

## Beclomethasone/formoterol and haematoma

### Introduction

Beclomethasone/formoterol (Foster®) is a combination product of a corticosteroid and a long-acting beta2-agonist, indicated for *the regular treatment of asthma where use of a combination product is appropriate or the symptomatic treatment of patients with severe COPD (FEV1 < 50% of predicted normal value).*

Beclomethasone dipropionate given by inhalation has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically. Formoterol is a selective beta2-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airway obstruction. The bronchodilating effect sets in rapidly, within one to three minutes after inhalation, and has a duration of 12 hours after dose administration. Beclomethasone/formoterol was granted market authorisation in the Netherlands in 2007 [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[2]. Elderly patients have more fragile skin and are more sensitive to haematoma.

For beclomethasone inhalation, increased sensitivity of the skin for haematomas is already labelled [3;4].

### Reports

From August 2009 until July 2017 the Netherlands Pharmacovigilance centre Lareb received six reports of haematoma associated with the use of beclomethasone/formoterol. Furthermore, Lareb received 17 reports of haematoma associated with the use of inhaled beclomethasone alone. These last reports are shown in the appendix. To retrieve these reports from the Lareb database the MedDRA Preferred Terms (PTs) haematoma, ecchymosis, purpura, terms containing haemorrhage, bleeding tendency and contusion were used.

Table 1. Reports of beclomethasone/formoterol associated with haematoma in the Lareb database

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 90639 F, 61-70 years, pharmacist	beclomethasone/formoterol aerosol 100/6ug/do, 2 dd 1, COPD	nifedipine, levothyroxine, tiotropium, theophylline, zopiclon	haematoma	10 months (8 hours after administration), dose not changed, recovering, positive rechallenge
B 107785, F, 31-40 years, General practitioner	beclomethasone/formoterol aerosol 100/6ug/do, 2 dd 1, Asthma, fluticasone-furoate nasal spray 27,5ug/do, 1 dd 2, Allergic rhinitis	levocetirizine	haematoma	5 months, dose not changed, unknown
C 180393, F, 51-60 years, Consumer	beclomethasone/formoterol inhalation 100/6ug/do, 2 dd 1, Asthma	montelukast	haematoma	4 weeks, drug withdrawn, unknown
D 208326, F, 61-70 years, other health profession- nal	beclomethasone/formoterol aerosol 100/6ug/do, COPD	salbutamol/ipratropium	haematoma, chronic obstructive pulmonary disease exacerbation	unknown, drug withdrawn, fatal due to underlying disease

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 241265, F, 61-70 years, Consumer	beclomethasone/formoterol aerosol 100/6ug/do, 2 dd 1, Drug use for unknown indication		ecchymosis	3 years, unknown, recovered with sequel
F 243271, M, 51-60 years, Consumer	beclomethasone/formoterol aerosol 100/6ug/do, 2 dd 1, Asthma		haematoma, skin atrophy, haemorrhagic diathesis	2 years, drug withdrawn, recovering

Additional information on the cases is given below:

**Case A:** Past use of the drug also led to a haematoma on the leg.

**Case B:** Large haematomas (10 cm). Suspicion of adverse drug effect of beclomethasone/formoterol was confirmed by her treating dermatologist.

**Case D:** The reporter mentions that the patient experienced a lot of frequently occurring haematomas. The patient started taking beclomethasone/formoterol on an unspecified date. In the same period, the patient experienced hematomas on legs, hands and arms.

**Case E:** Haematoma on her lower arms. It took three weeks for the haematomas to resolve and the last two years the haematomas got worse.

**Case F:** Haematomas on her whole body, especially on her arms and legs. Little skin damage results immediately in bleeding. A coagulation test did not show any abnormalities.

## Other sources of information

### SmPC

The SmPC of beclomethasone/formoterol does not mention haematoma as adverse drug reaction[1]. However, the SmPC of beclomethasone dipropionate (Qvar®) and the SmPC of beclomethasonedipropionate ERC do mention an increased sensitivity of the skin for haematomas [3;4].

### 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 of sixty-nine asthmatic subjects, in which, after a baseline period, they 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.

### Databases

Table 2. Reports of haematoma associated with the use of beclomethasone/formoterol in the Lareb, WHO and Eudravigilance database [9;10].

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	beclomethasone/formoterol	haematoma	5	6.8 [2.8-16.7]
	beclomethasone/formoterol	ecchymosis	1	-
WHO*	beclomethasone/formoterol	haematoma	6	3.0 [1.3-6.6]
	beclomethasone/formoterol	ecchymosis	2	-
	beclomethasone/formoterol	purpura	1	-

Database	Drug	ADR	Number of reports	ROR (95% CI)
Eudravigilance*	beclomethasone/formoterol	haematoma	6	2.2 [1.0-4.9]
	beclomethasone/formoterol	ecchymosis	2	-
	beclomethasone/formoterol	purpura	1	-

\*WHO and Eudravigilance data consist mainly of Lareb data.

#### Prescription data[11].

Drug	2011	2012	2013	2014	2015
beclomethasone/formoterol	52,497	68,360	87,202	109,850	129,870

#### Mechanism

Glucocorticoids reduce subcutaneous collagen and cause atrophic changes in the skin, resulting in haematoma and paper-thin skinfolds. Purpura has been observed during glucocorticoid treatment and an increased fragility of the capillaries is thought to occur in about 60% of these patients [12]. 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. Beclomethasone has a high lipophilicity and a long residence time at the glucocorticoid receptor. These factors increase the efficacy of beclomethasone, but also increase the ratio of airway to systemic activity and the potential for systemic adverse effects especially at higher doses [13].

#### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received six reports of haematoma associated with the use of beclomethasone/formoterol. These reports concerned five women and one man, with ages varying from 34 to 70 years. The risk of systemic adverse effects of inhaled corticosteroids increases with the duration of treatment which is in accordance with the long latency seen in four of the six reports (five months till three years). In elderly patients, senile purpura can occur, which could be an alternative explanation for the haematomas seen in these patients. Three patients were older than 60 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 beclomethasone/formoterol and haematoma is supported by a statistically significant disproportionality in the database of Lareb and the WHO.

Haematoma have been described for inhaled corticosteroids in literature. For beclomethasone, as well as for other inhaled corticosteroids. For inhaled beclomethasone alone, it is already mentioned in the SmPC. It is important that users of the beclomethasone/formoterol inhalation are also aware that increased sensitivity of the skin for haematomas can occur.

#### Reference List

- (1) Dutch SmPC Foster®. <https://db.cbg-meb.nl/IB-teksten/h34610.pdf> 2016 December 20 [cited 2017 Nov 6];
- (2) Saag KG, Furst DE, Barnes PJ. Major side effects of inhaled glucocorticoids. Up to Date® 2016 April 1 [cited 2017 Nov 6]; Available from: URL: <http://www.uptodate.com/>
- (3) Dutch SmPC Beclometasondipropionaat ERC. <https://db.cbg-meb.nl/IB-teksten/h21940.pdf> 2011 May 26 [cited 2017 Nov 6];
- (4) Dutch SmPC Qvar®. <https://db.cbg-meb.nl/IB-teksten/h21937.pdf> 2011 May 26 [cited 2017 Nov 6];
- (5) Malo JL, Cartier A, Ghezzi H, Mark S, Brown J, Laviolette M, Boulet LP. Skin bruising, adrenal function and markers of bone metabolism in asthmatics using inhaled beclomethasone and fluticasone. *Eur Respir J* 1999 May;13(5):993-8.
- (6) Tashkin DP, Murray HE, Skeans M, Murray RP. Skin manifestations of inhaled corticosteroids in COPD patients: results from Lung Health Study II. *Chest* 2004 Oct;126(4):1123-33.
- (7) Guillot B. Skin reactions to inhaled corticosteroids. Clinical aspects, incidence, avoidance, and management. *Am J Clin Dermatol* 2000 Mar;1(2):107-11.
- (8) Gerritsen RF, Borgsteede SD, Harmark LVD. Bekend, maar niet altijd herkend. *Pharmaceutisch Weekblad* 2008;143(36):38-9.
- (9) Eudravigilance database. <http://bi.eudra.org> (access restricted) 2016 [cited 2017 Nov 6];
- (10) WHO database Vigilyze. <https://vigilyze.who-umc.org/#/> 2017 October 28 [cited 2017 Nov 6];
- (11) GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board. <http://www.gipdatabank.nl> 2016 November 24 [cited 2017 Sep 25];
- (12) Corticosteroids - glucocorticoids. In: Aronson JK, editor. *Meyler's Side Effects of Drugs*. 15 ed. 2006. p. 921.
- (13) Review of Systemic Adverse Effects Associated with Corticosteroids. <http://www.micromedexsolutions.com> 2016 November 16 [cited 2017 Nov 9];

## Appendix: reports of haematoma associated with the use of inhaled beclomethasone alone

ID	Sex, age, source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
12050	F, 71 years and older, General Practitioner	beclomethasone inhalation 200ug, Asthma, salbutamol inhalation 400ug, Asthma	bisacodyl, lormetazepam, oxazepam, sotalol	purpura	After chronic use, dose not changed, unknown
12649	F, 71 years and older, Pharmacist	beclomethasone inhalation 400ug, drug use for unknown indication	paracetamol, salbutamol, acetylcysteine, acetazolamide, theophylline	purpura	Unknown, dose not changed, unknown
12675	M, 61-70, years, Pharmacist	beclomethasone inhalation 400ug, Asthma	salbutamol, perindopril	purpura	2 years, dose not changed, unknown
13465	M, 71 years and older, Pharmacist	beclomethasone inhalation 400ug, Bronchitis acute NOS	terbutaline, sterculiagom/rhamnus frangula granulate	purpura	10 years, dose not changed, unknown
13870	M, 61-70, years, Pharmacist	beclomethasone aerosol 250ug/do, drug use for unknown indication	temazepam, salbutamol, acetylcysteine	purpura	12 months, dose not changed, unknown
17665	F, 71 years and older, Pharmacist	beclomethasone inhalation 200ug, drug use for unknown indication	metoprolol, acetylsalicylic acid, kinidine, acetylcysteine, theophylline	bruise	18 months, dose not changed, unknown
19695	M, 71 years and older, Pharmacist	beclomethasone inhalation 200ug, drug use for unknown indication	terbutaline, salmeterol	bruise	10 years, drug withdrawn, unknown
20307	F, 71 years and older, Pharmacist	beclomethasone inhalation 400ug, drug use for unknown indication	salbutamol	purpura	Unknown, drug withdrawn, unknown
33373	F, 51-60, years, Pharmacist	Beclomethasone inhalation 400ug/do, drug use for unknown indication	ureum cream, pantoprazole, sumatriptan, estradiol/dydrogesterone	purpura	After chronic use, drug withdrawn, not recovered
34711	F, 61-70, years, Pharmacist	beclomethasone inhalation 400ug, Emphysema, beclomethasone inhalation 200ug,	fluticasone-propionate, pantoprazole	purpura	Years, dose not changed, recovered
42834	F, 51-60, years, General Practitioner	beclomethasone inhalation 400ug, drug use for unknown indication	pizotifen, paracetamol/codeine, atenolol	ecchymosis	9 years, dose not changed, unknown
78406	F, 41-50, years, Consumer	beclomethasone aerosol 100ug/do, Asthma		Haematoma, skin atrophy	4 years, dose not changed, recovering
86907	M, 71 years and older, Pharmacist	beclomethasone inhalation 100ug, Asthma	salbutamol	haematoma	Years, dose not changed, not recovered
108008	F, 71 years and older, Pharmacist	beclomethasone aerosol 100ug/do, Asthma		Nausea, purpura	1 month, dose not changed, not recovered
129309	F, 71 years and older, Consumer	formoterol inhalation 6ug/do, beclomethasone aerosol 50ug/do,	alendronate, calciumdiorotate, losartan	haematoma	Months, dose not changed, not recovered

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		COPD, tiotropium 2,5ug/do			
136909	M, 5-7, years, Other health professional	beclomethasone aerosol 100ug/do, Asthma		haematoma	2 weeks, unknown, not recovered
163348	F, 71 years and older, General Practitioner	beclomethasone aerosol 100ug/do, COPD	budesonide nasal spray, losartan, omeprazole, domperidone, hydrochlorothiazide, bisacodyl, nifedipine, vaselinecetomacrogol cream	Haematoma, rash	2 days, drug withdrawn, recovering

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*This signal has been raised on January 8, 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)*