Overview on reports of adverse drug reactions related to drug substitution

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bijwerkingen centrumlareb

Contents

Abstract

The Netherlands Pharmacovigilance Centre Lareb regularly receives reports of adverse drug reactions (ADRs) after patients' brand of drugs have been changed (generic substitution). Often, these reports also mention a reduced drug efficacy. Usually these switches between brands of drugs are a result of the Preference Policy of Dutch Health Insurance companies, but drug shortages of a particular brand can also play a role.

This report provides an overview of reports to Lareb on ADRs related to generic drug substitution. The past ten years a total of more than 2,500 reports was received. Upon further analysis of drugs with more than 25 reports, in the majority there appeared to be no distinct pattern in the switching (brands) or reported ADRs. Eight analysis did provide a clearer picture. Drugs which have indeed led to Signals of problems after substitution are:

- Dysregulation of patients after switches of the thyroid hormone levothyroxine
- Breakthrough bleeding on oral contraceptives with ethinylestradiole and levonorgestrel
- Reduced efficacy with inhalation drugs for the treatment of asthma; salbutamol and fluticasone/ salmeterol
- Skin reactions and curling of patches with rivastigmine
- Injection site pain and injection site reactions with methotrexate
- Reduced efficacy with anti-epileptics

Although generic drug substitution of certain classes of drugs, such as anti-epileptics, is not recommended in the guideline of pharmacists' organisation KNMP, the reports to Lareb demonstrate that in practice this does occur. Because of the Preference Policy of Health Insurance companies, but sometimes due to drug shortages, often large groups of patients are switched in a short time from one drug to another drug. It is currently difficult to find information about the timing of these switches, which products they entail and numbers of patients involved.

Often, these switches occur without any problems. But patients must be able to trust that when issues do occur, there will be quick insight and appropriate action can be taken.

A more pro-active monitoring of patients is desired in case large groups of patients are switched in a short period of time, in order to gain insight into the possible problems that patients encounter after drug substitution and to prepare patients for the switch.

Samenvatting

Bijwerkingencentrum Lareb ontvangt met regelmaat meldingen van bijwerkingen nadat patiënten van product gewisseld zijn (generieke substitutie). Vaak wordt daarbij ook een verminderd effect van het geneesmiddel aangegeven. Meestal vinden deze wisselingen plaatst in het kader van de vergoeding door zorgverzekeraars (Preferentie-beleid), maar ook tekorten aan een bepaald merk geneesmiddel kunnen hierbij een rol spelen.

In dit rapport wordt een overzicht gegeven van meldingen bij Lareb over bijwerkingen door geneesmiddel wisseling. De afgelopen tien jaar werden hierover in totaal ruim 2500 meldingen ontvangen. Bij nadere analyse van geneesmiddelen met meer dan 25 meldingen bleek bij de meerderheid geen sprake van een duidelijk patroon in de wisselingen (merken) en gemelde bijwerkingen. Acht analyses leveren wel een duidelijker beeld op. Geneesmiddelen waar Lareb de afgelopen jaren wél problemen na substitutie heeft gesignaleerd zijn:

- Ontregeling van schildklierwaarden bij het schildklierhormoon levothyroxine
- Doorbraakbloedingen bij anticonceptie pillen met ethinylestradiol en levonorgestrel
- Verminderde werkzaamheid bij inhalatie middelen voor de behandeling van astma; salbutamol en salmeterol/fluticason
- Huidreacties en omkrullende pleisters bij rivastigmine
- Pijn bij injectie en injectieplaatsreacties bij methotrexaat
- Verminderde werkzaamheid bij anti-epileptica

Hoewel generieke geneesmiddelsubstitutie bij bepaalde groepen geneesmiddelen, zoals anti-epileptica, wordt ontraden in een richtlijn van apothekersverenging KNMP, tonen de meldingen bij Lareb aan dat dit in de praktijk toch voorkomt. Door het preferentiebeleid van zorgverzekeraars, maar soms ook door geneesmiddeltekorten, worden vaak grote groepen patiënten in een korte tijd van het ene naar het andere geneesmiddel omgezet. Het is momenteel lastig om informatie te vinden over het moment van deze omzettingen, over welke producten en aantallen patiënten het gaat. Vaak verlopen wisselingen zonder problemen. Maar patiënten moeten er op kunnen vertrouwen dat als er toch problemen optreden, hier snel inzicht in is en adequate maatregelen genomen kunnen worden. Een meer pro-actieve monitoring van patiënten is daarom gewenst, wanneer het om wisselingen in een grote groep en korte periode gaat, om inzicht te krijgen in mogelijke problemen die patiënten ondervinden na geneesmiddelwisseling én om patiënten voor te bereiden op dergelijke wisselingen.

Introduction

A generic drug is based on a previously approved drug (reference drug) whose protection period has expired. It is equivalent to the reference product, but small differences may exist:

- It contains the same amount of active ingredient as the original
- It is used in the same doses as the original.
- It is administered in the same manner as the original, for example as a tablet, capsule or injection liquid.
- Other excipients may be used.
- The salt form of the active substance may be different.
- The colour may vary.

Generic drugs are subject to the same strict criteria as reference drugs. That means they must meet the same requirements of the pharmaceutical legislation. Manufacturers must demonstrate that the generic drug is of good quality and is bio-equivalent to the reference product (1). Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities (rate and extent) in the same molar dose after administration lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.

In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption. Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products. These concern the AUC, the area under the concentration time curve, reflects the extent of exposure. C, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, tmax, are parameters that are influenced by absorption rate (2).

Generics be considered as bioequivalent if the 90% confidence interval of the AUC ratio and Cmax is within 80-125 % of the reference product. According to the KNMP Guideline on Drug Substitution, for drugs with a narrow therapeutic the 90 % confidence interval of the AUC ratio and Cmax (where relevant)must be within 90 to 111.11 % (3).

In the Netherlands considerable emphasis is being placed on usage of generic drugs because of the economic benefits associated with their use. This is reflected by the 'Preference Policy' for generic drugs. Due to this policy, large groups of patients often have to switch from brand to generic medications or switch between different manufacturers of generics (4). Also products temporarily being out of stock may lead to the necessity to change patients to a different drug. Concurrently, there is increasing discussion in the lay media of perceived doubts regarding the quality and equivalence of generic medicines (5).

The Netherlands Pharmacovigilance Centre Lareb receives reports related to drug substitution on a regular basis and has issued more related to drug substitution in the past years. In this overview the drugs with more than 25 of these reports are reviewed.

Reports

For this review reports on drug substitution we selected reports containing the MedDRA® LLT 'Therapeutic response unexpected with drug substitution'. In the last ten years (from 01-01-2006 until 30-09-2016) Lareb has received 2667 reports on ADRs related to drug substitution. One report can relate to multiple drugs. See Figure 1 for an overview of the reports related to substitution reactions per year for drugs on ATC-7 level. In Appendix 1 the number of reports are shown on ATC-5 and ATC-7 in detail.

The drugs on ATC 7 with > 25 reports related to drug substitution level are shown in Table 1. These drugs be reviewed below in more detail.

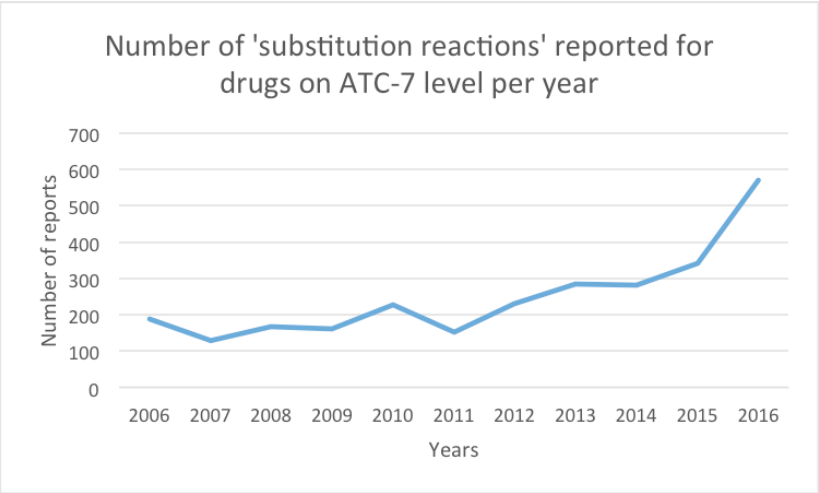

Figure 1. Reports related to drug substitution reported per year from 2006-2016.

Table 1. Drugs associated with drug substitution on ATC 7 > 25 reports

NUMBER OF REPORTS	DRUG (ATC 7 LEVEL)
295	LEVOTHYROXINE
191	ETHINYLESTRADIOL MET LEVONORGESTREL
130	OMEPRAZOL
107	METHYLFENIDAAT
93	METOPROLOL
91	SIMVASTATINE
63	ATORVASTATINE
49	PAROXETINE
47	SALBUTAMOL
45	VENLAFAXINE
45	METFORMINE
40	PERINDOPRIL
39	IRBESARTAN
37	RIVASTIGMINE
32	PANTOPRAZOL
32	SALMETEROL MET FLUTICASON
31	LOSARTAN
28	ENALAPRIL/ENALAPRILAAT
28	ESOMEPRAZOL
28	METHOTREXAAT

By accumulating the data, relevant trends in the timeline may be lost. A different method, which detects changes in the number of reports of a specific drug in time, could be valuable for the detection of signals. One such method, that determines whether changes have taken place in a time series, is the change point analysis (CPA). With the CPA the reports of a specific association are counted per time period, and changes in the mean counts per time period can be detected by different methods (open-source software R (6)). For the drugs (ATC-7) that were reported most often (>25 reports), the 'changepoint' package in R was used to get insight in the pattern of reports on drug substitution over time. The reports were counted per week, the Pruned Exact Linear Time (PELT) method with the 'Modified Bayesian Information Criterion (MBIC)' penalty was used to detect changes in the mean. The penalty provides a compromise between lots of small changes and no changes.

Changepoints are depicted as deviations in the red line, which would be one straight line without any changepoints. This method was used as an illustration of how a statistical method could give insight in the reporting pattern, however a clinical review of all cases remains the basis on whether Lareb issues a signal of a specific association or not.

Review drugs >25 reports on substitution

Levothyroxine

End of 2013, the packaging of the Thyrax® had been changed from a bottle to a blister. In the blister package the product is better protected against environmental factors. The formulation of the product had not been changed. From 11 April 2014 Lareb started receiving reports considering possible adverse drug reactions associated with changes of the package of Thyrax® from the bottle to the blister. The reports about the bottle to blister switch were coded as 'Pharmaceutical product complaint' and were therefore not included in the 2015 peak (figure 1). After media attention, more than 1800 adverse reaction reports on problems after the bottle to blister switch were received and a follow-up survey was performed. Lareb concluded that the packaging change led to dysregulation in patients using Thyrax®, both in respect to hypothyroidism and to hyperthyroidism. The most commonly reported adverse events were heart palpitations, fatigue and headache. The most reported patterns of adverse reactions match with symptoms of an overactive thyroid gland (hyperthyroidism) by increased thyroid hormone, but also partly in a delayed action of the thyroid gland (hypothyroidism) due to decreased thyroid hormone. These reactions are not further reviewed here, more information can be found in a report on the packaging change (9). Due to media attention for the Thyrax® packaging switch in 2015, Lareb also received new reports on levothyroxine switching between brands.

In January 2016 the company Aspen Pharma Trading announced that there were production issues with Thyrax Duotab® (levothyroxine). Due to a change in production facility Aspen Pharma Trading was temporarily unable to produce this product. This led to an out-of-stock situation for Thyrax Duotab® 0.025mg in February 2016 and it was predicted that the 0.100mg and 0.150mg tablets would be out-of stock around June 2016. This out-of-stock situation would last during most of 2016 (10). It was advised to start no new patients on Thyrax Duotab® and patients currently using Thyrax Duotab® should switch to a different product with levothyroxine when their own stock ran out (10). From 1 February 2016 until 30 May 2016 the Netherlands Pharmacovigilance Centre Lareb received 75 reports concerning reactions associated with the substitution of Thyrax Duotab into a different brand levothyroxine. Lareb concluded that it could be expected that the substitution of Thyrax® in a large group of patients led to some patient experiencing dysregulation of their thyroid levels. However, healthcare professionals and patients probably anticipated these effects and therefore a large peak in reporting levels was not seen. The reported ADRs follow the expected pattern of known levothyroxine-related reactions. The MEB was informed about these reports (11).

In the statistical analysis, with which the pattern of drug substitution reports over time for levothyroxine was studied, several change-points were detected in 2015 and 2016 (figure 2). This means that at these moments there was a statistical change in the reporting pattern.

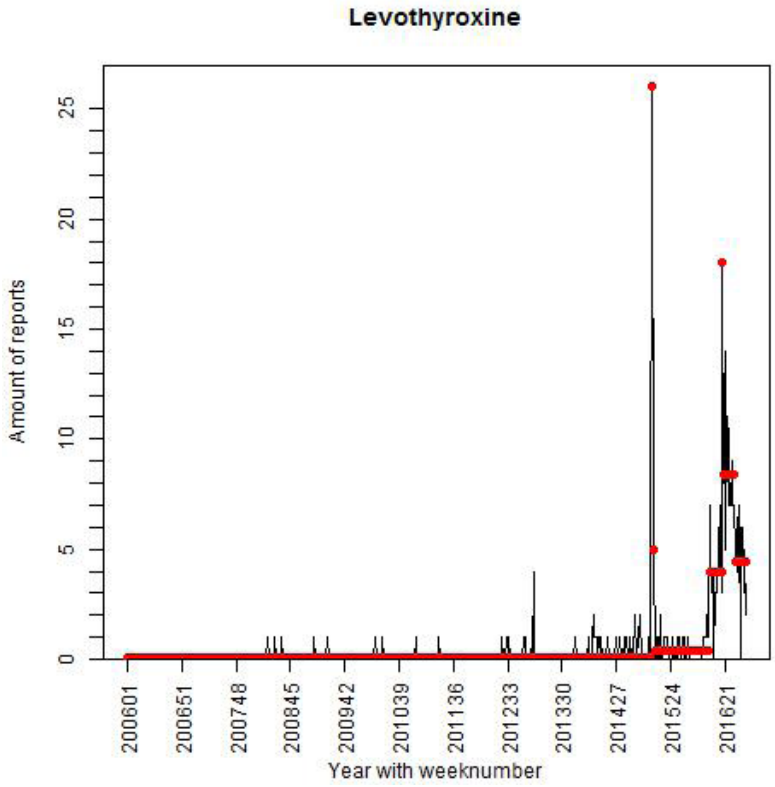

Figure 2: plot of the reports per week on the association between the drug levothyroxine and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Ethinylestradiol and levonorgestrel

A total amount of 191 reports on substitution was related to ethinylestradiole and levonorgestrel. Adverse effects after substitution of ethinylestradiole and levonorgestrel were mainly received in 2006 (n=60), 2007 (n=37) and 2008 (n=26). In 2006 a signal was published about substitution of oral contraceptives such as Microgynon® to the generic Rigevidon® leading to break-through bleeding. In 2012 an overview of problems related to substitution of oral contraceptives was presented. At that moment Lareb had received 149 reports of adverse drug reactions related to substitution of one oral contraceptive pill by another oral contraceptive pill with the ATC code G03AA07. The number of reports per drug on the level of the HPK-code was the highest for Rigevidon® (87 reports) and ethinylestradiol/levonorgestrel 0,03/0,15 Apothecon® (40 reports), which are the same product with a different name. Of the 149 received reports, 55 included the MedDRA Lower Level Term (LLT) break-through bleeding as an adverse drug reaction. The majority of reports about break-through bleeding that Lareb received occurred after switching from Microgynon 30 to Rigevidon® (29 reports) and ethinylestradiol/levonorgestrel 0,03/0,15 Apothecon® (12 reports) (12). It is striking that the majority of the reports in this overview are about the product of one Marketing Authorization Holder. In the analysis of the reporting pattern over time, several changepoints were detected between 2006 and 2008 (figure 3).

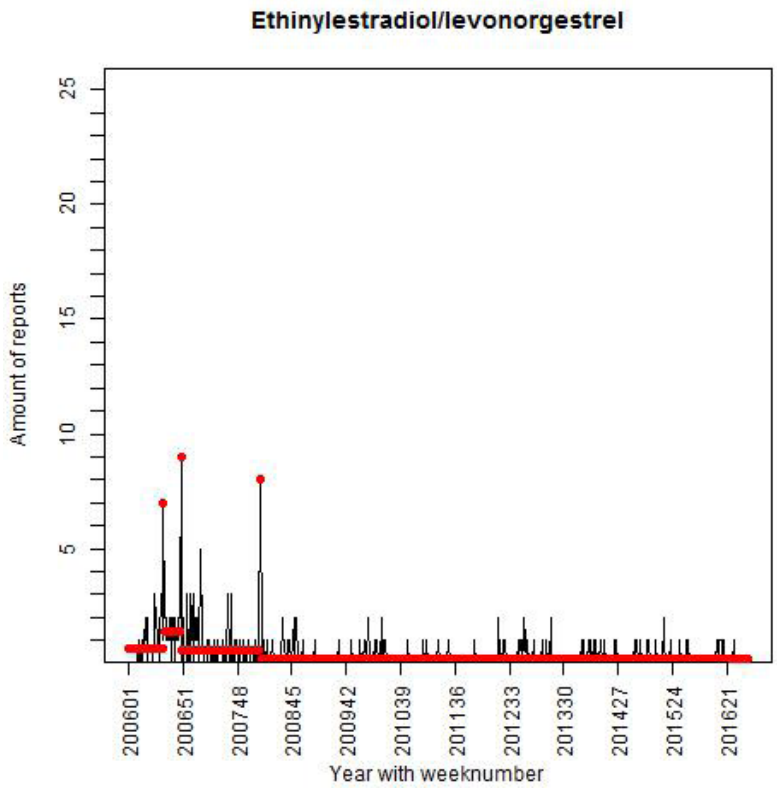

Figure 3: plot of the reports per week on the association between the drug ethinyl estradiol and levonorgestrel and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'

Omeprazole

A total amount of 130 reports on substitution was related to omeprazole. From the beginning of 2016 Lareb began receiving reports on lack of efficacy or symptoms that could be due to a lack of efficacy after substitution from various omeprazole products to omeprazole Omecat®. A signal on lack of efficacy was published 2016 (13). In 2016 a total of 80 reports had been received on this association. Lareb concluded that although the active substance is equal to that of the reference product Losec®, the reports suggest problems as a direct result of the substitution to Omecat®.

Following assessment of all currently available data in August 2016, no explanation could be identified by the MEB for the occurrence of the events of 'drug ineffective' / 'gastrointestinal disorders' and switching to Omecat®. According to the assessment, the product complies with the required quality limits including the current specifications after storage in open air. Also no batch related problems could be identified.

The reports before 2016 do not describe substitution to one distinct product like Omecat®, but switching from Losec® to various generic products or switching between varying generic products. In the analysis of the reporting pattern over time, several change-points were detected in 2016 (figure 4).

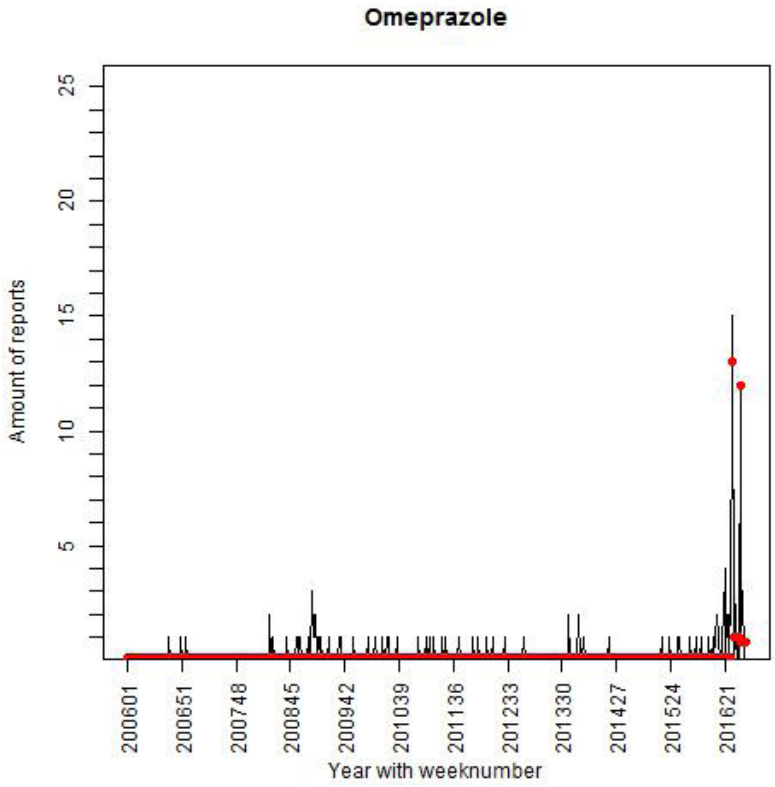

Figure 4: plot of the reports per week on the association between the drug omeprazole and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'

Methylphenidate

A total amount of 107 reports on substitution was related to methylphenidate. Lareb previously analysed 45 reports received between April 2014 and October 2015, concerning substitution after switching from Concerta® to the generic methylphenidate retard products. In 38 out of the 45 cases a change in behaviour was reported (agitation, restlessness, disturbance in attention). A similar analysis was found from the Danish Health and Medicines Authority (DHMA), written in 2015. The DHMA performed a number of tests to measure the active substances in the original and generic product, but did not discover any defects in quality (14). However, Lareb keeps this association under close review, as 23 more reports on ADRs after drug substitution have been received in 2016. Patients mostly switched from brand Concerta® to methylphenidate prolonged release of the manufacturer Sandoz or Mylan. Lack of efficacy (or symptoms thereof) were reported in 13 cases. A few other cases mention reaction like depressive symptoms or aggression after the switch. Change inefficacy after switching methylphenidate products was also reported by 60 per cent of the responders, in a survey on experiences of adults with ADHD medication in a Lareb report (15).

No changepoints in the reporting pattern were detected (figure 5).

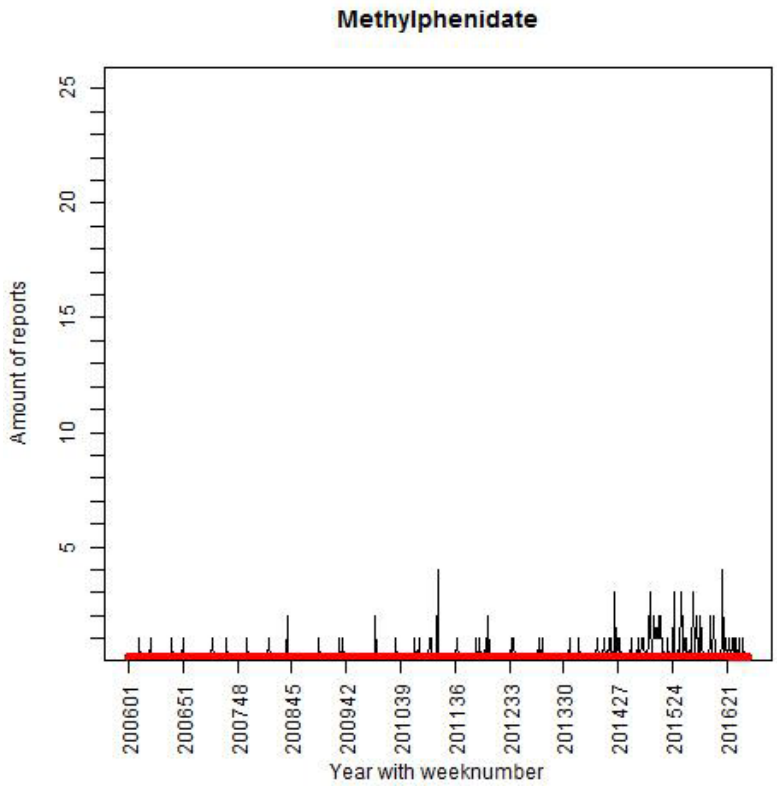

Figure 5: plot of the reports per week on the association between the drug methylphenidate and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Metoprolol

A total amount of 93 reports on substitution was related to metoprolol. The amount of reports received is evenly distributed over the years and describes substitution between a variety of brands and also variety of reported ADRs. A few reports describe symptoms that could be related to lack of efficacy after switching, however there was no distinct pattern of drugs that patients where switched to and hence these reports have not led to a signal regarding substitution related ADRs for metoprolol. No changepoints were detected in the analyses of the reporting pattern (figure 6).

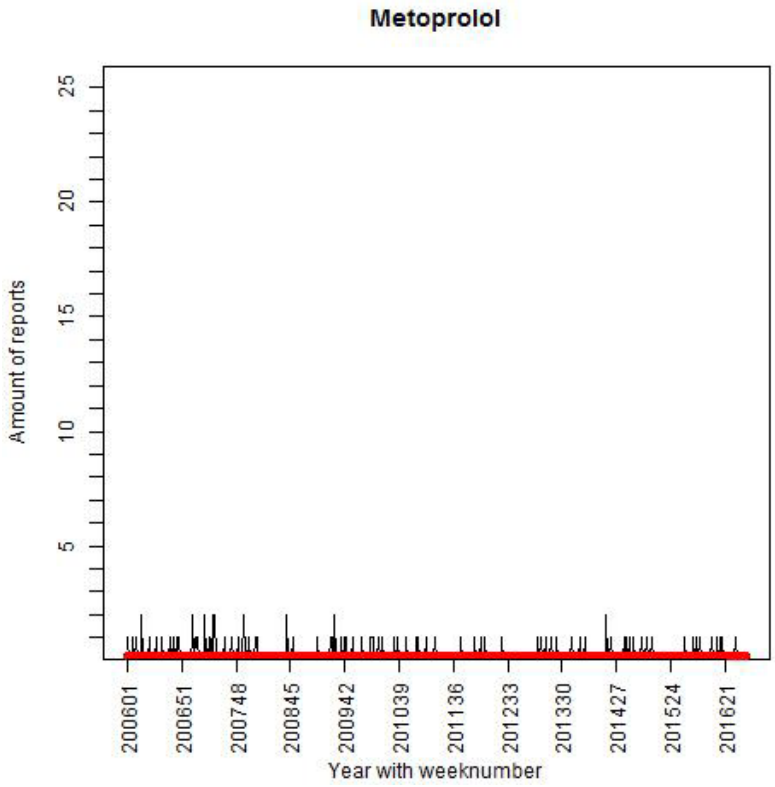

Figure 6: plot of the reports per week on the association between the drug metoprolol and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Simvastatin

A total amount of 91 reports on substitution was related to simvastatin. In September of 2008 a tumult broke out around the company Ranbaxy, because the US Food and Drug Administration (FDA) banned the import of 30 Ranbaxy medicines. The ban was enforced after inspection revealed that two manufacturers did not adhere to the US quality criteria for medicine production (16). This also led to commotion in the Netherlands, resulting in a higher amount of reports on (Ranbaxy) simvastatin. In 2014 the MEB requested further investigation; A Lareb analysis did not show a significant increase in the substitution related reports for Ranbaxy simvastatin. Also, the spectrum in adverse drug reactions was not different for simvastatin from Ranbaxy, compared to other simvastatin products. This was communicated to the MEB.

No changepoints were detected (figure 7). Apart from a small peak in the amount of reports received in 2008 (n=24), they have been evenly distributed over the years.

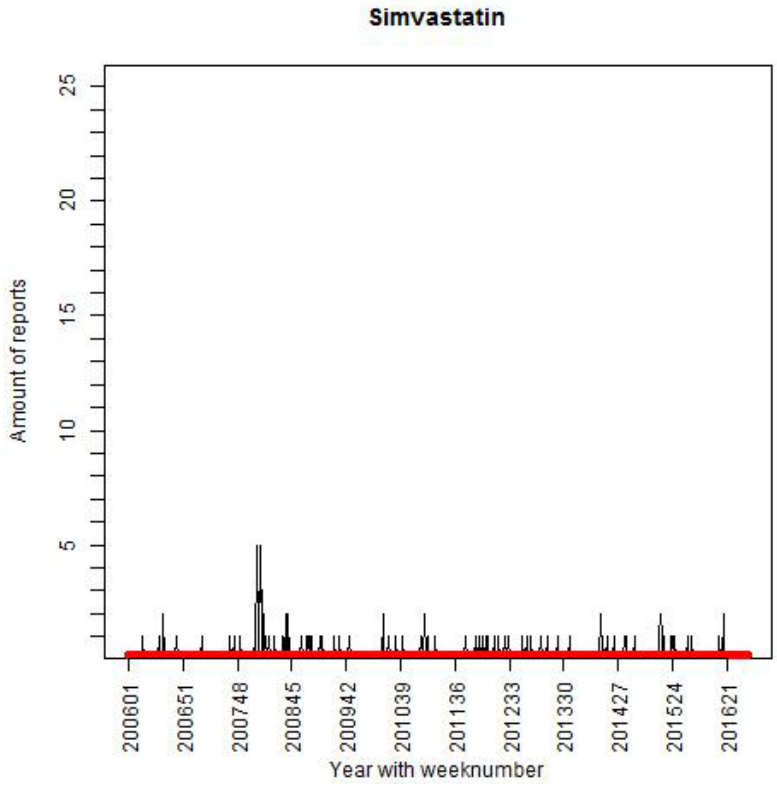

Figure 7: plot of the reports per week on the association between the drug simvastatin and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'. No changepoints were detected.

Atorvastatin

A total amount of 63 reports on substitution was related to atorvastatin. In March 2012 the generic atorvastatin, instead of Lipitor®, became available on the Dutch market. Influenced by the health insurance companies, 80% of the Lipitor® switched to the generic atorvastatin within 2 months (17). However, the amount of reports remained low after the generics became available (n=11 in 2012), and no distinct pattern in the reports was seen. For Lipitor® itself Lareb noticed in 2011 that there had been a small change in the formulation of Lipitor®; benzoic acid was added to the tablets and Lareb received reports on urticaria, dyspnea, pruritis and dry cough from patients switching from the old formulation to the new. Benzoic acid (E210) and benzoates may liberate histamine in some people and thus cause pseudo-allergic reactions (18). However, since the number of reports possibly relating to this issue remained limited, the MEB was not informed with a Signal.

No changepoints were detected (figure 8). Slightly more reports were received from 2012-2014, compared to the other years.

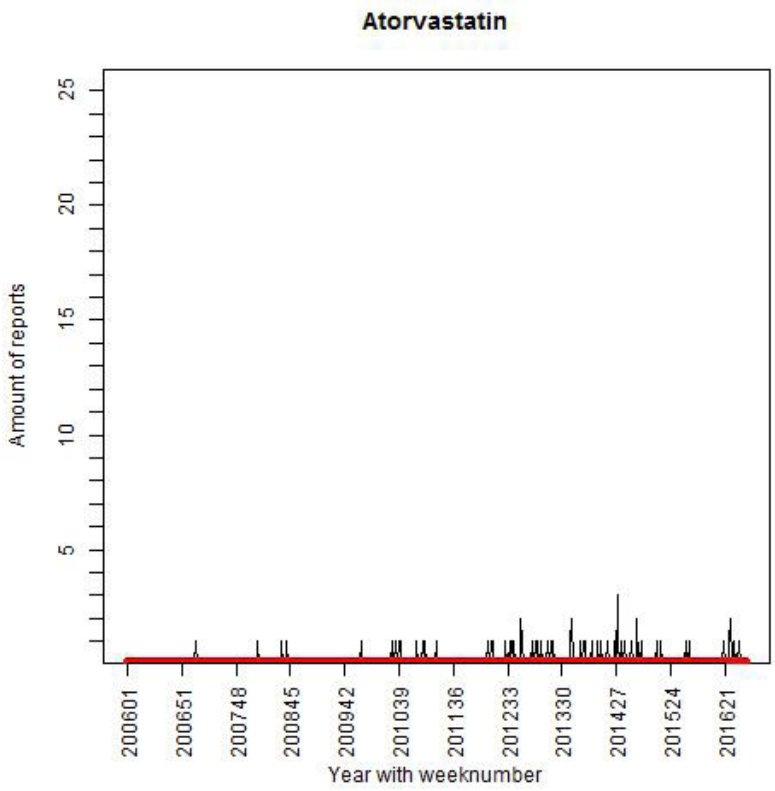

Figure 8: plot of the reports per week on the association between the drug atorvastatin and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Paroxetine

A total amount of 49 reports on substitution was related to paroxetine. Approximately half of these reports describe the return of depressive symptoms or other psychiatric ADRs. However there was no distinct pattern in the manufactures of paroxetine that patients were switched to.

No changepoints were detected in the analyses of the reporting pattern (figure 9). The amount of reports received is evenly distributed over the years.

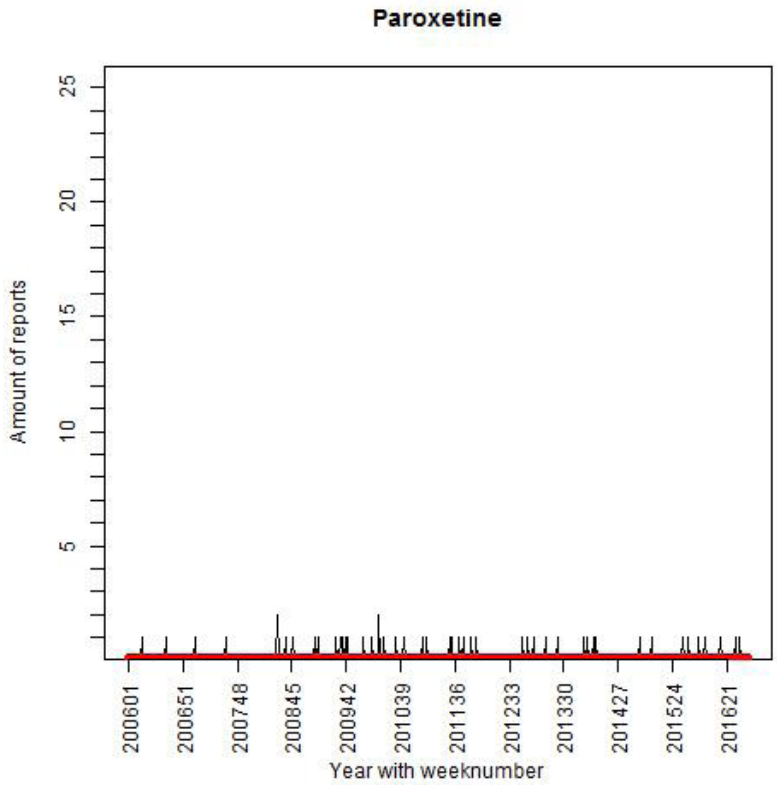

Figure 9: plot of the reports per week on the association between the drug paroxetin and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Salbutamol

A total amount of 47 reports on substitution was related to salbutamol. Since 2015, but especially in 2016, reports were received concerning lack of drug effect after substitution to a new generic salbutamol Sandoz®. Many of these ADRs described exacerbations, some of which occurred in children and were reported by paediatricians. Lareb has issued a signal and several updates (19). Lareb concluded that the reports received suggest the salbutamol aerosol from Sandoz is less effective since the revision. The pharmaceutical company Sandoz should investigate whether this concerns a quality issue or another problem like a difficulty in the use in combination with the spacer. Not all ADR-reports described in this signal occurred after substitution, the lack of drug effect also occurred in patients who used salbutamol Sandoz® for the first time, amounting to a total of 124 reports received in 2015 and 2016 on lack of efficacy of this product. A public assessment report on this signal is available from the website of the MEB (20). According to the assessment of the MEB, the complaints about the Sandoz salbutamol inhaler cannot be attributed to the product itself. However, the MEB remarks, the substitution of many asthma and COPD patients to this type of inhaler, in a short time is a possible explanation for the number of complaints.

Several changepoints were detected in 2016 (figure 10).

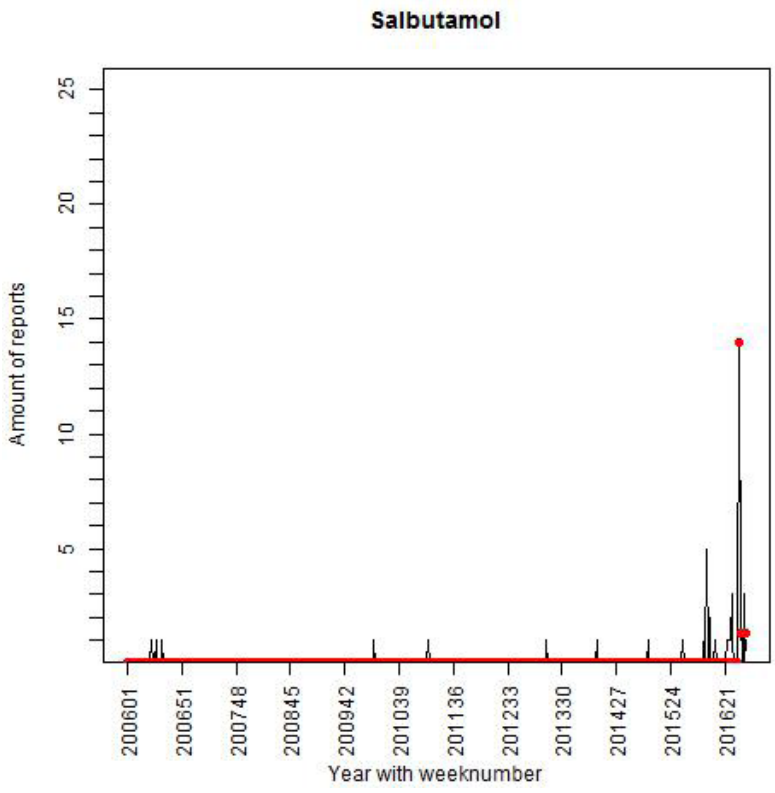

Figure 10: plot of the reports per week on the association between the drug salbutamol and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Venlafaxine

A total amount of 45 reports on substitution was related to venlafaxine. Psychiatric symptoms were described in patients switching from venlafaxine (Efexor®) capsules with regulated control (XR) to regular venlafaxine and vice versa. Also lack of drug effect was reported, among other ADRs, in patients switching from brand medication Efexor® to various generic venlafaxine generic products and also between different generics. Because there was no clear pattern in the generics that patients reported about, no signal was issued.

In the analyses of the reporting pattern, no changepoints were detected (figure 11). Besides a small, insignificant peak in 2009 (n=13), the amount of reports received is evenly distributed over the years.

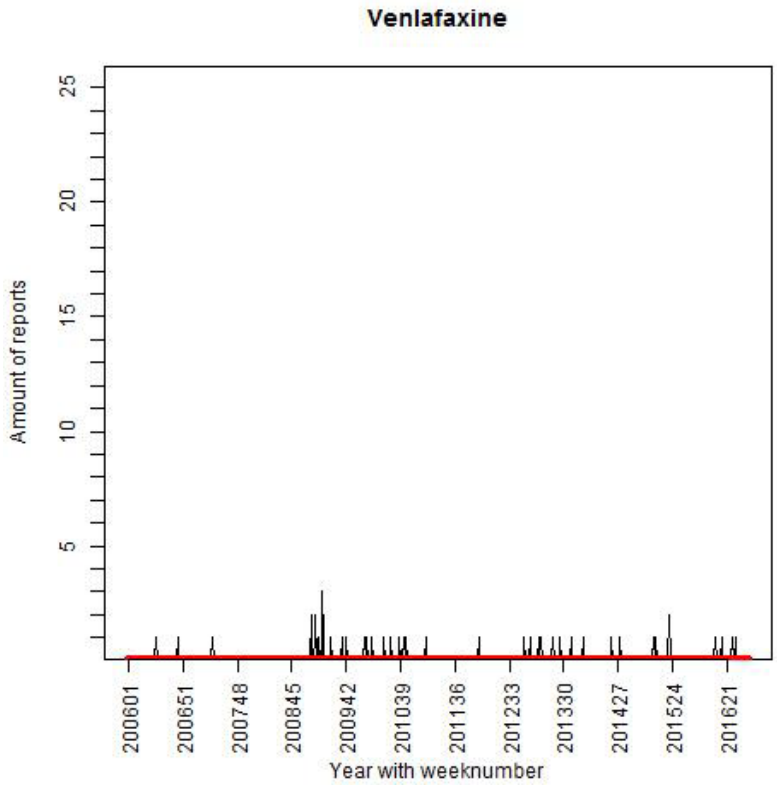

Figure 11: plot of the reports per week on the association between the drug venlafaxine and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'. .

Metformin

A total amount of 45 reports on substitution was related to metformin. Gastro-intestinal disorders like diarrhoea were most often reported after switching between products (mostly from generic to generic). Also changes in blood glucose (hyperglycaemia, 'fluctuations' in blood glucose and hypoglycaemia) where reported after switching between products. However, there was no distinct pattern in the manufactures of metformin that patients were switched to.

In the analyses of the reporting pattern, no changepoints were detected (figure 12).

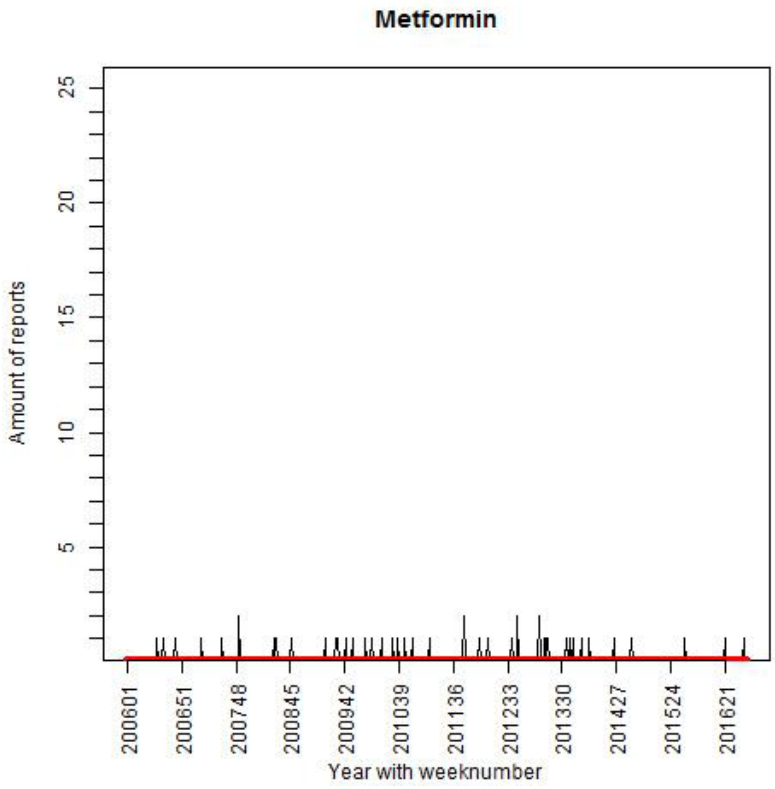

Figure 12: plot of the reports per week on the association between the drug metformin and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Perindopril

A total amount of 40 reports on substitution was related to perindopril. The reported ADRs after drug substitutions are diverse, reports from 2008 mention the switch from brand Coversyl® to generics, later reports describe switching between various generic products.

In the analyses of the reporting pattern, no changepoints were detected (figure 13).

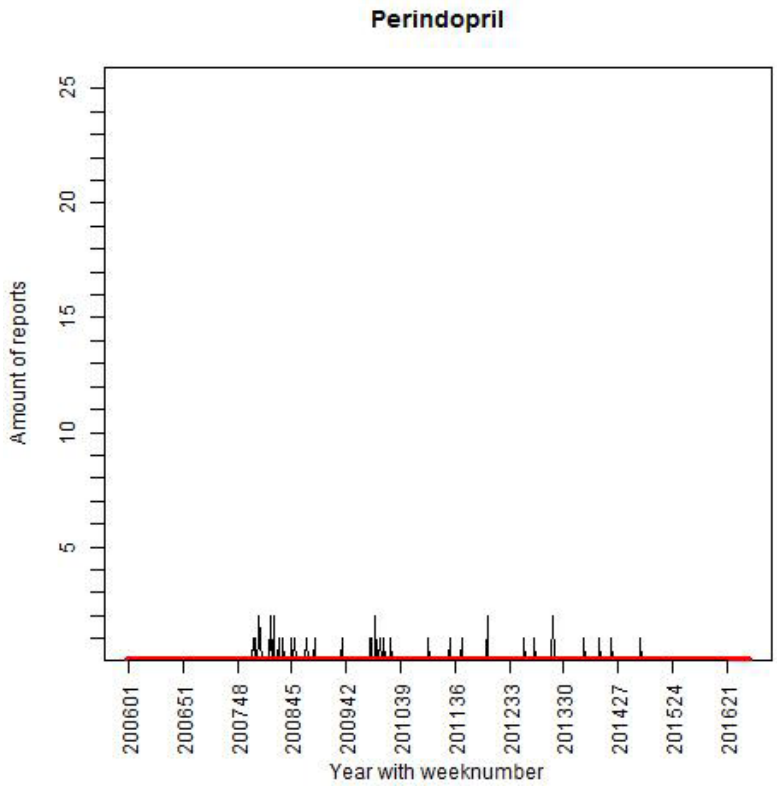

Figure 13: plot of the reports per week on the association between the drug perindopril and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Irbesartan

A total amount of 40 reports on substitution was related to irbesartan. The first generic versions of irbesartan Aprovel® became available in 2012 (21). Lareb received the first report on substitution for this drug on 23-11-2012. Especially the oldest reports describe the switch from Aprovel® to generic products, later reports also describe switching between generics. The type of the reported ADRs was diverse, although blood pressure increase/hypertension (symptom of lack of efficacy) was reported multiple times. However, these reports could not be related to one specific product.

In the analyses of the reporting pattern, no changepoints were detected (figure 14).

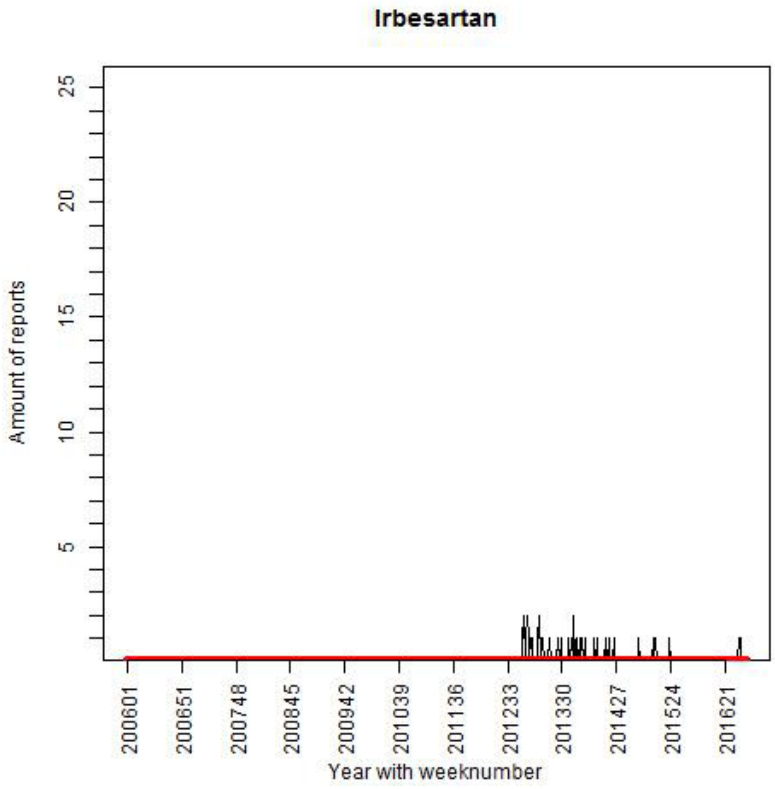

Figure 14: plot of the reports per week on the association between the drug irbesartan and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Rivastigmine

A total amount of 37 reports on substitution was related to rivastigmine. In 2013 Lareb issued a signal on adhesion problems with the new generic of rivastigmine (Permente®), an issue that had not occurred during previous use of the innovator product Exelon® (22). It appeared that the manner in which the film of the patch is removed is of influence on the curling of the patch. The MAH adapted the instructions on how to use these patches in the product information, in order to prevent that the patches will curl due to incorrect removal of the foil. The MAH was also asked to investigate the influence of the curling of the patches on the adhesion of the patch (23).

In 2014 Lareb published a signal about skin reactions (erythema, rash, pruritus, blisters) following shortly after substitution of rivasigmine plasters of the brand Exelon® to rivasigmine plasters of the brand Permente® (24). In 2015 only one report on a skin reaction with the use of Permente® was reported. In 2016 there were no new reports on this association, see figure 15.

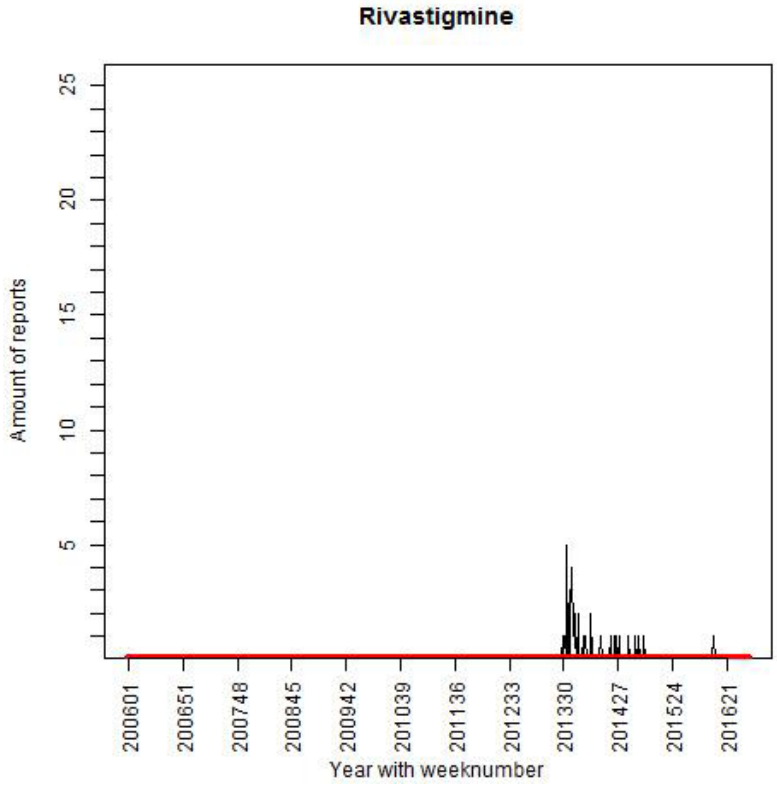

Figure 15: plot of the reports per week on the association between the drug Rivastigmine and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'. No changepoints were detected.

Pantoprazole

A total amount of 37 reports on substitution was related to pantoprazole. The first generic of pantoprazole brand Pantozol® became available in the Netherlands in 2009 (25). Most patients were switched from Pantozol® to different generics and reported ADR varied. There were a few reports on dyspepsia/lack of drug effect, but not enough to have triggered a Signal.

In the analyses of the reporting pattern, no changepoints were detected (figure 16).

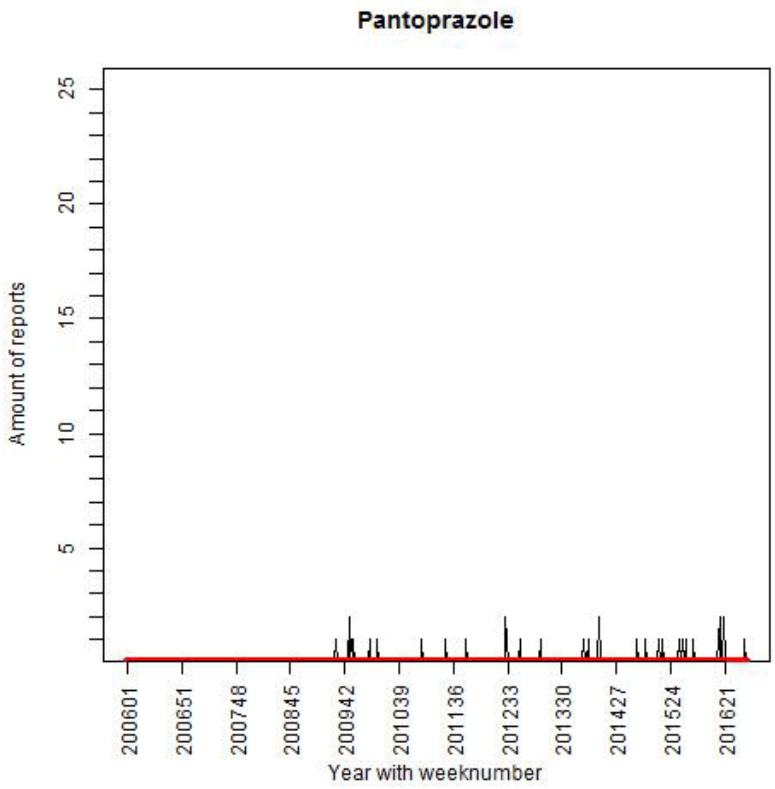

Figure 16: plot of the reports per week on the association between the drug Pantoprazole and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Salmeterol/fluticasone

A total amount of 32 reports on substitution was related to salbutamol/fluticasone and 22 of these reports concerned decreased therapeutic response or pulmonary complaints after substitution from Seretide® to the generic salmeterol/fluticasone Vincion® or Focus®. The Dutch Foundation for Pharmaceutical Statistics (SFK) has published an article about the use of inhalation medication for asthma/COPD. Due to the preference policy of health insurance companies the use of the generic salmeterol/fluticasone has increased in 2016 (26). Lareb has disseminated a signal about this issue (27). According to the assessment of the MEB, based on the reported cases as presented by Lareb in the initial signal and the additional information presented by the MAH in this response, there is no information that could explain the perceived lack of efficacy with salmeterol/fluticasone. No handling problems or batch related issues were observed (28).

Several changepoints were detected in 2016 (figure 17).

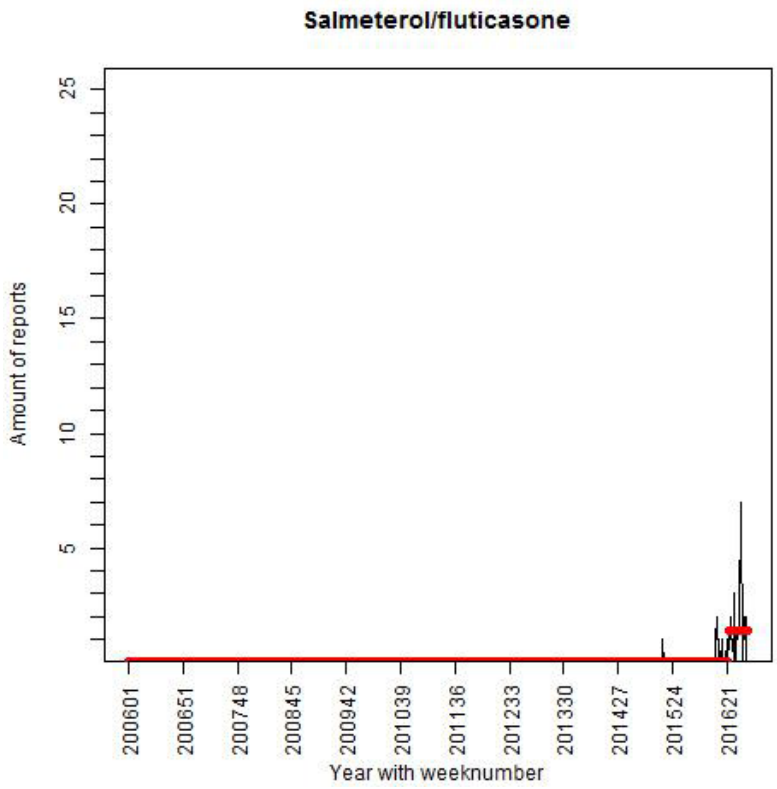

Figure 17: plot of the reports per week on the association between the drug salmeterol/fluticason and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Losartan

A total amount of 31 reports on substitution was related to losartan. Patients mostly switched from the brand Cozaar® or Losanox® to various generic products. There was no distinct pattern in the type of ADRs that were reported. In the analyses of the reporting pattern, no changepoints were detected (figure 18).

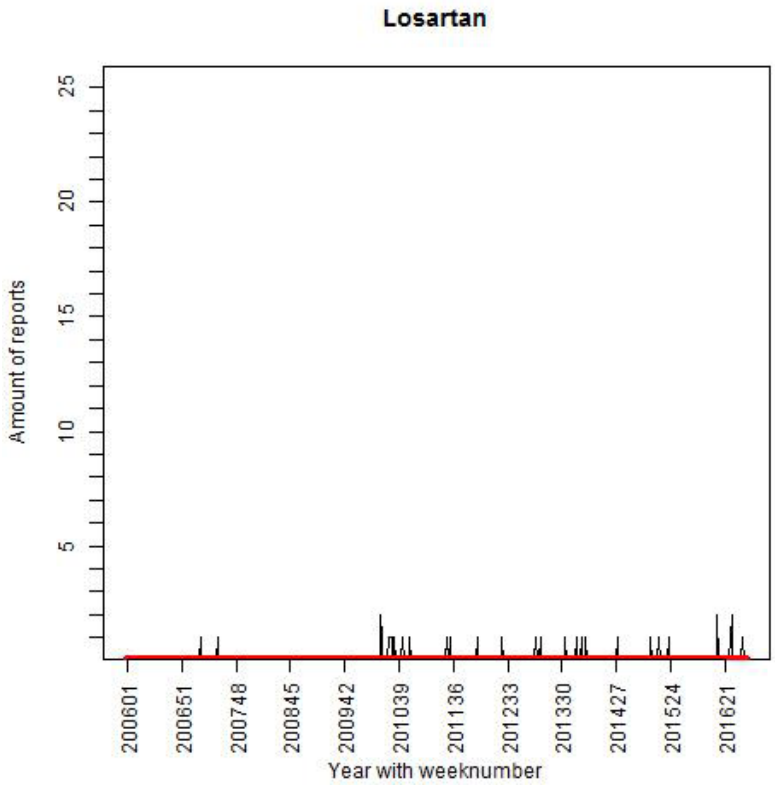

Figure 18: plot of the reports per week on the association between the drug Losartan and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Enalapril

A total amount of 28 reports on substitution was related to enalapril. Patients mostly switched between various generic products. There was no distinct pattern in the type of ADRs that were reported. In the analyses of the reporting pattern, no changepoints were detected (figure 19).

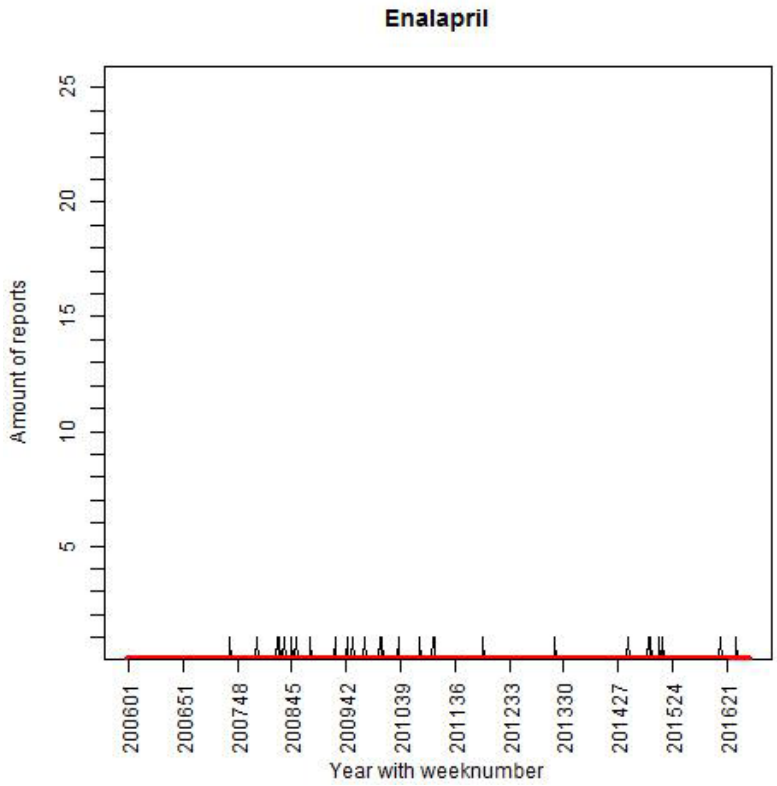

Figure 19: plot of the reports per week on the association between the drug Enalapril and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'..

Esomeprazole

A total amount of 28 reports on substitution was related to esomeprazole. Patients mostly switched from Nexium® to various generic products. Lack of efficacy, or symptoms thereof (like pyrosis, bloating etc) were reported in about half of the cases. However, there was no distinct pattern in the type products that patients switched to. In the analyses of the reporting pattern, no changepoints were detected (figure 20).

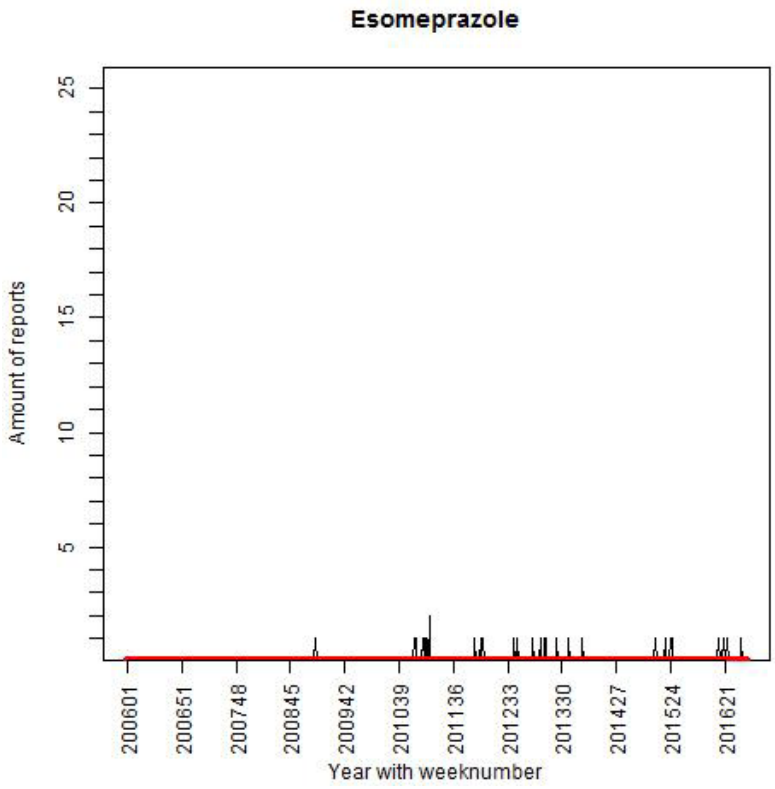

Figure 20: plot of the reports per week on the association between the drug Esomepazole and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'.

Methotrexate

A total amount of 28 reports on substitution was related to methotrexate, almost all following substitution to methotrexate Metoject®. In 2011 Lareb disseminated a Signal about device complications after switch to this product. In the signal 10 reports were described. Patients reported injection site haematoma and pain after switch to this product due to bluntness of the needles (29). This subject had also been discussed during a meeting of the MEB Medical Practice Committee. The MEB has informed the Reference Member State about this issue (30).

In the statistical analyses no changepoints were detected (figure 21).

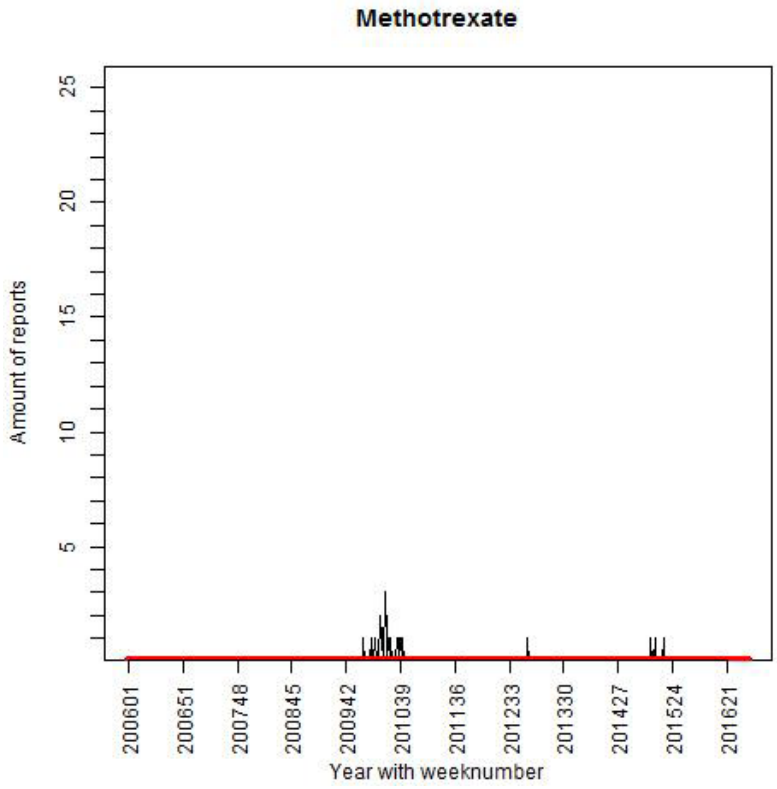

Figure 21: plot of the reports per week on the association between the drug Esomepazole and the MedDRA LLT 'Therapeutic response unexpected with drug substitution'. No changepoints were detected.

Anti-epileptic drugs

The reviews so far, were on specific drugs. For anti-epileptic drugs, in 2016, Lareb disseminated an overview on the reports after (generic) drug substitution (31). Until 1 March 2016 Lareb received 87 reports concerning the PT therapeutic response unexpected, with 29 reports associated with convulsion/possible lack of efficacy. Although (generic) substitution of anti-epileptic drugs is not recommended by the KNMP, this does occur in clinical practice. In some reports the preference policy of health insurance companies is mentioned as a motive for this substitution. In addition, supply issues can cause certain drugs to be (temporarily) out of stock and patients have to be switched to a different brand subsequently.

On February 22 2016, the KNMP issued a notice that carbamazepine 200 mg generic tablets may presently not be provided by various manufacturers because of production problems. Carbamazepine retard tablets of 200 and 400 mg are available in reduced quantities because one of the manufacturers has production problems and some other manufactures have decided to stop the supply of these tablets (31).

Since that previous overview (March 2016) Lareb has received 11 reports of ADRs after drug substitution, including five reports on lack of efficacy/convulsions. Three reports describe substitution of carbamazepine (Reports 216947, 216954 and 218286), 1 report substitution of lamotrigine (218286) and 1 report substitution of phenobarbital (218286). Reported reactions were a (severe) increase in the frequency (and severity) of epileptic seizures or the return of seizures in a patient who had been seizure free for several years .

No changepoint analysis was made, due to the broad ATC-Class of drugs involved.

Discussion and conclusion

Lareb regularly receives reports of adverse reactions after (generic) drug substitution. These reports are all individually assessed and only if further analysis shows that more attention is warranted, a signal on an association will be issued. This overview gives insight in the drugs where ADRs related drug substitution were reported.

There are drugs with more than 25 reports on generic drug substitution over the years, but where no signals were issued. In these cases, the amount of reports received was evenly distributed over the years and describe substitution between a variety of brands and/or also variety of reported ADRs. For drugs used in the treatment of depression, like paroxetine and venlafaxine, return of depressive symptoms was reported in a large proportion of cases related to drug substitution. However, analyses of these reports did not show a signal on lack of efficacy for one particular product.

For other drugs signals related to drug substitution were found; Lareb warned for substitution between levothyroxine brands which are not always bioequivalent (7;11) and signals related to substitution of two inhalation drugs (salbutamol (19) and salmeterol/fluticasone (27)), two signals on a generic rivastigmine patch relating to curling of the patch (22) and localized skin reactions(24), signals on break-through bleeding after switching between brands of oral contraceptive pills (12) and lack of efficacy after switching between anti-epileptic drugs were issued (31). Also for methotrexate, more painful injections and injections-ite reactions were reported after patients switched to a new brand injections (29).

A retrospective changepoint analyses showed the pattern of reports in time. Most often a statistical 'changepoint' coincided with action that Lareb has undertaken on the basis of case-by-case analyses. This is a logical outcome as a relatively high number of reports were received in a limited period, for instance related to changes in the preference policy of health insurers, will trigger an analyses based on the assessment of the incoming reports. Also, media attention can boost the number of reports about a potential drug safety issue. However, lack of a statistical change in the reporting pattern doesn't necessarily rule out that problems due substitution did arise, an example is the Signal on methotrexate and injection-site bruising and pain after patients switched to a different brand of injections (29). This is also due to the chosen sensitivity of the change-point analyses method, which prevents too much false-positive signals to arise. Therefore, an amount of reports, received over a prolonged period could still indicate that a certain switch between products warrants further attention and this will be decided bases on Lareb's clinical evaluation of incoming reports. Also for drugs, where Lareb didn't issue a Signal, this doesn't mean that on an individual level the patient could not have suffered an ADR related to the switch of products.

Although (generic) substitution of certain drugs, like anti-epileptics, is not recommended by the KNMP in their guideline on substitution (3), this does occur in clinical practice. The guideline explains for which drugs or situations generic drug substitution should and shouldn't be considered. There is no requirement to adhere to the guideline. The rationale between switching between products in the described associations was often due to less expensive generic products becoming available and/or the Preference Policy of the Dutch Insurance Companies. Also, in some cases a product (like Thyrax®) was temporarily out of stock. However, it is difficult for Lareb to find information about the timing, nature and mag-

nitude of patients switching between products. Often, these switches occur without any problems. But patients must be able to trust that when issues do occur, there will be quick insight and appropriate action can be taken. Current methods of being prepared to switches and thereby potential problems by substitution fall short. For products where large groups of patients have to be switched due to the preference of the health insurance companies or drug-shortages, ideally a more pro-active monitoring of possible problems related to drug switching is desired.

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Appendix

Note that the number of reports on ATC-5 (N=2729) and ATC-7 (N=2732) level differ from total unique number of reports (N=2667) on the MedDRA® LLT 'Therapeutic response unexpected with drug substitution'. These differences can occur because one unique report can contain multiple drugs, and in a few reports these drugs differed on ATC-7 level, but not on the level of ATC-5.

Table 1. Reports on drug substitution per year on ATC-5 level.

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eind-totaal
	2	1	1	1	4	7	3	1	1			21
(MIDDEL)LANG- MET SNELWERKENDE INSULINES VOOR INJECTIE			1			1						2
ACEETANILIDEDERIVATEN				1	3		2					6
ACE-REMMERS	1	4	23	13	12	7	5	11	8	7	3	94
ACE-REMMERS MET CALCIUMANTAGONISTEN							1					1
ACE-REMMERS MET DIURETICA		1		1	1	1	4		2			10
ALDOSTERONANTAGONISTEN						1				1	1	3
ALFA-BLOKKERS	8	2	3	3	4	1		3	2	3	2	31
AMINOCHINOLINES			1		1						2	4
ANGIOTENSINE-II-ANTAGONISTEN		3	1	4	11	3	21	28	14	11	8	104
ANGIOTENSINE-II-ANTAGONISTEN MET DIURETICA				1	2	2	7	7	16	7	4	46
ANTI-ANDROGENEN					2			1	1			4
ANTI-ANDROGENEN MET OESTROGENEN	1	5		3	5	1	1	2				18
ANTI-ARITMISCHE MIDDELEN KLASSE IC	1		1	1					3	2	1	9
ANTI-ARITMISCHE MIDDELEN KLASSE III								1				1
ANTIMYCOTICA VOOR SYSTEMISCH GEBRUIK	1						1					2
ANTI-OESTROGENEN				1		1	2		4	4	3	15
ANTIVIRALE MIDDELEN						1						1
ANTIVIRALE MIDDELEN VOOR HIVINFECTIE, COMBINATIEPREPARATEN			1									1
AROMATASEREMMERS						6	6	4	2	1	2	21
AZIJNZUURDERIVATEN EN VERWANTE VERBINDINGEN	2		1	1				1	2	2		9
BARBITURATEN EN VERWANTE VERBINDINGEN											1	1
BENZODIAZEPINEDERIVATEN	1	3	2	1	2	2	2	4	1	5	6	29
BENZODIAZEPINE-GERELATEERDE MIDDELEN		1			1					1	2	5
BENZOTHIAZEPINEDERIVATEN					2	1	2	1	2			8
BETA-BLOKKERS					1	1	2	2	1	2	1	10
BETALACTAMASE-GEVOELIGE PENICILLINES											4	4
BIGUANIDEN	3	4	3	6	7	3	5	9	5	1	1	47
BISFOSFONATEN	16	2	1	2	1	4	3	2	1	2		34
BISFOSFONATEN, COMBINATIEPREPARATEN					1					1		2
BUTYROFENONDERIVATEN									1		1	2
CALCINEURINEREMMERS					2	1			1			4
CALCIUM MET VITAMINE D EN/OF ANDERE MIDDELEN		1							1	1	6	9

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eind-totaal
CARBOXAMIDEDERIVATEN	1		1	4		1		2		4	5	18
CENTRAALWERKENDE SYMPATHICOMIMETICA	4	2	5	3	4	8	7	4	18	39	26	120
CHOLESTEROLSYNTHESEREMMERS	11	8	28	11	14	11	25	19	26	15	13	181
CHOLESTEROLSYNTHESEREMMERS MET ANDERE ANTILIPAEMICA					1							1
CHOLINESTERASEREMMERS						1	4	25	11	1	1	43
COMBINATIEPREPARATEN					1							1
CONTACTLAXANTIA			1									1
CORTICOSTEROIDEN	1	1		1	1	2	1		4	6		17
CORTICOSTEROIDEN MET LOKALE WERKING							1					1
COXIBS			1					1				2
DIAZEPINEN, OXAZEPINEN,THIAZEPINEN EN OXEPINEN							6	5	2	3	4	20
DIFENYLBUTYLPIPERIDINEDERIVATEN								6	2			8
DIHYDROPYRIDINEDERIVATEN	8	8	2	2	1	1	5	5	3	3	3	41
DOPA EN -DERIVATEN			1	1	1	2		3		2	1	11
DOPAMINE-AGONISTEN			1		1	2	2			5		11
ENZYMPREPARATEN			1			1						2
FENYLALKYLAMINEDERIVATEN		1			1	1	1	2				6
FENYLPIPERIDINEDERIVATEN	1						3	1	4	1		10
FIBRATEN									1			1
FOLIUMZUUR EN DERIVATEN	1											1
FOLIUMZUURDERIVATEN					18		1			3		22
GALZUURBINDENDE HARSEN									1		1	2
GLUCOCORTICOIDEN	1	1		2	3	1	2	1	5	3	1	20
GONADORELINE-ANALOGEN								1		1	1	3
H2-ANTAGONISTEN			1	1	1	2	1			1	1	8
HEPARINEGROEP			2						1			3
IMIDAZOOL- EN TRIAZOOLDERIVATEN								1				1
INTERFERONEN				1								1
KOOLZUURANHYDRASEREMMERS					1	1	1					3
LANGWERKENDE INSULINES VOOR INJECTIE			2		1					1	4	8
LEUKOTRIEENANTAGONISTEN	1						1	4	4	4	1	15
'LOW-CEILING' DIURETICA MET KALIUMSPARENDE MIDDELEN		2	1	1			1	2				7
MACROLIDEN		1					1				1	3
MAO-REMMERS, NIET-SELECTIEF											3	3
MATIG STERK WERKZAME CORTICOSTEROIDEN (GROEP II)									1			1
MELATONINERECEPTORAGONISTEN					1				1			2
MESALAZINE EN VERWANTE VERBINDINGEN	2					1		2	1			6
MIDDELEN BIJ ALCOHOLVERSLAVING									1			1
MIDDELEN BIJ ERECTIESTOORNIS								2	2			4
MIDDELEN BIJ HEREDITAIR ANGIO-OEDEEM										1		1
MIDDELEN BIJ NICOTINEVERSLAVING				1								1
MIDDELEN BIJ OPIOIDVERSLAVING					3					3		6

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eindtotaal
MIDDELEN BIJ URGE-INCONTINENTIE								1	2			3
MIDDELEN MET REMMENDE WERKING OP DE URINEZUURPRODUCTIE			1									1
MIDDELLANGWERKENDE INSULINES VOOR INJECTIE										1		1
MOTILITEITSBEVORDERENDE MIDDELEN		1										1
MOTILITEITSREMMENDE MIDDELEN							1					1
NATUURLIJKE EN SEMISYNTHETISCHE OESTROGENEN	1				1		1	1	1			5
NATUURLIJKE OPIUMALKALOIDEN				1				3		1	2	7
NIET-NUCLEOSIDE REVERSE-TRANSCRIPTASEREMMERS									1	2		3
NIET-SELECTIEVE BETA-BLOKKERS	3	3	1		2	1	1	1	2			14
NIET-SELECTIEVE MONOAMINE-HEROPNAMEREMMERS			2			1	2	2		3	3	13
NITRATEN	1	2	3					1	3			10
NITROFURAANDERIVATEN	1			1				1	1		1	5
NORMAAL HUMAAN IMMUNOGLOBULINE											4	4
NUCLEOSIDEN EN NUCLEOTIDEN (EXCL. REVERSE-TRANSCR-REMMERS)							1	1	2			4
OESTROGENEN MET PROGESTAGENEN COMBINATIEPREPARATEN				1								1
OESTROGENEN MET PROGESTAGENEN IN VASTE VERHOUDING	60	37	27	6	12	10	17	11	14	14	7	215
ORIPAVINEDERIVATEN										1	1	2
OSMOTISCH WERKENDE LAXANTIA		1			3	1	1	3	2	2	3	16
OVERIGE ALKYLERENDE MIDDELEN					1				1			2
OVERIGE ANTIDEPRESSIVA	2	1	1	13	8	1	4	7	2	4	11	54
OVERIGE ANTI-EPILEPTICA	4	1		2	4	2	3	4	1	5	6	32
OVERIGE ANTIHISTAMINICA VOOR SYSTEMISCH GEBRUIK			1				8	2	4	3		18
OVERIGE ANTIPSYCHOTICA				3	1				1	1	1	7
OVERIGE BOTMINERALISATIEBEINVLOEDENDE MIDDELEN											1	1
OVERIGE CENTRAAL WERKENDE MIDDELEN			1	1	1		1			1	1	6
OVERIGE EMOLLIENTIA EN PROTECTIVA											1	1
OVERIGE IMMUNOSUPPRESSIVA	1				2	2	2			3	1	11
OVERIGE KALIUMSPARENDE MIDDELEN	1											1
OVERIGE MIDDELEN BIJ ULCUS PEPTICUM EN OESOFAGEALE REFLUX							1					1
OVERIGE MIDDELEN VOOR OOGHEELKUNDIG GEBRUIK							1	1	2			4
OVERIGE OESTROGENEN											1	1
OVERIGE ONCOLYTICA					1	1						2
OVERIGE OPIOIDEN	1						2	2		1		6
OXICAMDERIVATEN	1		1		2							4
PARASYMPATHICOLYTICA			1							2	4	7
PENICILLINES MET BREED SPECTRUM							1		1			2
PIPERAZINEDERIVATEN				1	4	3	1		3	1	2	15
PLATINAVERBINDINGEN			1									1
PROGESTAGENEN								1	1			2
PROPIONZUURDERIVATEN		1			1							2

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eindtotaal
PROSTAGLANDINE-ANALOGA							3		1		1	5
PROTEINEKINASEREMMERS										1		1
PROTONPOMPREMMERS	2	1	7	24	9	16	15	16	9	20	80	199
PYRIMIDINEDERIVATEN									4			4
RETINOIDEN VOOR ACNE				1							2	3
RETINOIDEN VOOR PSORIASIS										1		1
SALICYLZUUR EN DERIVATEN								1				1
SCHILDKLIERHORMONEN			3	2	2	2	5	6	23	51	201	295
SELECTIEVE BETA-2-SYMPATHICOMIMETICA	10	1			1	1		3	1	2	40	59
SELECTIEVE BETA-BLOKKERS	14	17	10	12	9	6	7	12	11	9	6	113
SELECTIEVE BETA-BLOKKERS MET THIAZIDEN	1	1	2					1		2		7
SELECTIEVE IMMUNOSUPPRESSIVA							2					2
SELECTIEVE SEROTONINE-AGONISTEN	2	1		2	1	2		4	7	6		25
SELECTIEVE SEROTONINE-HEROPNAMEREMMERS	3	7	6	10	16	10	8	10	13	28	13	124
SEROTONINE-ANTAGONISTEN	1											1
SNELWERKENDE INSULINES VOOR INJECTIE			2					1		1	1	5
STERK WERKZAME CORTICOSTEROIDEN (GROEP III)										1		1
SULFONAMIDEN	1		1	1	2			4			1	10
SULFONYLUREUMDERIVATEN	4	2		2	1	1	1		1	2	1	15
SYMPATHICOMIMETICA + CORTICO'S/OVERIGE GNM, EXCL ANTICHOL	1				2			3	1	7	36	50
SYMPATHICOMIMETICA MET ANTICHOLINERGICA	1							1				2
SYMPATHICOMIMETICA VOOR GLAUCOOM										1		1
TAXANEN						1		6				7
TESTOSTERON-5-ALFA-REDUCTASEREMMERS				1		1				2		4
TETRACYCLINES					1			1				2
THIAZIDEN	1	1	1		3	2		1	2	1	1	13
THIAZOLIDINEDIONEN										1		1
TRIAZOOLDERIVATEN			1		1			1	2		1	6
TROMBOCYTENAGGREGATIEREMMERS EXCL HEPARINE	1			3	12	4	5	5	2	3	14	49
TUMORNECROSEFACTOR-ALFA-ANTAGONISTEN					1		1			1	2	5
VASELINE EN VETPRODUCTEN									1			1
VERBINDINGEN ZONDER WERKING OP HET URINEZUURMETABOLISME	1											1
VERTIGOMIDDELEN									1			1
VETZUURDERIVATEN					1		1	1	1			4
VITAMINE B COMPLEX						1						1
VITAMINE B12 (CYANOCOBALAMINE EN ANALOGEN)			5	4	1		2	1	1		1	15
VITAMINE D EN ANALOGE VERBINDINGEN										1	5	6
VITAMINE K-ANTAGONISTEN	2		2	3	3	2	1	2	1	6	1	23
VOLUMEVERGROTENDE LAXANTIA					1	1				1		3
ZEER STERK WERKZAME CORTICOSTEROIDEN (GROEP IV)								1				1
ZWAVELBEVATTENDE IMIDAZOOLDERIVATEN										1		1
Eindtotaal	188	129	166	161	225	151	229	286	282	341	571	2729

Table 2. Reports on drug substitution per year on ATC-7 level.

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eindtotaal
ACENOCOUMAROL	1		2	1	2	2		2	1	5	1	17
ACETAZOLAMIDE					1							1
ACETYLSALICYLZUUR	1			1	3	3	1	2		1	3	15
ACICLOVIR						1						1
ACITRETINE										1		1
ALENDRONINEZUUR	16	2	1	2	1					1		23
ALENDRONINEZUUR MET COLECALCIFEROL					1					1		2
ALFUZOSINE	4	1	2		2	1		1				11
ALLOPURINOL			1									1
ALPRAZOLAM			1						1	1		3
AMIODARON								1				1
AMITRIPTYLINE			2				1	2		3	2	10
AMLODIPINE	2	3	2	2	1	1	5	2	2	2	2	24
AMOXICILLINE							1		1			2
AMOXICILLINE MET ENZYMREMMER					1							1
ANASTROZOL						6	3		1		1	11
ARIPIPRAZOL										1	1	2
ATENOLOL	1		1				1	1				4
ATORVASTATINE		1	3		5	4	11	13	16	4	6	63
AZATHIOPRINE						2	1				1	4
AZITROMYCINE											1	1
BACLOFEN			1	1			1			1	1	5
BARNIDIPINE									1		1	2
BECLOMETASON		1			2			1	1	1		6
BENZYLPENICILLINEBENZATHINE											4	4
BETAHISTINE									1			1
BICALUTAMIDE					2			1				3
BISACODYL			1									1
BISOPROLOL	1	1		1		1	2	2	2	3	1	14
BISOPROLOL MET THIAZIDEN										2		2
BRIMONIDINE										1		1
BROMAZEPAM							1				1	2
BUDESONIDE	1			2		1	2			2		8
BUMETANIDE				1								1
BUPRENORFINE										1	1	2
C1-ESTERASEREMMER, UIT PLASMA										1		1
CALCIUM MET VITAMINE D EN/OF ANDERE MIDDELEN		1							1	1	6	9
CANDESARTAN		1	1	1		1	1	1	2	1		9
CANDESARTAN MET DIURETICA								3			1	4
CAPECITABINE									4			4
CARBAMAZEPINE	1		1	4		1		1		3	5	16
CARBASALAATCALCIUM					4			2	1	2	4	13

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eindtotaal
CARBIMAZOL										1		1
CELECOXIB			1									1
CETIRIZINE									1		2	3
CHLOORTALIDON	1							2				3
CHLOROQUINE			1									1
CICLOSPORINE					1							1
CITALOPRAM	1	2	2		6	2	1	2		6	3	25
CLARITROMYCINE							1					1
CLOBAZAM								1			1	2
CLOBETASOL								1				1
CLOMIPRAMINE						1	1				1	3
CLONAZEPAM								3		2	1	6
CLOPIDOGREL				2	5	1	4	1	1		5	19
COLCHICINE	1											1
COLECALCIFEROL										1	5	6
COLESTYRAMINE									1		1	2
COMBINATIEPREPARATEN								1				1
CYPROTERON									1			1
CYPROTERON MET OESTROGEEN	1	5		3	5	1	1	2				18
DENOSUMAB											1	1
DESLORATADINE							7	2	3	2		14
DESOGESTREL									1			1
DEXAMFETAMINE										1	9	10
DIAZEPAM		3	1		1					1	1	7
DICLOFENAC	1		1	1				1	2	2		8
DICLOFENAC, COMBINATIEPREPARATEN	1											1
DILTIAZEM					2	1	2	1	2			8
DIPYRIDAMOL											2	2
DOCETAXEL						1		1				2
DOMPERIDON		1										1
DORZOLAMIDE						1	1					2
DOXAZOSINE					1							1
DOXYCYCLINE					1			1				2
DULOXETINE											6	6
DUTASTERIDE						1				1		2
EMTRICITABINE MET TENOFOVIR EN EFAVIRENZ			1									1
ENALAPRIL MET DIURETICA							1		1			2
ENALAPRIL/ENALAPRILAAT		1	6	4	4	3	1	1	2	4	2	28
EPITIZIDE MET KALIUMSPARENDE MIDDELEN		1						1				2
EPLERENON										1	1	2
ESCITALOPRAM									7	11	2	20
ESOMEPRAZOL				1	1	6	5	7		4	4	28
ESTRADIOL	1				1		1					3
ETANERCEPT					1		1					2

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eindtotaal
ETHINYLESTRADIOL (TABL. 0,01 - 0,05 MG)								1				1
ETHINYLESTRADIOL MET DESOGESTREL					1	4		1	1		1	8
ETHINYLESTRADIOL MET DROSPIRENON							3	2	2	3		10
ETHINYLESTRADIOL MET GESTODEEN			1	2		1			1	1		6
ETHINYLESTRADIOL MET LEVONORGESTREL	60	37	26	4	11	5	14	8	10	10	6	191
ETORICOXIB								1				1
EXEMESTAAN							2	2	1	1	1	7
FAMCICLOVIR									1			1
FELODIPINE		1										1
FENOBARBITAL											1	1
FENOTEROL MET IPRATROPIUMBROMIDE	1											1
FENPROCOUMON	1			2	1		1			1		6
FENTANYL	1						3	1	4	1		10
FEXOFENADINE			1						1	1		3
FINASTERIDE				1						1		2
FLECAINIDE	1		1	1					3	2	1	9
FLUCONAZOL					1				2		1	4
FLUOXETINE				1	2			1	2	1	2	9
FLUTICASON	1	1				1	1			2		6
FLUTICASON (FUROAAT)				1	1							2
FLUVASTATINE		2			1			1	1			5
FLUVOXAMINE					1							1
FOLIUMZUUR	1											1
FORMOTEROL	7	1									2	10
FORMOTEROL MET BECLOMETASON								2	1			3
FORMOTEROL MET BUDESONIDE	1				2			1		6	5	15
FOSINOPRIL				1				1	1			3
FOSINOPRIL MET DIURETICA		1										1
FUROSEMIDE			1		2			2				5
GABAPENTINE	1			1	3					1		6
GALANTAMINE							4			1		5
GEFITINIB										1		1
GEMFIBROZIL									1			1
GLICLAZIDE				1	1				1	2		5
GLIMEPIRIDE	4	2		1	1	1	1					10
GRANISETRON	1											1
HALOPERIDOL											1	1
HYDROCHLOORTHIAZIDE	1	1	1		3	2		1	2	1	1	13
HYDROCHLOORTHIAZIDE MET KALIUMSPARENDE MIDDELEN		1	1	1			1	1				5
HYDROCORTISON									1			1
HYDROXOCOBALAMINE			5	4	1		2	1	1		1	15
HYDROXYCARBAMIDE					1	1						2
HYDROXYCHLOROQUINE					1						2	3

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eindtotaal
IBANDRONINEZUUR							1	2		1		4
IMMUNOGLOBULINE, NORMAAL, INTRAVASCULAIR											4	4
INDACATEROL								1				1
INDAPAMIDE											1	1
INFLIXIMAB										1	2	3
INSULINE (HUMAAN)								1		1		2
INSULINE ASPART			3			1				1		5
INSULINE GLARGINE			2		1					1	4	8
INSULINE LISPRO											1	1
INTERFERON BETA 1A				1								1
IPRATROPIUM										2	3	5
IRBESARTAN							7	21	6	3	2	39
IRBESARTAN MET DIURETICA							1	3	9	2	1	16
ISOSORBIDEDINITRAAT	1	1							2			4
ISOSORBIDEMONONITRAAT			2					1	1			4
ISOTRETINOINE				1							2	3
ITRACONAZOL			1					1				2
KETOCONAZOL								1				1
KUNSTTRANEN EN ANDERE INDIFFERENTE PREPARATEN							1	1	2			4
LACTULOSE											1	1
LAMOTRIGINE	3			1	1		1	2			2	10
LATANOPROST							3		1		1	5
LERCANIDIPINE								1				1
LETROZOL							1	2				3
LEUPRORELINE								1		1	1	3
LEVETIRACETAM							2	2	1	4	1	10
LEVOCETIRIZINE				1	4	3	1		2	1		12
LEVODOPA										1		1
LEVODOPA MET DECARBOXYLASEREMMER			1	1	1	2		3		1	1	10
LEVOTHYROXINE			3	2	2	2	5	6	23	51	201	295
LISINOPRIL		1	1	4				2	2	3	1	14
LISINOPRIL MET DIURETICA					1		2					3
LOPERAMIDE							1					1
LORATADINE							1					1
LORAZEPAM					1		1					2
LOSARTAN		2			10	2	2	6	1	3	5	31
LOSARTAN MET DIURETICA				1	2	2	2	1	3	1	1	13
MACROGOL, COMBINATIEPREPARATEN		1			3	1	1	3	2	2	2	15
MEDROXYPROGESTERON								1				1
MELATONINE					1				1			2
MELOXICAM	1		1		1							3
MESALAZINE	2					1		1	1			5
METFORMINE	3	4	3	6	7	3	5	9	3	1	1	45
METHADON					3					3		6

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eindtotaal
METHOTREXAAT	1				20		2			5		28
METHYLFENIDAAT	4	2	4	3	4	8	7	4	16	38	17	107
METOPROLOL	12	16	9	9	9	5	4	9	9	6	5	93
METOPROLOL MET THIAZIDEN	1	1	2					1				5
MIRTAZAPINE			1		1		1	1				4
MODAFINIL			1						2			3
MOMETASON									3	4		7
MONTELUKAST	1						1	4	4	4	1	15
MORFINE				1							2	3
MULTI-ENZYMEN (LIPASE, PROTEASE, ENZ)			1			1						2
MYCOFENOLZUUR							2					2
NADROPARINE			2									2
NALTREXON									1			1
NAPROXEN		1			1							2
NARATRIPTAN										1		1
NEBIVOLOL				2								2
NEVIRAPINE									1	2		3
NIET INGEVULD	2	1	1	1	4	7	3	1	1			21
NIFEDIPINE	6	4						2		1		13
NITRAZEPAM	1					1						2
NITROFURANTOINE	1			1				1	1		1	5
NITROGLYCERINE		1	1									2
NIZATIDINE				1								1
OESTROGEEN MET NORETHISTERON				1								1
OESTROGENEN, GECONJUGEERD									1			1
OLANZAPINE							2	4				6
OMEPRAZOL	2	1	7	18	6	7	6	5	1	7	70	130
OVERIGE EMOLLIENTIA EN PROTECTIVA											1	1
OXALIPLATINE			1									1
OXAZEPAM										1	2	3
OXCARBAZEPINE								1		1		2
OXYBUTYNINE								1				1
OXYCODON								3		1		4
PACLITAXEL								5				5
PANTOPRAZOL				5	2	3	4	2	4	7	5	32
PARACETAMOL				1	3		2					6
PAROXETINE	2	2	4	7	7	7	3	5	3	5	4	49
PENFLURIDOL								6	2			8
PERINDOPRIL			16	4	7	3	3	4	3			40
PERINDOPRIL MET AMLODIPINE							1					1
PERINDOPRIL MET DIURETICA				1		1	1		1			4
PIOGLITAZON										1		1
PIPAMPERON									1			1
PIROXICAM					1							1

Som van AANTAL	JAAR											
ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Eind-totaal
PRAMIPEXOL					1	1	1			5		8
PRAVASTATINE	6		1	1	3		1	1			2	15
PREDNISOLON					1		1		4	1		7
PREDNISON						1					1	2
PREGABALINE		1									3	4
PROGUANIL, COMBINATIEPREPARATEN									2			2
PROPRANOLOL	3						1		2			6
PSYLLIUMZAAD					1	1				1		3
PYRIDOSTIGMINE						1						1
QUETIAPINE							4	1	2	3	4	14
QUINAPRIL/QUINAPRILAAT								1				1
RABEPRAZOL								2	4	2	1	9
RAMIPRIL	1	2			1	1	1	2				8
RANITIDINE			1		1	2	1			1	1	7
RISEDRONINEZUUR						4	2					6
RISPERIDON				3	1				1			5
RIVASTIGMINE								25	11		1	37
RIZATRIPTAN	1							2	3	4		10
ROPINIROL			1			1	1					3
ROSUVASTATINE		1				1	1		1	1	2	7
ROXITROMYCINE		1										1
SALBUTAMOL	3				1	1		1	1	2	38	47
SALBUTAMOL MET IPRATROPIUMBROMIDE								1				1
SALMETEROL								1				1
SALMETEROL MET FLUTICASON										1	31	32
SERTRALINE		3		2		1	4	2	1	5	3	21
SILDENAFIL								2	2			4
SIMVASTATINE	5	4	24	10	5	6	12	4	8	10	3	91
SIMVASTATINE MET EZETIMIB					1							1
SOTALOL		3	1		2	1		1				8
SPIRONOLACTON						1						1
SUCRALFAAT							1					1
SULFASALAZINE								1				1
SUMATRIPTAN	1	1		2	1	2		2	2	1		12
TACROLIMUS					1	1			1			3
TAMOXIFEN				1		1	2		4	4	3	15
TAMSULOSINE	4	1	1	3	1			2	2	3	2	19
TELMISARTAN				2	1		1		4	3		11
TELMISARTAN MET DIURETICA									2	2		4
TEMAZEPAM				1		1						2
TEMOZOLOMIDE					1				1			2
TERBINAFINE	1						1					2
THALIDOMIDE										1		1
TIBOLON											1	1

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