

Factors affecting the choice of budesonide in the therapy of croup, asthma and chronic obstructive pulmonary disease

Magdalena Olszanecka-Glinianowicz¹, Jerzy Chudek², Anna Urcus³, Agnieszka Almgren-Rachtan⁴

¹Health Promotion and Obesity Management Unit, Department of Pathophysiology, Medical Faculty in Katowice, Medical University of Silesia, Katowice, Poland

²Department of Internal Medicine and Oncological Chemotherapy, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland

³Adamed Pharma, Poland

⁴Pharmacovigilance Department, Europharma, Katowice, Poland

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Abstract

Introduction: Budesonide is one of inhaled corticosteroids with an established position in the therapy of croup, bronchial asthma and chronic obstructive pulmonary disease (COPD).

Aim: To assess factors affecting the choice of budesonide in the therapy of croup, asthma and COPD by specialists and general practitioners in daily clinical practice.

Material and methods: This multicentre, open-label, post-marketing survey was performed nation-wide with the participation of 1113 doctors and 100,980 patients treated with budesonide. The study questionnaire included questions about factors affecting the choice of budesonide and assessing the prescription pattern of the drug.

Results: The doctors frequently declared use of budesonide in monotherapy in patients with croup, and in polytherapy in asthma and COPD (with salmeterol or formoterol and with formoterol, respectively). The most important factors affecting the choice of budesonide, as declared by doctors, were safety, efficacy, good personal experience with the use of this medication and recommendations of scientific associations. Budesonide in monotherapy was prescribed in 63.7%, 49.7%, and only 13.5% of patients with croup, asthma and COPD, respectively. The most important factors which determined the choice of this drug were safety (from 78.7% to 91.0%), efficacy (from 78.9% to 90.5%) and good personal experience of doctors (from 65.6% to 84.5%).

Conclusions: Budesonide is still frequently chosen in the treatment of croup, asthma and COPD by Polish specialists and general practitioners because of its efficacy, safety and considerable experience in the application. Acquired clinical experience of physicians prevails over the issued recommendations of scientific societies regarding the use of budesonide in daily clinical practice.

Key words: croup, asthma, chronic obstructive pulmonary disease, budesonide, therapeutic preferences, efficacy, safety

Introduction

Inhaled corticosteroids (ICS) have been used in the treatment of respiratory tract diseases since 1973. The local use of corticosteroids in the respiratory tract diseases increases their efficacy and safety. The first registered ICS beclomethasone was followed by betamethasone. Budesonide and fluticasone (introduced in the 1980s), and mometasone (introduced in the 1990s) had

increased anti-inflammatory action and decreased bio-availability [1].

Croup syndrome is an acute subglottic laryngitis caused by viral infection of the upper respiratory tract. Developing inflammation causes swelling of the mucous membrane of the throat, larynx and trachea. This results in a disruption of the air flow and is manifested by stridor, cough and hoarseness. In most cases, the disease has a fairly mild and self-limited course. However,

Address for correspondence: Prof. Magdalena Olszanecka-Glinianowicz MD, PhD, Health Promotion and Obesity Management Unit, Department of Pathophysiology, Medical University of Silesia, 18/20 Medyków St, 40-752 Katowice, Poland, e-mail: molszanecka@sum.edu.pl
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in infants it may cause severe dyspnoea and be a life-threatening condition that requires prompt treatment. The first line of drugs recommended in croup treatment includes corticosteroids administered systemically (one dose of dexamethasone orally or intramuscularly). However, it has also been shown that use of budesonide by nebulization is effective [2–5]. The second key drug in the treatment of croup is adrenalin by nebulization, recommended in severe clinical conditions in polytherapy with corticosteroids [6, 7].

ICS, including budesonide, are the most effective anti-inflammatory drugs recommended in long-term control of persistent asthma, administered once or twice daily, depending on the severity of symptoms. ICS are also recommended as a part of polytherapy with long-acting β_2 -adrenoceptor agonists (LABA) [8].

ICS have a lower position in the management of chronic obstructive pulmonary disease (COPD) than in the treatment of asthma. However, a meta-analysis of several randomized trials involving 3,976 patients with COPD showed a reduction in the risk of exacerbation in patients treated with high doses of ICS compared to those receiving placebo [9]. Long-term, regular use of ICS brings benefits to patients with severe and very severe obturation, who also have frequent exacerbations (at least 2 per year) [10, 11]. However, it should be noted that monotherapy with ICS reduces frequency of exacerbations and improves quality of life but does not decrease the rate of annual loss of FEV₁ and general mortality [12]. Thus, ICS monotherapy is not recommended in the treatment of COPD. In addition, a meta-analysis of 11 randomized trials has shown that polytherapy with budesonide and formoterol or fluticasone and salmeterol significantly decreased frequency of exacerbations and risk of death in patients with COPD with moderate and severe bronchial obstruction [13].

In Poland, budesonide was approved for the treatment of croup, asthma and COPD in the 1980s. However, little is known about factors affecting the choice of budesonide in daily clinical practice.

Aim

Therefore, the aim of the multicentre, open-label, post-marketing, observational survey was to assess factors affecting the choice of budesonide in the therapy of croup, asthma and COPD by specialists and general practitioners in daily clinical practice.

Material and methods

One thousand one hundred thirteen doctors (573 paediatricians, 210 general practitioners, 175 pulmonologists, 99 allergists and 56 internal medicine specialists) participated in a nation-wide, multicentre, open-label,

post-marketing survey performed from August 2017 to December 2018. They interviewed 100,980 patients treated with budesonide (54,603 diagnosed with croup, 37,408 with asthma and 8,969 with COPD). The survey did not meet the criteria of a medical experiment and thus did not require any Bioethics Committee approval.

The inclusion criteria for doctors were: specialty in family medicine or internal medicine or paediatrics or pulmonology or allergy, current license to practice, having, in one's practice, an appropriate number of patients who meet the inclusion criteria for the study, completing and signing the Application Form for the Study and sending it to Europharma.

The inclusion criteria for outpatients were: diagnosis of croup or asthma or COPD, use of budesonide in mono- or polytherapy. The exclusion criterion was inability to obtain answers to questions contained in the survey.

The physicians participating had a dual role in the survey. They answered the questions regarding their medical practice, filled out questionnaires for minimum 20 patients that fulfilled the inclusion criteria during one visit survey resulting from a clinical need of the patient.

The first part of the questionnaire included demographic data of the doctors (specialty, work experience, place of work) and data on their clinical practice (the frequency of using budesonide in mono- and polytherapy in patients with croup or asthma or COPD and factors affecting these decisions).

The second part of the questionnaire included patient demographic data (gender, age, education level, place of residence and professional activity), clinical data (main diagnosis, duration of asthma or COPD, clinical symptoms of croup, severity of croup, number of asthma and COPD exacerbations and hospitalizations during the last 3 months, the degree of asthma and COPD control, the need of hospitalization due to croup, recommended treatment regimen and the occurrence of concomitant diseases).

In addition, the patients' opinion on effectiveness and tolerance of budesonide were assessed on the basis of a 4-point scale (1 – no efficacy, 2 – moderate, 3 – good, 4 – very good and 1 – difficult to accept discomfort, 2 – acceptable discomfort, 3 – good tolerance, 4 – very good tolerance, respectively).

Statistical analysis

Statistical analysis was performed with Statistica 12.0 software (TIBCO Software Inc., Palo Alto, CA, USA). Values of variables were presented as percentages and the mean values with standard deviations (SD). Separate groups were compared using the χ^2 test and χ^2 test for trend. The value of $p < 0.05$ was considered to be statistically significant.

Results

Doctors' therapeutic preferences

The study group of doctors (characteristics presented in Table 1) declared the use of monotherapy with budesonide in over 50% of patients with croup. Much fewer (up to 10%) doctors declared use of polytherapy with adrenalin and budesonide. The most important factors declared by physicians as decisive for the choice of budesonide use in the treatment of croup were: efficacy (93.8%), safety (87.4%), good own experience with the use of this drug (84.1%) and convenience of the use (75.2%). These factors were followed by recommendations of scientific associations and age (65.7% and 64.6%, respectively). Meanwhile, the least importance was attributed to the cost of therapy (49.3%) and concomitant diseases (30.5%) – data not shown.

In asthma, doctors more frequently declared the use of budesonide in polytherapy than in monotherapy in over 50% of patients (36.1% vs. 15.5%). In polytherapy, doctors most frequently declared the use of budesonide with salmeterol or formoterol (56.0% and 42.0%, respectively). The most important factors declared by physicians as decisive for the choice of budesonide in the treatment of asthma were: efficacy (87.7%), safety (85.2%), good own experience with the use of this drug (75.9%) and recommendations of scientific associations (70.0%). These factors were followed by age and impact on the quality of life (QoL) (65.2% and 65.2%, respectively). Meanwhile, the least importance was attributed to the cost of therapy (47.6%), etiological factors causing the development of the disease (45.2%) and concomitant diseases (41.1%) – data not shown.

Doctors declared use budesonide in patients with COPD in polytherapy, most often with formoterol (46.3%). The most important factors declared by physicians as decisive for the choice of budesonide use in the treatment of asthma were: safety (77.5%), efficacy (73.6%), good own experience with the use of this drug (64.3%) and recommendations of scientific associations (63.6%). These factors were followed by impact on QoL and age (53.0% and 46.3%, respectively). Meanwhile, the least importance was attributed to the occurrence of concomitant diseases (42.8%), the cost of therapy (41.2%) and etiological factors causing development of the disease (38.7%) – data not shown.

Factors determining choice of budesonide in the enrolled patients

The analysis included 54,603 patients with croup, 37,408 with asthma, and 8,969 with COPD (Table 2).

The most common symptoms in patients with croup were barking cough (88.7%), hoarseness (74.1%) and inspiratory stridor (52.0%). The severity of symptoms was mild in 42.0%, moderate in 52.7% and severe in 5.3% of patients. Hospitalization was required in 4.4% of the patients (Table 3).

Table 1. Characteristics of the study group of doctors (N = 1113)

Variable	N; %
Specialty:	
Family medicine	210; 18.9
Internal medicine	56; 5.0
Paediatrics	573; 51.5
Allergology	99; 8.9
Pulmonology	175; 15.7
Professional experience [years]:	
2–5	30; 2.7
6–10	51; 4.6
11–15	141; 12.7
16–20	73; 6.6
> 20	818; 73.5
Workplace:	
Public hospital	25; 2.2
Public outpatient clinic	691; 62.1
Private outpatient clinic	270; 24.3
Private practice	127; 11.4
Workplace location:	
Village	163; 14.6
City < 50 000 residents	466; 41.9
City 50–200 000 residents	263; 23.6
City > 200 000 residents	221; 19.9
The percentage of patients with croup in relation to all patients taking the drug:	
0%	5.6
1–10%	65.8
11–20%	22.2
21–50%	5.5
> 50%	0.9
The percentage of patients with asthma in relation to all patients taking the drug:	
0%	0
1–10%	49.4
11–20%	28.3
21–50%	11.4
> 50%	10.9
The percentage of patients with COPD in relation to all patients taking the drug:	
0%	36.9
1–10%	39.9
11–20%	18.1
21–50%	4.2
> 50%	0.8

Table 2. Characteristics of study groups of patients treated with budesonide

Variable	Croup (N = 100,980)	Asthma (N = 37,408)	COPD (N = 8,696)	P-value
Age [years]	7 ±9	21 ±19	59 ±16	< 0.001
Gender, n; %:				
Women	28,585; 52.4	20,891; 55.8	3,591; 40.0	< 0.001
Men	26,018; 47.6	16,517; 44.2	5,378; 60.0	< 0.001
Education levels, n; %:				
Not applicable	49,751; 91.1	20,669; 55.3	282; 3.1	
Primary	1,604; 2.9	2,699; 7.2	1,077; 12.0	
Vocational	604; 1.1	2,927; 7.8	3,648; 40.7	< 0.001
Secondary	1,775; 3.3	7,015; 18.8	2,656; 29.6	
Higher	869; 1.6	4,098; 11.0	1,306; 14.6	
Place of residence, n; %:				
Village	18,751; 34.3	9,792; 26.2	3,438; 38.3	< 0.001
City < 50 000 residents	15,174; 27.8	11,047; 29.5	3,442; 38.4	
City 50–200 000 residents	13,758; 25.2	9,063; 24.2	1,179; 13.1	
City > 200 000 residents	6,920; 12.7	7,506; 20.1	910; 10.1	
Professional activity, n; %:				
Intellectual work	1,417; 2.6	5,869; 15.7	1,392; 15.5	
Physical work	931; 1.7	4,744; 12.7	2,097; 23.4	
Not working	970; 1.8	1,828; 4.9	908; 10.1	
Sickness pension	50; 0.1	598; 1.6	936; 10.4	
Pension	124; 0.2	1,016; 2.7	3,241; 36.1	
Not applicable	51,111; 93.6	23,353; 62.4	395; 4.4	

Patients with asthma were characterized by varied duration of the disease, assessed as controlled in 68.0%, partially controlled in 27.5% and uncontrolled in 4.4% of the study group. In the last 3 months, exacerbations of the disease were reported in 39.3% of patients (in 80.1% one, 17.2% two and 2.7% more than two), and hospitalizations due to exacerbations in the last 3 months in 9.3% of patients with asthma. Concomitant diseases were reported in 39.4% of patients, most often other allergic diseases (Table 3).

Patients with COPD were characterized by varied duration of the disease, assessed as category A in 23.1%, B in 47.2%, C in 25.3% and D in 4.5% of patients. During the last 3 months, exacerbations of the disease and related hospitalizations were reported in 37.9% (in 66.0% one, 24.2% two and 9.8% more than two) and 11.2% of patients, respectively. Concomitant diseases, mostly cardiovascular and metabolic, occurred in 71.0% of patients (Table 3).

Budesonide was used in monotherapy in 63.7% and in polytherapy in 36.3% of patients with croup. The most important factors determining the use of budesonide in the treatment of croup were: safety, efficacy, own experience of the doctor with the use of this drug, convenience

of use, age of patients and recommendation of scientific associations (Tables 3 and 4).

Budesonide was used in monotherapy in 49.7% and in polytherapy (most often with formoterol and salmeterol) in 50.3% of patients with asthma. In monotherapy, it was commonly used in patients with controlled asthma. The most important factors determining the use of budesonide in treatment of asthma were: safety, efficacy and own experience of the doctor with the use of this drug (Table 3 and 4).

Budesonide was used in monotherapy in 13.5% and in polytherapy (most often with formoterol and salmeterol) in 86.5% of patients with COPD. Budesonide in monotherapy was commonly used in patients with COPD meeting category A. The most important factors determining the use of budesonide in treatment of croup were: efficacy, safety and considerable experience of the doctor with the use of this drug (Tables 3 and 4).

The efficacy and tolerance of pharmacotherapy including budesonide

Efficacy and tolerance of the therapy with budesonide are presented in Figures 1 and 2. In all cases they were

Table 3. Clinical characteristics of the study groups

Variable	Croup (N = 100,980)	Asthma (N = 37,408)	COPD (N = 8,696)	P-value
Duration of the disease, n; %:				
> 5 years		13,807; 36.9	4,550; 51.7	< 0.001
4–5 years		5,966; 15.9	1,846; 21.0	
2–3 years		7,363; 19.7	1,293; 14.7	
12–23 months		3,888; 10.4	258; 2.9	
7–11 months		2,384; 6.4	198; 2.2	
3–6 months		2,463; 6.6	515; 5.8	
< 3 months		1,537; 4.1	149; 1.7	
Clinical symptoms, n; %:				
Fever	26,458; 48.5			
Hoarseness	40,461; 74.1			
Inhalation stridor	28,400; 52.0			
Barking cough	48,435; 88.7			
Wheezing	14,443; 26.5			
Dyspnoea	11,677; 21.4			
Faster breathing	8,772; 16.1			
Visible movement of the wings of the nose	2,238; 4.1			
Visible intercostal retraction	2,021; 3.7			
Patients requiring hospitalization, n; %	2,388; 4.4			
Severity of the disease, n; %:				
Mild	22,942; 42.0			
Moderate	28,788; 52.7			
Severe	2,873; 5.3			
GINA criteria, n; %:				
Controlled asthma		25,437; 68.0		
Partially controlled asthma		10,287; 27.5		
Uncontrolled asthma		1,684; 4.5		
GOLD criteria, n; %:				
Category A			2,068; 23.1	
Category B			4,229; 47.2	
Category C			2,269; 25.3	
Category D			403; 4.5	
Use of budesonide, n; %:				
Monotherapy	34,779; 63.7	18,578; 49.7	1,211; 13.5	
Polytherapy	19,824; 36.3	18,830; 50.3	7,758; 86.5	
Drugs used in polytherapy with budesonide (%):				
Formoterol		25.1	40.8	
Salmeterol		23.3	35.0	
Indacaterol		1.9	10.7	
Exacerbation of the disease during the last 3 months (%):				
Once		55.3	66.0	
Twice		33.2	24.2	

Table 3. Cont.

Variable	Croup (N = 100,980)	Asthma (N = 37,408)	COPD (N = 8,696)	P-value
More than twice		11.5	9.8	
Hospitalization during the last 3 months (%):		9.3	11.2	
Once		80.1	86.4	
Twice		17.2	8.7	
More than twice		2.7	5.0	
Concomitant diseases (%):		39.4	71.0	
Obesity		8.0	21.5	
Type 1 diabetes		0.8	2.0	
Type 2 diabetes		2.3	19.2	
Hypertension		9.5	60.4	
Dyslipidaemia		3.2	31.2	
Coronary heart disease		2.2	21.4	
Other allergic diseases		20.7	3.0	
Other chronic diseases		4.3	9.2	

assessed as very good and good by more than 95% of patients.

Discussion

The presented study is the first large survey that assessed factors affecting doctors' therapeutic preferences for the use of budesonide in patients with croup or asthma or COPD among specialists and general practitioners in daily clinical practice, performed in Poland. It should also be noted that so far such a study has not been performed in other countries.

Our study has shown that in patients with croup, budesonide is more frequently used in mono- than in polytherapy and the drug choice is related to its safety, efficacy, and considerable experience with the use of the drug. The results obtained in the observed group are in accordance with doctors' declarations contained in the first part of survey. In both cases, the low position of recommendations of scientific associations may surprise. However, it should be noted that prescription profiles – the result of therapeutic decisions are in the majority in line with them [14]. Meanwhile, the small significance attributed by doctors to the cost of therapy is understandable in view of the nature of this acute illness, constituting a significant threat to the life and health of children, as well as partial reimbursement of these drugs by the Polish National Health Fund (NFZ). In addition, according to clinical trials [15], our study showed that budesonide is effective in the treatment of croup and very well tolerated. The subjective assessment of efficacy is supported by observation that less than 5% of patients with croup required hospitalization.

Doctors more frequently declared use of budesonide in the treatment of asthma in polytherapy with salmeterol or formoterol than in monotherapy. Meanwhile, the analysis of prescription profiles in the observed group showed that budesonide is used in mono- and polytherapy with formoterol or salmeterol with similar frequency. Budesonide in monotherapy was used mainly in well-controlled asthma. It should be noted that use of budesonide in monotherapy is not compatible with GINA recommendations [8] although 70% of doctors declared and 62% indicated in patient survey that recommendations of scientific associations are among the most important factors affecting the choice of budesonide in the treatment of asthma. However, it should be noted that in the observed group the most important factors determining the use of budesonide in treatment of asthma were: safety, efficacy and doctors' considerable experience with the use of this drug. The doctors paid little attention to the costs of this chronic therapy, which is most probably associated with high refunding of this group of drugs by NFZ. In addition, according to clinical trials [16], our study showed that budesonide is effective and very well tolerated in the treatment of asthma. The subjective assessment of efficacy is supported by the observation that less than 10% of patients required hospitalization due to exacerbation of asthma during the last 3 months.

In treatment of COPD, doctors declared mostly the use of budesonide in polytherapy in up to 50% of patients. Despite these declarations that are in accordance with present recommendations [8], in the observed group budesonide was used in monotherapy only in 13.5% and in polytherapy with LABA (usually with formoterol or salmeterol) in 86.5%. Budesonide in combination with formoterol was used frequently and it was consistent with

Table 4. Factors influencing the use of budesonide

Variable	Croup (N = 100,980)	Asthma (N = 37,408)	COPD (N = 8,696)	P-value
Patients' age (%):				
Insignificant	9.0	17.9	23.5	< 0.001
Important	18.5	26.5	33.3	
Very important	72.5	55.6	43.3	
The etiological factor causing the development of the disease (%):				
Insignificant	–	20.6	21.5	< 0.001
Important	–	32.3	39.9	
Very important	–	47.1	38.6	
Convenience of use (%):				
Insignificant	4.1	–	–	–
Important	17.4	–	–	
Very important	78.5	–	–	
Comorbidities (%):				
Insignificant	38.8	32.4	14.2	< 0.001
Important	19.8	29.6	38.3	
Very important	41.3	37.9	47.5	
Efficacy (%):				
Insignificant	0.2	0.3	0.0	
Important	9.3	15.6	21.3	
Very important	90.5	84.1	78.7	
Safety (%):				
Insignificant	0.1	0.1	0	
Important	8.9	15.1	21.1	
Very important	91.0	84.9	78.9	
One's own good experience with the use of the drug (%):				
Insignificant	0.6	0.6	1.1	
Important	14.9	23.5	33.3	
Very important	84.5	75.9	65.6	
Cost of therapy (%):				
Insignificant	16.6	16.5	11.7	
Important	29.0	30.8	37.5	
Very important	54.4	52.6	50.9	
Recommendation of the Scientific Association (%):				
Insignificant	3.7	3.0	1.5	< 0.001
Important	26.2	34.8	38.9	
Very important	70.1	62.2	59.6	
Effect on patients' quality of life (%):				
Insignificant	–	7.8	9.7	< 0.001
Important	–	28.2	31.3	
Very important	–	64.0	59.0	

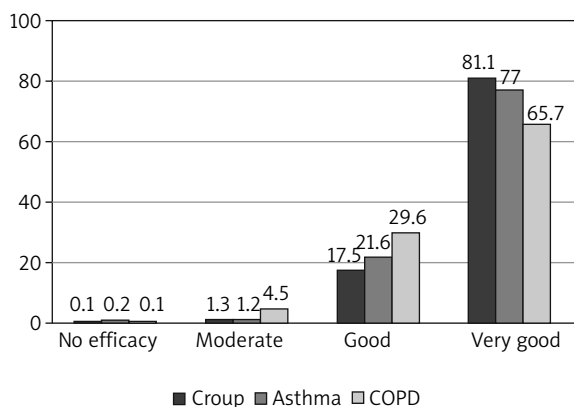


Figure 1. The assessment of the efficacy of the therapy with budesonide

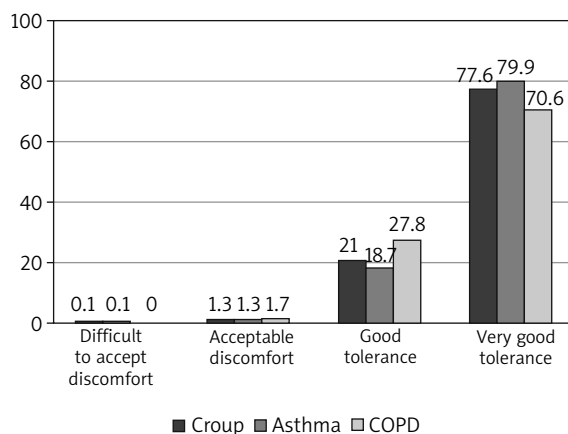


Figure 2. The tolerance of the use of budesonide

doctors' declarations. Doctors declared that the most important factors affecting the choice of budesonide in the treatment of COPD are safety, efficacy and their own considerable experience with the use of this drug. The same factors determined the choice of budesonide in the study group. Also in the case of COPD, little importance was paid to the costs of this chronic therapy, which is most likely associated with high refunding of this group of drugs by NFZ. In addition, according to meta-analysis [17], our study showed that budesonide in polytherapy with LABA is effective in COPD treatment and very well tolerated. The subjective assessment of efficacy is supported by the observation that 11.2% of patients required hospitalization due to asthma exacerbation during the last 3 months.

In summary, our multicentre, open-label, post-marketing survey showed that budesonide is willingly used in treatment of croup, asthma and COPD by Polish general practitioners and specialists and its use, excluding asthma, is in accordance with recommendations.

Conclusions

Budesonide is still frequently chosen in the treatment of croup, asthma and COPD by Polish specialists and general practitioners because of its efficacy, safety and considerable experience in the application. Acquired clinical experience of physicians prevails over the issued recommendations of scientific societies regarding the use of budesonide in daily clinical practice.

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Conflict of interest

Magdalena Olszanecka – Glinianowicz received honorarium for study concept from Europharma. Jerzy Chudek received honorarium for co-edition from Europharma. Anna Urcus – employed by the funding organization. Agnieszka Almgren-Rachtan – received honorarium for co-edition from Europharma.

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