R, 202926, M, 51-60 years, Consumer	methylphenidate hcl Mylan retard tablet 36mg, Attention deficit-hyperactivity disorder	fluticasone	dry mouth, agitation, sleep disorder, hyperhidrosis, abnormal dreams	1 day, Drug withdrawn, Recovered
S*, 203660, F, 31-40 years, Consumer	methylphenidate hcl Mylan retard tablet 36mg, methylphenidate hcl Mylan retard tablet 54mg, Attention deficit disorder	methylphenidate mga (Medikinet CR), ethinylestradiol/ levonorgestrel	therapeutic response unexpected (controlled release unreliable), product quality issue	3 hours, Drug withdrawn, Recovered
T, 204234, M, 11-20 years, Specialist doctor	methylphenidate hcl Mylan retard tablet 36mg, Attention deficit-hyperactivity disorder		therapeutic response decreased, product quality issue	Within 2 months, Drug withdrawn, Recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug outcome
U, 205598, F, 21-30 years, Consumer	methylphenidate hcl Mylan retard tablet 36mg, methylphenidate hcl Mylan retard tablet 18mg, Attention deficit disorder		drug ineffective, rebound effect	1 hour, Drug withdrawn, Recovered
V, 207748, F, 11-20 years, Consumer	methylphenidate hcl Mylan retard tablet 36mg, Attention deficit-hyperactivity disorder		drug ineffective, initial insomnia, product quality issue	8 hours, Drug withdrawn, Recovered
W, 213200, F, 11-20 years, Consumer	methylphenidate hcl Mylan retard tablet 54mg, Attention deficit disorder		peripheral coldness, depressed mood, drug effect decreased	1 day, Drug withdrawn, Recovered
X, 218118, F, 11-20 years, Specialist doctor	methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit-hyperactivity disorder	melatonine	irritability, disturbance in attention, abnormal behaviour	1 day, Drug withdrawn, Not recovered
Y, 219149, F, 21-30 years, Consumer	methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit disorder		depressed mood, panic attack	1-7 hours, Drug withdrawn, Recovered
Z, 223929, F, 31-40 years, Consumer	methylphenidate hcl Mylan retard tablet 54mg, methylphenidate hcl Mylan retard tablet 36mg, ADHD	methylphenidate	nausea, affect lability	10 minutes, Unknown, Not recovered
AA, 225356, F, 31-40 years, Consumer	methylphenidate hcl Mylan retard tablet 54mg, Attention deficit/hyperactivity disorder		Aggression, depressed mood, mood swings	Unknown, Drug withdrawn, Recovered
AB, 228966, M, 51-60 years, Consumer	methylphenidate hcl Mylan retard tablet 36 mg, methylphenidate hcl Mylan retard tablet 54 mg, Attention deficit-hyperactivity disorder	venlafaxine	product quality issue (irregular release)	Unknown, Dose not changed, Unknown
AC, 233240, M, 31-40 years, Consumer	methylphenidate hcl Mylan retard tablet 27 mg, Attention deficit/hyperactivity disorder		agitation, head discomfort, fatigue, disturbance in attention	4 days, Unknown, Not recovered
AD, 236234, F, 11-20 years, Physician NOS	methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit/hyperactivity disorder	melatonine	disturbance in attention, therapeutic response shortened, executive dysfunction	1 week, Drug withdrawn, Recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug outcome
AE, 236235 = 236237, M, 8-10 years, Physician NOS	methylphenidate Mylan tablet 10mg, methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit/hyperactivity disorder		rebound effect, irritability, restlessness, therapeutic response shortened, disturbance in attention	METHYLPHENIDATE TABLET 10MG 2 weeks, Drug withdrawn, Recovered, METHYLPHENIDATE TABLET MGA 36MG 2-3 weeks, Drug withdrawn, Recovered
AF, 236236, F, 11-20 years, Physician NOS	methylphenidate hcl Mylan retard tablet 27 mg, Attention deficit/hyperactivity disorder	melatonine	disturbance in attention, therapeutic response shortened, fatigue, educational problem	1 week, Drug withdrawn, Recovered
AG, 236238, M, 8-10 years, Physician NOS	methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit/hyperactivity disorder	melatonine	therapeutic response shortened, tic, disturbance in attention, condition aggravated	1 week, Drug withdrawn, Recovered
AH, 236239, M, 11-20 years, Physician NOS	methylphenidate hcl Mylan retard tablet 36 mg, Autism	Short-acting methylphenidate	therapeutic response shortened, disturbance in attention, malaise, executive dysfunction, irritability	2 weeks, Drug withdrawn, Recovered
AI, 236242, F, 11-20 years, Physician NOS	methylphenidate hcl Mylan retard tablet 54 mg, Attention deficit/hyperactivity disorder	Short-acting methylphenidate	therapeutic response shortened, rebound disturbance in attention, effect, educational problem	1 week, Drug withdrawn, Recovered
AJ, 236244, M, 8-10 years, Physician NOS	methylphenidate hcl Mylan retard tablet 27 mg, Attention deficit/hyperactivity disorder	melatonine	irritability, disturbance in attention, nausea, abdominal pain, abnormal behaviour	Several days, Drug withdrawn, Recovered

* Reporter mentions the split tablets result in a decreased effect
Patient C, D, E, F, H, I, J, L, M, N, P, R, S, U, V, AA, AD, AF, AG, AH, AI, AJ: Recovered after withdrawal of Mylan and switching back to Concerta®
Patient AE: Recovered after withdrawal of Mylan and switching back to Concerta®. Also these reaction with short-acting methylphenidate Mylan of which patient recovered after switching to short-acting methylphenidate Sandoz
Patient K, O, Q, X : Unknown if patient recovered after withdrawal Sandoz and switching back to Concerta®
Patient G, T, W, Y: Unknown if patient switched back to Concerta® after withdrawal Mylan
Patient A, B, Z, AB, AC: Unknown if Mylan was withdrawn

Patient B: Effect of Mylan is 2-3 hours shorter then Concerta®
Patient I: Effect Concerta® 11-12 hours, Mylan 7-8 hours
Patient J: Effect Concerta® 11 hours, Mylan 6,5 hours
Patient L: Effect Concerta® 10 hours, Mylan 5 hours
Patient M: Effect Concerta® 7-8 hours, Mylan 4 hours.
Patient AD, AE, AF: Effect Concerta® 12 hours, Mylan 8 hours
Patient AG: Effect Concerta® 11 hours, Mylan unknown

Table 3. Reports of ADRs after drug substitution of methylphenidate rolonged-release Sandoz into methylphenidate prolonged-release Mylan

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected ADRs (other than therapeutic response unexpected with drug substitution)	Time to onset, Action with drug outcome
A, 188089, M, 21-30 years, Consumer	methylphenidate hcl Mylan retard tablet 18 mg, ADHD		therapeutic response decreased	6 hours, Drug withdrawn, Recovered
B, 235541, M, 41-50 years, Pharmacist	methylphenidate hcl Mylan retard tablet 36 mg, Attention deficit/hyperactivity disorder	olanzapine, folic acid	drug ineffective	1 hour, Drug withdrawn, Recovered

Patient A: Recovered after withdrawal of Mylan and switching back to Sandoz. Had no complaints when switching from Concerta® to Sandoz
Patient B: Recovered after withdrawal of Mylan and switching back to Sandoz

Patient A: Effect Concerta, Sandoz 8-9 hours, Mylan 5-6 hours

This signal has been raised on October 30, 2017. 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