bijwerkingen centrumlareb

Tiotropium and decreased efficacy after substitution from brand Spiriva® to Tiotrus®

Introduction

Tiotropium (Tiotrus®) is a long-acting muscarinic antagonist (LAMA) and is indicated *as bronchodilator for maintenance treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD)* (1). Tiotropium is not the first choice in the treatment of COPD. When short-acting muscarinic antagonists (SAMA) and short-acting beta-2-antagonists (SABA) do not have sufficient therapeutic effect, therapy with tiotropium is indicated (2). On the Dutch market, several single unit dose inhalation devices for tiotropium are available, produced by different pharmaceutical companies. Tiotrus® of company Teva has been on the Dutch market since 2016 (1). Other tiotropium devices include Spiriva® of company Boehringer Ingelheim International GmbH, which was granted marketing authorization in the Netherlands in 2001 (3).

Reports

From December 1st, 2016 until January 7th, 2018 the Netherlands Pharmacovigilance Centre Lareb received 10 reports concerning possible decreased efficacy associated with tiotropium substitution from brand Spiriva® to Tiotrus®. The reports are listed in table 1.

Six cases involved women and four cases involved men. The ages varied between 63 and 80 years. Tiotrus® was withdrawn in seven cases, in all these cases the patients switched back to brand Spiriva®. In four of these reports it was described that at the moment of reporting, the patients recovered or were recovering after switching back to brand Spiriva® (B, C, F, I). One patient was recovering after treatment of dyspnea with prednisolone and doxycycline, and switching back to Spiriva® (D). One patient did not recover at time of reporting, after Tiotrus® was replaced by Spiriva® (A) and in one patient the outcome was unknown (J). One patient was recovering at time of reporting, while the dose was not changed (E). In two cases it was unknown which action was taken with respect to the drug (G, H).
One patient (case C) had metastatic lung cancer and one patient (case E) had a possible lung infection at the time of start of the adverse drug events. Two reporters mentioned that Tiotrus® was more difficult to handle than Spiriva®. Inhaling was harder with Tiotrus® (case D) and the Tiotrus® Zonda® haler was more difficult to open than the Spiriva® Handihaler® (case I). In one report (case A) the patient tasted granules in the mouth. One reporter (B) mentioned that they had noticed complaints after substitution from Spiriva® to Tiotrus® more often; these complaints were not further specified.

Table 1. Reports of possible decreased efficacy with drug substitution from brand Spiriva® to brand Tiotrus® in the Lareb database

Patient, Sex, Age, (years), Source	**Drug, Indication for use**	**Concomitant medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug, Outcome**
A: 230500, F, 61-70, Pharmacist	Tiotrus®, 18 mcg, 1dd1, COPD		Therapeutic response unexpected with drug substitution Therapeutic response decreased Itchy throat Pharmaceutical product complaint	Hours, withdrawn, not recovered/not resolved

Patient, Sex, Age, (years), Source	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, Outcome
B: 233147, F, 71 years and older, Pharmacist	Tiotrus®, 18 mcg, 1dd1, asthma/COPD	Metformin Paroxetine Valsartan Gliclazide Doxycycline Isosorbide mononitrate Insulin detemir Insulin aspart Salbutamol/ipratropium Formoterol/budesonide Salmeterol/fluticasone Salbutamol Atorvastatin Sotalol Acenocoumarol Prednisolone Fluticasone nasal spray Lansoprazole	Therapeutic response unexpected with drug substitution Dyspnoea	2 weeks, withdrawn, recovered/resolved
C: 234711, F, 61-70, Other	Tiotrus®, 18 mcg, 1dd1, COPD	Paracetamol Cholecalciferol Diazepam Prednisolone Pantoprazole Acetylsalicylic acid Escitalopram Salbutamol/ipratropium Formoterol/beclomethasone	Therapeutic response unexpected with drug substitution Exercise tolerance decreased COPD exacerbated	5 days for the reaction exercise tolerance decreased and 4 weeks for the reaction COPD exacerbated, withdrawn, recovering/resolving
D: 235534, F, 61-70, Pharmacist	Tiotrus®, 18 mcg, 1dd1, COPD	Salmeterol/fluticasone	Therapeutic response unexpected with drug substitution Pharmaceutical product complaint COPD exacerbation	Unknown, withdrawn, recovering/resolving
E: 236470, M, 61-70, Other	Tiotrus®, 18 mcg, 1dd1, COPD	Benzbromaron Pantoprazole Carvedilol Macrogol Fentanyl Beclomethasone/formoterol Spironolactone Bumetanide Acetazolamide Acenocoumarol Digoxin Salbutamol Ipratropium Tamsulosin	Therapeutic response unexpected with drug substitution COPD exacerbation	2 weeks, dose not changed, recovering/resolving
F: 243752, F, 71 years and older, Consumer	Tiotrus®, 18 mcg, 1dd1, dyspnoea	Amiodarone Atorvastatin Colecalciferol solution Furosemide Acenocoumarol Alfacalcidol Lisinopril Temazepam Brimonidine Ezetimib Bimatoprost	Therapeutic response unexpected with drug substitution Dyspnoea Oral pain Cardiac disorder	Days, withdrawn, recovered/resolved
G: 244592, M, 61-70, Consumer	Tiotrus®, 18 mcg, 1dd1, asthma		Therapeutic response unexpected with drug substitution Dyspnoea Cough Nausea Headache	1 minute, unknown, not recovered

Patient, Sex, Age, (years), Source	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, Outcome
H: 244962, M, 61-70, Consumer	Tiotrus®, 18 mcg, unknown, COPD		Therapeutic response unexpected with drug substitution Dyspnoea	Within a month, unknown, not recovered
I: 259509, F, 61-70, Consumer	Tiotrus®, 18 mcg, 1dd1, dyspnoea *Batchnumber: LC31445*	Indacaterol	Therapeutic response unexpected with drug substitution, Lack of drug effect Dyspnoea	2 days, withdrawn, recovering/resolving
J: 260503, M, 71 years and older, Pharmacist	Tiotrus®, 18 mcg, 1dd1, COPD		Therapeutic response unexpected with drug substitution COPD exacerbation Cough	24 days, withdrawn, unknown

Seven other comments on the Tiotrus® substitution were found on the website meldpuntmedicijnen.nl where people can post about the problems they are experiencing with their medication (4). This website is maintained by the Instituut voor Verantwoord Medicijngebruik. The narratives of these comments are translated from Dutch. These were reported between 11-09-2017 and 06-04-2018.One of the patients mentions that the powder sticks to the capsules.

"I am using Tiotrus® 10 mcg as a replacement for the Spiriva® 18 mcg now for over a week. My experience is that the powder precipitates in the back of my throat/palate. Inhaling with the Zonda® inhaler is more difficult for me because of my dyspnoea, which I did not experience with the Handihaler® of Spiriva®. My complaints of coughing, mucus secretion and dyspnoea increased immediately. Fortunately, I am back on the Spiriva® again, which immediately gave me a reduction of the symptoms."

"There is a lot of powder stuck in my mouth and throat. I am therefore afraid that the drug is less effective than Spiriva®, which I had before. I tried to put a capsule of Tiotrus® in the Spiriva® inhaler and then there was also much more powder in my mouth/throat than with the Spiriva® capsules, while I inhaled in the same way."

"I used Spiriva® and that worked perfectly. The symptoms of dyspnoea, coughing and mucus secretion decreased. Now I am on Tiotrus® and the symptoms get worse again."

"I have used Spiriva® for years. I have switched to Tiotrus®. I have a sore throat with cough and I have dyspnoea. I am switching back to Spiriva®."

"I always used Spiriva®, to great satisfaction. Suddenly I got switched to Tiotrus®, an unpleasant surprise. I immediately noticed that the powder partly sticks to the capsules. Before use, I try to loosen the powder in the capsule, which is hardly working. It just sticks to it. I often have to inhale hard 4 times. I taste the powder, it does not or only partly reaches the lungs. After the first use I had a sore throat, I had to cough and I had dyspnoea. All complaints that I do not have with Spiriva®."

"Before I used Spiriva®. With Tiotrus® the powder stays in the mouth and on the inhaler".

"The small inhaler (green/white) works very bad. Mostly the powder is in the mouth instead of the lungs. I used to have Spiriva® which I really liked."

Other sources of information

SmPC

Tiotropium of brand Tiotrus® contains the excipient hypromellose (E464) whereas tiotropium of brand Spiriva® does not. Tiotrus® (Zonda® inhaler) and Spiriva® (Handihaler®) are similar in device (4), but the capsules that contain the tiotropium are different. Tiotrus® capsules are stored in a bottle, whereas Spiriva® capsules are produced in blisters. Because the drug is stored differently, this possibly influences the availability of the powder, due to a difference in humidity.

Spiriva® capsules contain 18 microgram tiotropium, whereas Tiotrus® capsules contain 13 microgram tiotropium. However, the dose that leaves the mouthpiece of the inhalers is claimed to be the same for both devices, which is 10 microgram (1;3;5). Table 2 shows the composition of Tiotrus® and Spiriva® capsules (1;3;5).

Table 2. Capsule composition of Tiotrus® and Spiriva®.

	Tiotropiumbromide	*Tiotropium*	*Lactose*
Tiotrus®	16 µg	13 µg	18 mg
Spiriva®	22.5 µg	18 µg	5.5 mg

Literature

The guideline for generic substitution of the Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP) recommends for tiotropium (categorized as "f" in the guideline), to switch only after permission from the prescriber, which in practise usually means that doctors and pharmacists make agreements about this (6).

Mechanism

The efficacy of dry-powder inhalers depends on several factors which are patient, drug or device related. Patient related factors include inhalation technique, compliance and inspiratory flow rate. The lung deposition of tiotropium (when using Handihaler®) is sufficient at an inspiratory flow rate of 20 L/min. This inspiratory flow rate can also be attained by patients with severe COPD. Device related factors like excipients, drug formulation and particle size also affect the lung deposition of tiotropium. The particle size in dry-powder inhalers depends on inspiratory flow rates of the patient, which also depends on the resistance within the device (7-11).

Prescription data

Table 4. Number of patients using tiotropium in the Netherlands between 2012 and 2016 (12).

Drug	**2012**	**2013**	**2014**	**2015**	**2016**
Tiotropium	245,140	244,150	238,920	236,870	229,700

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 10 reports of a possible decreased efficacy associated with tiotropium substitution from brand Spiriva® to Tiotrus®. In four reports it was described that the patients switched back to brand Spiriva® and recovered or were recovering at the moment of reporting.

It needs to be further investigated whether a difference in capsule storage, difficulty in handling, difference in excipients and a possible difference of resistance within the devices, could lead to a decreased efficacy of tiotropium after substitution from brand Spiriva® to Tiotrus®.

Reference List

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(2) Nederlands Huisartsen Genootschap (NHG). NHG-Standaard COPD. (version date 2015, access date 12-3-2018) https://www.nhg.org/standaarden/volledig/nhg-standaard-copd;
(3) Dutch SmPC Spiriva® 18 microgram, inhalatiepoeder in harde capsules. (version date 9-12-2016, access date 12-3-2018) https://db.cbg-meb.nl/IB-teksten/h26191.pdf;
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(5) Teva. Tiotrus Zonda® productinformation. (version date 28-6-2016, access date 13-3-2018) https://www.apotheekkennisbank.nl/system/files/free/scheurblok_a5_tiotrus_zonda_110_245_16_high_res.pdf;
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(11) Chodosh S, Flanders JS, Kesten S, Serby CW, Hochrainer D, Witek jr TJ. Effective delivery of particles with the HandiHaler dry powder inhalation system over a range of chronic obstructive pulmonary disease severity. J Aerosol Med. 2001;14:309-15.
(12) GIP database - Drug Information System of Dutch Health Care Insurance Board. (version date 21-11-2017, access date 13-3-2018) http://www.gipdatabank.nl.

This signal has been raised on June 7, 2018. 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