

## Overview of inhaled and nasal corticosteroids and haematoma

### Introduction

Inhaled glucocorticoids (ICS) are widely used *to treat asthma and chronic obstructive pulmonary disease (COPD)*. Nasal glucocorticoids are used to treat *allergic rhinitis*. ICS and nasal glucocorticoids are associated with fewer and less severe adverse effects than orally-administered glucocorticoids. However, systemic effects can occur, particularly when they are used in high doses over long periods of time. A patient's risk of developing adverse systemic effects from ICS is influenced by several factors, including the dose delivered to the patient, the site of delivery, the delivery system used, individual differences in the response to the glucocorticoid and individual characteristics (e.g. age, sex, smoking, dietary calcium and vitamin D and activity level) [1].

Topical and oral glucocorticoids cause thinning of the skin, telangiectasia, and easy bruising. These effects may result from loss of extracellular ground substance within the dermis, due to an inhibitory effect on dermal fibroblasts. There are reports of increased skin bruising and purpura in patients using inhaled corticosteroids. Easy bruising in association with inhaled corticosteroids is more frequent in elderly patients [1]. Elderly patients have more fragile skin and are more sensitive to haematoma.

Lareb reported about haematoma and inhaled or nasal corticosteroids in the past. In 2008, the Signal "Inhaled and intranasal fluticasone propionate and haematoma" [2] and in 2017 "Beclomethasone/formoterol and haematoma" were reported [3].

At the request of the Medicines Evaluation Board (MEB) we will provide an overview of the cases of haematoma associated with the use of inhaled or nasal corticosteroids reported to Lareb.

### Reports

Until January 19<sup>th</sup> 2018 the Netherlands Pharmacovigilance centre Lareb received 97 reports of haematoma associated with the use of inhaled or nasal glucocorticoids (Table 1). To retrieve these reports from the Lareb database the MedDRA Preferred Terms (PTs) haematoma, ecchymosis, purpura, skin haemorrhage, bleeding tendency and contusion were used.

Table 1. Number of reports associated with the various products\*

	Inhaled glucocorticoid	Nasal glucocorticoid
Fluticasone	13	10
Salmeterol + fluticasone	22	-
Formoterol + budesonide	19	-
Beclomethasone	17	-
Budesonide	8	3
Formoterol + beclomethasone	7	-
Ciclesonide	5	-
Mometasone	-	1

\*8 reports contained 2 products as suspect drugs.

The majority of reports concerned women (n=65), while 32 reports concerned men. Age varied from five to 85 years, median age was 62 years. Reported indications were asthma/COPD (n=69), allergic rhinitis (n=5), nasal polyps (n=2), viral infection (n=1), sarcoidosis (n=1) and drug use for unknown indication (n=27). PTs reported were haematoma (n=55), purpura (n=24), contusion (n=9), ecchymosis (n=7), skin haemorrhage (n=2) and increased tendency to bruise (n=1). Latency ranged from one hour to 20 years, with a median latency of five months. Ten patients reported that they recovered or were recovering after drug withdrawal and one patient reported that he was recovering after dose reduction.

Some representative cases will be described in detail below:

#### 218677

This non-serious report from a consumer concerns a woman aged 41-50 years with hematoma following administration of formoterol and budesonide for asthma with a latency of 10 months after start. The dose for formoterol/budesonide was not changed. The patient had not recovered. Concomitant medication was not reported. The patient used formoterol/budesonide in the past and also experienced hematoma.

**243271**

This non-serious report from a consumer concerns a man aged 51-60 years, with skin atrophy, bleeding tendency (after little skin damage) and hematomas (especially on the arms and legs) following administration of formoterol/beclomethasone for asthma with a latency of 2 years after start. The drug formoterol/beclomethasone was withdrawn. It was replaced by mono-preparations of formoterol and beclomethasone in order to adapt the doses separately. The patient recovered from bleeding tendency and the occurrence of hematomas. The patient had not recovered from skin atrophy. Concomitant medication was not reported. Coagulation tests showed no abnormalities.

**60889**

This non-serious report from a pharmacist concerns a woman aged 51-60 years, with the occurrence of haematoma following administration of salmeterol/fluticasone for asthma with a latency of months after start. The dose was not changed. The patient had not recovered. Concomitant medication was pantoprazole and macrogol. The patient also had haematoma following previous treatment with beclomethasone. Coagulation tests showed no abnormalities.

**169409**

This non-serious report from another health professional concerns a male aged 5-7 years with haematoma following administration of fluticasone for asthma with a latency of two months after start. The drug fluticasone was withdrawn. The patient recovered two months later. Concomitant medication was desloratadine.

**107785**

This non-serious report from a general practitioner concerns a woman aged 31-40 years, with a large haematoma (diameter of 10 cm, after scratching on clinically normal skin) following administration of beclomethasone/formoterol for asthma and fluticasone (furoate) for allergic rhinitis with a latency of five months after start. The dose was not changed. The patient outcome was unknown. Concomitant medication was levocetirizine.

**Other sources of information**

*SmPC*

When looking in the SmPC [4] of the inhaled or nasal corticosteroids with the lowest RVG number only six SmPCs mention bruise or contusion in paragraph 4.8 (Table 2.).

Table 2. Overview of mentioning bruise/contusion in SmPC of inhaled or nasal glucocorticoids.

<b>Corticosteroid with beta2-sympathomimetics</b>	<b>SmPC</b>
Formoterol + beclomethasone	-
Formoterol + budesonide	Bruise
Formoterol + fluticasone	-
Salmeterol + budesonide	Contusion, haematoma of the skin
Salmeterol + fluticasone	Contusion
Vilanterol + fluticasone	-
<b>Inhalation corticosteroid</b>	
Beclomethasone	-
Budesonide	Bruise
Ciclesonide	-
Fluticasone	Contusion
<b>Nasal corticosteroid</b>	
Beclomethasone	-
Budesonide	Contusion
Fluticasonefuroate	-
Fluticasonepropionate	-
Fluticasone + azelastine	-
Mometasone	-
Triamcinolone	-

### Literature

There are several publications that describe the occurrence of haematoma when using inhaled corticosteroids. Malo et al. [5] performed a double-blind crossover study, where after a baseline period, sixty-nine asthmatic subjects received inhaled beclomethasone or fluticasone (at half the dose of beclomethasone) for two 4-month periods each. Although the frequency of bruising reported by the questionnaire was not different, there were more bruises on examination for inhaled beclomethasone than for inhaled fluticasone (p=0.04).

Tashkin et al [6]. performed a double-blind, randomized, placebo-controlled clinical trial of triamcinolone acetonide versus placebo in participants with mild-to-moderate COPD. Their goal was to define the relationship between skin bruising and inhaled corticosteroid therapy versus placebo in subjects with COPD. Moderate-to-high doses of inhaled corticosteroids resulted in an increased incidence of easy bruising and impairment in skin healing in middle-aged to elderly persons with COPD. A review by Guillot [7] described that thinning of the skin and easy bruising of inhaled corticosteroids are frequent and dose dependent. These adverse effects are probably present in about half of the patients treated with inhaled corticosteroids. The risk of these adverse effects is more important among elderly people and increases with the duration of the treatment and the daily dosage. Gerritsen et al. [8] describe the occurrence of haematoma when using inhaled fluticasone based on the cases received by the Netherlands Pharmacovigilance Centre Lareb.

Roy et al. [9] found in a study of 100 asthmatic subjects, that taking high doses of inhaled budesonide or beclomethasone (800-2000 ug/day for 3 months or more) was associated with increased occurrence of skin bruising by comparison with controls, particularly in older subjects.

### Databases

Table 3. Reports of haematoma associated with the use of inhaled or nasal corticosteroids in the Lareb [10] and WHO database [11]

Database	Drug	ADR*	Number of reports	ROR (95% CI)
Lareb	Inhaled corticosteroids combination products	Combination of terms representing haematoma	48	7.1 [5.3-9.6]
	Inhaled corticosteroids monopreparations	Combination of terms representing haematoma	43	5.4 [4.0-7.4]
	Nasal corticosteroids	Combination of terms representing haematoma	14	2.0 [1.2-3.4]
WHO	Inhaled corticosteroids combination products	Combination of terms representing haematoma	505	0.9 [0.8-1.0]
	Inhaled corticosteroids monopreparations	Combination of terms representing haematoma	452	1.2 [1.1-1.3]
	Nasal corticosteroids	Combination of terms representing haematoma	654	1.2 [1.1-1.3]

\*Several PTs were combined: haematoma, ecchymosis, purpura, skin haemorrhage, bleeding tendency and contusion

Table 4. Prescription data. Number of patients using inhaled or nasal corticosteroids in the Netherlands between 2012 and 2016 [12].

Drug	2012	2013	2014	2015	2016
<b>Corticosteroid with beta2-sympathomimetics</b>					
Formoterol + beclomethasone	68,324	87,159	109,840	129,280	149,190
Formoterol + budesonide	229,980	215,580	202,190	192,090	184,120
Formoterol + fluticasone	758	4,477	6,085	7,255	8,171
Salmeterol + budesonide	.	.	.	.	12
Salmeterol + fluticasone	362,940	342,140	319,500	295,930	275,150
Vilanterol + fluticasone	.	.	2,618	7,847	11,481
<b>Inhalation corticosteroid</b>					
Beclomethasone	84,848	79,061	77,170	75,682	74,927
Budesonide	75,564	68,013	64,734	62,615	60,936
Ciclesonide	53,034	56,050	59,175	61,799	65,732
Fluticasone	240,930	221,510	215,080	207,890	202,130
<b>Nasal corticosteroid</b>					
Beclomethasone	84,382	80,160	78,085	74,433	74,162
Budesonide	122,970	126,300	129,680	135,200	143,110
Fluticasonefuroate	220,530	217,020	222,280	226,560	232,470
Fluticasonepropionate	400,900	409,420	416,680	422,510	439,300
Fluticasone + azelastine	.	.	.	20,926	48,703
Mometasone	420,610	407,430	393,250	380,470	379,300
Triamcinolone	22,150	19,352	17,548	15,572	14,945

### Mechanism

Glucocorticoids reduce subcutaneous collagen and cause atrophic changes in the skin, resulting in fragile skin and haematoma. Purpura has been observed during glucocorticoid treatment and an increased fragility of the capillaries is thought to occur in about 60% of these patients [13]. Numerous physicochemical properties of inhaled corticosteroids including lipophilicity, the rate of dissolution, receptor-binding affinity, and receptor-binding half-life affect systemic availability and potentially systemic adverse effects. Fluticasone and beclomethasone have a high lipophilicity and a long residence time at the glucocorticoid receptor. These factors increase the efficacy of fluticasone and beclomethasone, but also increase the ratio of airway to systemic activity and the potential for systemic adverse effects especially at higher doses [14].

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 97 reports of haematoma associated with the use of inhaled or nasal corticosteroids. These reports concerned 65 women and 32 men, with ages varying from five to 85 years. The risk of systemic adverse effects of inhaled corticosteroids increases with the duration of treatment which is in accordance with the long median latency seen in these reports (five months). In elderly patients, senile purpura can occur, which could be an alternative explanation for the haematomas seen in these patients. In half of the reports patients were older than 62 years. The received reports do not describe the degree to which these patients were also receiving intermittent oral

glucocorticoids. Furthermore, information about thrombocytes and INR of these patients was not available.

The association of inhaled or nasal corticosteroids and haematoma shows a statistically significant disproportionality in the database of Lareb. Haematomas have been described for inhaled corticosteroids in literature. It is likely that haematomas are a class effect of inhaled and nasal corticosteroids.

#### Reference List

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*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](http://www.cbg-meb.nl)*