

## 1.1. Salmeterol with fluticasone and lack of efficacy after drug substitution

### Introduction

Salmeterol with fluticasone (Seretide<sup>®</sup>, Airflusal<sup>®</sup>) is a combination of a selective long-acting  $\beta_2$ -adrenoreceptor agonist and a locally-acting glucocorticoid. It is registered in the Netherlands since 1999 [1]. Salmeterol with fluticasone is indicated for *the treatment of asthma in patients who are inadequately controlled with an inhalation corticosteroid and a short-acting  $\beta_2$ -adrenoreceptor agonist or in patients who are already adequately controlled with a corticosteroid and a long-acting  $\beta_2$ -adrenoreceptor agonist*. Also, salmeterol with fluticasone can be used for *the symptomatic treatment of patients with chronic obstructive pulmonary disease (COPD) with repeated exacerbations despite the use of a bronchodilator* [2-4].

Drug substitution is the mutual replacement of drugs having the same active ingredient, the same dose and the same pharmaceutical form. The generic product is equivalent to the reference product, but may differ in excipients, salt form or color. Generic drugs are subject to the same criteria as the reference drug, which means that they must meet the same requirements of the pharmaceutical legislation [5,6].

Since the start of 2016, the generic products of salmeterol with fluticasone of brand Vincion<sup>®</sup> are included in the preference policy of three of the largest health insurers in the Netherlands, namely VGZ, CZ and Menzis [7-9]. This means that these health insurers no longer reimburse the proprietary brand of salmeterol with fluticasone, except for patients with a medical necessity for Seretide<sup>®</sup>. Although, there have been several generic products of salmeterol with fluticasone on the market for some years, the use of these inhalers lagged behind till January 2016. This changed with the inclusion in the preference policy which resulted in an increase in the generic supply from 2.6% in December 2015 to 19.3% in April 2016 [10].

This signal concerns the reports of a lack of efficacy or pulmonary complaints that may indicate a decreased therapeutic response after substitution of salmeterol with fluticasone of brand Seretide<sup>®</sup> to brand Vincion<sup>®</sup> or brand Focus<sup>®</sup>. The generic products of brand Focus<sup>®</sup> are parallel imported products of salmeterol with fluticasone of brand Vincion<sup>®</sup>. The manufacturers of both Focus<sup>®</sup> and Vincion<sup>®</sup> are Cipla (EU) and Cipla Europe NV. Besides Cipla, S&D Pharma CZ is another manufacturer of salmeterol with fluticasone of brand Focus<sup>®</sup> [1,4,11].

### Reports

Between March 17<sup>th</sup> 2016 and November 17<sup>th</sup> 2016 the Netherlands Pharmacovigilance Centre Lareb received 22 reports of a decreased therapeutic response or pulmonary complaints after drug substitution of salmeterol with fluticasone of brand Seretide<sup>®</sup> to brand Vincion<sup>®</sup> or Focus<sup>®</sup>. In addition, Lareb received two reports of a pharmaceutical product complain after substitution to brand Vincion<sup>®</sup>. Besides, during the same period five more reports of an unexpected drug effect were received after substitution to an unknown brand of salmeterol with fluticasone. However, since there is no certainty about the manufacturer of those products, these reports were excluded.

Table 1. Reports of a decreased therapeutic response, pulmonary complaint or pharmaceutical product complain after drug substitution of salmeterol with fluticasone of brand Seretide<sup>®</sup> to brand Vincion<sup>®</sup> or brand Focus<sup>®</sup>.

Number, Sex, Age, Reporter	Suspect drug, Dose, Indication, Batch/ lot number, RVG number	Concomitant medication	Reaction	Time to onset, Action with drug, Outcome
A: 223842, M, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 $\mu$ g/do 2dd1, COPD, unknown, 115996	digoxin, furosemide, tiotropium, atorvastatin, thiamine, calcium carbonate/cholecalciferol	pneumonia, dyspnoea, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	3 weeks, unknown, fatal

<b>Number, Sex, Age, Reporter</b>	<b>Suspect drug, Dose, Indication, Batch/ lot number, RVG number</b>	<b>Concomitant medication</b>	<b>Reaction</b>	<b>Time to onset, Action with drug, Outcome</b>
B: 215667, M, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion®/Focus®)*, 25/250 µg/do 2dd2, COPD, unknown, unknown	acetylsalicylic acid, albuterol, omeprazole	COPD exacerbation, therapeutic response unexpected with drug substitution from Seretide®	2 weeks, dose not changed, unknown
C: 215758, F, 51-60, pharmacist	salmeterol/fluticasone (Vincion®), 25/250 µg/do 2dd2, asthma/COPD, unknown, 115996	ipratropium	lack of drug effect (dyspnoeic again), therapeutic response unexpected with drug substitution from Seretide®	1 day, unknown, not recovered
D: 216495, M, 31-40, consumer	salmeterol/fluticasone (Focus®), 25/250 µg/do 2dd1, asthma, unknown, 118648//115996 OR 118867//115996	desloratadine	cough, dyspnoea, chest pressure, therapeutic response decreased, therapeutic response unexpected with drug substitution from Seretide®	2 days, drug withdrawn (returned to Seretide®), recovered
E: 217581, F, 31-40, pharmacist	salmeterol/fluticasone (Vincion®), 25/250 µg/do 2dd1, asthma, unknown, 115996	-	dyspnoea exacerbated, therapeutic response unexpected with drug substitution from Seretide®	2 weeks, drug withdrawn, recovered
F: 219482, F, 61-70, consumer	salmeterol/fluticasone (Vincion®), 25/250 µg/do 2dd1, COPD, unknown, 115996	glycopyrronium	dyspnoea, oxygen saturation decreased, therapeutic response unexpected with drug substitution from Seretide®	12 hours, drug withdrawn (returned to Seretide®), recovered 1 day after withdrawal
G: 220205, M, 8-10, pharmacist	salmeterol/fluticasone (Vincion®), 25/125 µg/do 2dd1, asthma, unknown, 115995	mometasone nose spray	dyspnoea, fatigue extreme, migraine, therapeutic response unexpected with drug substitution from Seretide®	2 days, drug withdrawn (started with Flixotide® and albuterol), recovered 17 days after start of the reaction
H: 220671, M, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion®), 25/250 µg/do 2dd1 asthma/COPD, unknown, 115996	beclomethasone, pantoprazole, tamsulosin, colecalciferol	coughing, therapeutic response unexpected with drug substitution from Seretide®	5 days, drug withdrawn, recovering
I: 222174, F, 61-70, consumer	salmeterol/fluticasone (Seroflo®)**, 25/250 µg/do 2dd1, chronic bronchitis/COPD, GB50095/A, 118648//115996	oxazepam, diltiazem, omeprazole, albuterol, mometasone nose spray, carbasalate calcium, codeine, thiamine, citalopram, tiotropium, nitroglycerin spray, buprenorphine plaster, levocetirizine, bisoprolol	dyspnoea, dysphonia, throat irritation, cough, therapeutic response unexpected with drug substitution from Seretide®	1 minute, drug withdrawn, recovering

<b>Number, Sex, Age, Reporter</b>	<b>Suspect drug, Dose, Indication, Batch/ lot number, RVG number</b>	<b>Concomitant medication</b>	<b>Reaction</b>	<b>Time to onset, Action with drug, Outcome</b>
J: 222305, M, 7 years and older, general practitioner	salmeterol/fluticasone (Focus <sup>®</sup> ), 25/250 µg/do 2dd2, COPD, gb50078/a 118648//115996	enalapril/hydrochlorothiazide, carbasalate calcium, dipyridamole, latanoprost, pantoprazole, simvastatin, tamsulosin, hydrochlorothiazide, amlodipine	dyspnoea, cardiac failure, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	1 day, drug withdrawn (returned to Seretide <sup>®</sup> ), recovered
K: 223245, M, 50-60, consumer	salmeterol/fluticasone (Focus <sup>®</sup> ), 25/250 µg/do 2dd2, asthma, GB50059/A, 118648//115996	-	dyspnoea exacerbated, cough aggravated, therapeutic response decreased, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	within 2 days, drug withdrawn (returned to Seretide <sup>®</sup> ), recovered from dyspnea 1 day after withdrawal and recovered from cough within 1 week after withdrawal.
L: 223880, F, 60-70, consumer	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 4dd2, COPD, GB60740, 115996	tiotropium, fluticasone furoate	cough, chest pain, dyspnea, sputum increased, wheezing, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	7 days, drug withdrawn (returned to Seretide <sup>®</sup> ), recovered 1 week after withdrawal
M: 224558, M, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/125 µg/do 2dd1, unknown, unknown, 115995	metformin, pravastatin, mirtazapine, omeprazole, tiotropium	wheezing, dry mouth, dyspnoea, cough aggravated, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	15 days, drug withdrawn (returned to Seretide <sup>®</sup> ), recovered
N: 224616, M, 60-70, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 2dd2, unknown, unknown, 115996	albuterol, psyllium, levocetirizine, nitroglycerin, fluticasone furoate, clopidogrel	hoarseness, dyspnea, common cold, loss of voice, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	2 months, drug withdrawn (returned to Seretide <sup>®</sup> ), recovered
O: 224617, F, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 2dd2, unknown, unknown, 115996	acenocoumarol, diazepam, bisoprolol, levocabastine, ipratropium, calcium carbonate/colecalciferol, alendronic acid	productive cough, pulmonary function test decreased, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	unknown, drug withdrawn, unknown
P: 224618, F, 50-60, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 2dd2, unknown, unknown, 115996	isradipine, telmisartan, tiotropium, indacaterol	therapeutic response decreased, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	2 months, drug withdrawn, unknown

<b>Number, Sex, Age, Reporter</b>	<b>Suspect drug, Dose, Indication, Batch/ lot number, RVG number</b>	<b>Concomitant medication</b>	<b>Reaction</b>	<b>Time to onset, Action with drug, Outcome</b>
Q: 224619, F, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/125 µg/do 2dd2, unknown, unknown, 115995	betahistine, ketotifen, tiotropium, hypromellose eye drops, polyethylene glycol, paroxetine, colecalciferol, enteral nutrition (Respifor <sup>®</sup> & Nutridrink <sup>®</sup> )	dyspnoea, cough, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	6 weeks, drug withdrawn, recovered
R: 224621, F, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 2dd2, unknown, unknown, 115996	spironolactone, digoxin, furosemide, acenocoumarol, simvastatin, nebivolol	pneumonia, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	5 months, unknown, recovered
S: 226098, F, 70 years and older, pharmacist	salmeterol/fluticasone (Focus <sup>®</sup> ), 25/250 µg/do 3dd2, asthma, unknown, 118648//115996 OR 118867//115996	calcium carbonate, isosorbide mononitrate, paroxetine, omeprazole, rosuvastatin, colecalciferol, alendronic acid, fluticasone furoate	shortness of breath, therapeutic response decreased, therapeutic response unexpected with drug substitution from brand unknown	5 minutes, drug withdrawn (returned to previous brand), recovered
T: 227521, M, 51-60, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 2dd1, COPD, GB60873, 115996	fluoxetine, diclofenac, fenoterol/ipratropium	wheezing, dyspnoea, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	1 day, drug withdrawn (returned to Seretide <sup>®</sup> ), recovering
U: 229687, M, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 2dd2, COPD, unknown, 115996	-	lung function decreased, therapeutic response decreased	weeks, unknown, unknown
V: 229674, M, 8-10, consumer	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/125 µg/do 2dd1, asthma, gb60775, 115995	-	dyspnea, therapeutic response decreased, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	days, drug withdrawn (returned to Seretide <sup>®</sup> ), not recovered
W: 215824, M, 51-60, consumer	salmeterol/fluticasone (Vincion <sup>®</sup> ), unknown 4dd1, asthma, unknown, 115995 OR 115996	-	spot before eyes, headache, pharmaceutical product complain, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	20 minutes, drug withdrawn, not recovered
X: 224620, F, 70 years and older, pharmacist	salmeterol/fluticasone (Vincion <sup>®</sup> ), 25/250 µg/do 2dd2, unknown, unknown, 115996	acetylsalicylic acid 80mg, bisoprolol 5mg, simvastatin 40mg, candesartan 16mg, montelukast 10mg, pantoprazole 20mg, calcium carbonate/colecalciferol 500mg/800IE	pharmaceutical product complain, therapeutic response unexpected with drug substitution from Seretide <sup>®</sup>	unknown, drug withdrawn, unknown

\* unclear whether brand Vincion<sup>®</sup> or brand Focus<sup>®</sup> was administrated

\*\* Seroflo is brand Focus<sup>®</sup>

A: Serious report. Three weeks after substitution to Vincion® the patient had a pneumonia for which he was treated with amoxicillin. In the three following months the patient received three more antibiotic treatments and prednisolone. Eventually the patient died several months after substitution to Vincion®. The cause of death is unknown. The medical history indicates that the patient had a pneumonia before in 2015 for which he was treated with doxycycline.

D: The reporter mentioned that he was constantly coughing (every 2 minutes). He also felt a new asthma attack rising and became more and more dyspnoeic each day. The patient uses a spacer device (Volumatic®).

E: The patient was treated with prednisolone. The reporter mentioned that she had more patients with similar complaints and increased mucus production after substitution to Vincion®. Some of them were also treated with prednisolone.

F: The reporter mentioned that 12 hours after substitution her oxygen saturation level decreased to 86 during the whole day. Normally, her oxygen saturation level was well above 90. After 3 days the patient returned to Seretide®. After one day her oxygen saturation level increased to 94-95 again.

H: The reporter mentioned that the patient uses an Aerochamber®.

I: The patient was treated with extra albuterol, codeine and honey. The reporter mentioned that her COPD /chronic bronchitis was well controlled for years. After substitution to Seroflo® her COPD/ chronic bronchitis was dysregulated for almost three months. The reporter also described that the inhaler was impractical and that she had to push much harder. Also, the Seroflo® did not show the exact number of the remaining doses, but reflected a range of 60 to 80 doses. The patient uses a spacer device (Volumatic®).

J: The patient was treated with ipratropium. The reporter mentioned that there may be some coincidence with heart failure (pro BNP 153.9). The medical history indicates that the patient had a cerebrovascular accident, atrial fibrillation, cardiac failure and hypertension.

K: The reporter mentioned that one week after substitution he increased the dose from once a day two doses to twice a day two doses. Increasing the dose did not improve the symptoms. In addition, the reporter mentioned that the opening of the inhaler fits more tightly in the Aerochamber plus flow-vu®, that the whistle of the Aerochamber® does not work with the inhaler of Focus® and that a lot of air is leaking along the metal aerosol container.

L: The patient was treated with prednisolone and antibiotics. The reporter mentioned that it felt that the salmeterol with fluticasone of brand Vincion® came not as deep into the lungs compared to Seretide®. The patient uses a spacer device.

O: The patient was treated with doxycycline and prednisolone. The patient returned to Seretide®, but after 13 days the Seretide® was also withdrawn and replaced by beclomethasone with formoterol.

P: The reporter mentioned that inhalation with this device felt different.

Q: Positive re-challenge. The drug salmeterol with fluticasone of brand Vincion® was withdrawn and the patient returned to Seretide®. The patient recovered and experienced no dyspnea anymore. After 1 month, the patient switched to the generic product of Vincion® again after which the complaints returned. Two weeks later, salmeterol with fluticasone of Vincion was withdrawn and the patient returned to Seretide® after which she recovered.

R: The patient was treated with doxycycline, prednisolone and albuterol.

S: The reporter mentioned that this is the second patient in one week with this kind of complaint.

T: The patient consulted the pulmonologist. The reporter mentioned that the patient did not notice any differences in inhaling.

W: The reporter mentioned that the generic product of Vincion® does not work, has a different appearance and holding the product feels different as well.

X: The reporter mentioned that it is difficult to push the button of the aerosol of brand Vincion®. With the salmeterol with fluticasone of brand Seretide® she could do this with one hand, but with brand Vincion® it is even difficult using two hands.

Note: Reports A,M,N,O,P,Q,R and X have the same reporter.

## Other sources of information

### *SmPC*

The generic salmeterol with fluticasone of brands Vincion® and Focus® contain the same excipient (norflurane HFA 134a) as salmeterol with fluticasone of brand Seretide®. They also have an identical pharmaceutical form (aerosol, suspension). What differs is that salmeterol with fluticasone of brand Seretide® is registered for children of 4 years and older, while the product information of the generic products of brands Vincion® and Focus® specify that they are not suitable for children [2,4,11].



### Literature

In the guideline for generic substitution of the Royal Dutch Pharmacist Association it is recommended to be very cautious regarding substitution with inhalants like salmeterol and fluticasone. They stated that continuing the same type of inhaler is important for compliance and an appropriate and safe use, especially in patients who use more than one inhaler [5].

Several articles describe the possible effects of generic substitution of inhaler devices on the treatment of asthma or COPD. Substitution without an appropriate training for the patient can contribute to poor clinical outcomes [12,13]. Since each device has its own inhalation technique, substitution can cause confusion and inappropriate use, resulting in less inhalation of the medication. Also, the different appearance of the generic products, might negatively impact the compliance [14]. Incorrect use and non-compliance are major factors in worsening the asthma control and COPD outcomes. Substitution may exacerbate these aspects, especially in patients which are unwilling to switch [15].

### Prescription data

Table 2. Number of patients using salmeterol with fluticasone (Seretide®) in the Netherlands between 2010 and 2014 [16].

Drug	2010	2011	2012	2013	2014
salmeterol/fluticasone (Seretide®)	378,500	373,260	363,160	342,580	321,320

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 22 reports of a decreased therapeutic response or pulmonary complaints after drug substitution of salmeterol with fluticasone of brand Seretide® to brand Vincion® or brand Focus®. In addition, two reports of a pharmaceutical product complain were received concerning the generic products of brand Vincion® (W, X). In six reports, a pneumonia (A, R), chest pressure (D), cardiac failure (J), chest pain (L) or common cold (N) were also reported. Although symptoms in patients with asthma or COPD can fluctuate over time due to various (environmental) factors, it is remarkable that most patients recovered after withdrawal of the generic product of brand Vincion® or brand Focus®. In addition, one patient showed a positive de- and re-challenge.

For both salmeterol and fluticasone generic substitution is not recommended, since this might negatively affect the patients compliance, the adequate use of the device and the treatment outcome [5,12,14,15]. The decreased therapeutic responses and pulmonary complaints which may indicate a lack of efficacy cannot be explained by a difference in excipients, since both the generic and reference product contain norflurane HFA 134a. A possible explanation for the perceived lack of efficacy of the substituent formulas might be differences in handling characteristics and/or altered flow characteristics of the medication in combination with certain inhalation devices.

Besides this, it is noteworthy that the generic salmeterol with fluticasone of brands Vincion® and Focus® are not suitable for children, while Seretide® is registered for children of 4 years and older. Among the received reports, there were two reports in children (age 8 and 9) who received the Vincion® inhaler. Lareb wished to bring this to the attention of the MEB.

### References

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*This signal has been raised on January 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](http://www.cbg-meb.nl)*