

Roflumilast Usage from 2010 to 2016: A Danish Nationwide Drug Utilization Study

Øyvind Nicolay Ulland Salvesen¹, Jesper Rømhild Davidsen¹, Anton Pottegård² and Daniel Pilsgaard Henriksen^{1,3}

¹Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark, ²Department of Public Health, Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense, Denmark and ³Department of Clinical Biochemistry & Pharmacology, Odense University Hospital, Odense, Denmark

(Received 21 November 2017; Accepted 14 March 2018)

Abstract: Roflumilast, a phosphodiesterase-4-inhibitor, is marketed as add-on treatment to inhaled bronchodilators and corticosteroids in COPD patients with frequent exacerbations. Although marketed since 2010, usage pattern of roflumilast for an entire nation has not previously been explored. This study aimed to estimate the total utilization of roflumilast in Denmark during 2010 to 2016, using the Danish nationwide health registers. We identified 1573 individuals (47% males) who used roflumilast during the study period, of whom 705 (45%) redeemed only one prescription. Of all patients initiating roflumilast, 67% discontinued treatment within the first year. The rate of treatment initiation decreased 73% from 2011 (7.5/100,000 person-years) to 2016 (2.0/100,000 person-years) concurrent with a stable prevalence of 3.0–4.0/100,000 persons throughout the study period. The median duration of roflumilast use was 76 days. Patients with severe comorbidity tended to exhibit a lower degree of early discontinuation (Charlson Comorbidity Index 3+: odds ratio [OR]: 0.59; 95% confidence interval [CI] 0.33–1.04), as well as patients with a COPD-related admission within a year prior to roflumilast initiation (OR 0.62; 95% CI 0.49–0.80). The decreasing incidence and high level of early roflumilast discontinuation could be due to lack of benefit, a low awareness of roflumilast's indication among physicians, secondary to a challenging prescribing procedure or to adverse effects.

Chronic obstructive pulmonary disease (COPD) is estimated to affect more than 430,000 individuals in Denmark, and the prevalence of moderate and severe-to-very severe COPD has been estimated to 9% and 2%, respectively [1]. The disease is estimated to be the third leading cause of death worldwide in 2020 with more than 3 million deaths per year [2]. Roflumilast is a phosphodiesterase-4-inhibitor (PDE4), which was introduced to the European market in July 2010 [3]. The drug was approved as a prophylactic treatment for COPD patients with frequent exacerbations [4] and has been included in the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines [5]. In such, patients with COPD must experience chronic cough and sputum production, as well as having a history of exacerbations before roflumilast is indicated [4]. The European Medicines Agency (EMA) summary has approved roflumilast as an 'add-on' treatment to bronchodilators, and according to the GOLD guidelines, there is also an effect when treating patients who are not 'controlled on fixed-dose long-acting beta-2-agonists (LABA)/inhaled corticosteroid (ICS) combinations' [5].

Studies from 2009 concluded that roflumilast reduced the number of exacerbations in patients with more than two exacerbations a year by 17% [6], consistent with observations in the REACT study from 2015 in which roflumilast reduced the number of severe exacerbations by 24% among well-selected patients with COPD [7]. Only sparse data on roflumilast utilization are available from Northern European COPD populations.

However, a new Danish clinical cross-sectional study of 547 patients found that only one in four (22.6%) patients with COPD eligible for treatment was prescribed roflumilast [8]. A recent Cochrane review found roflumilast to be beneficial over placebo in improving lung function and reducing the likelihood of exacerbations. However, only a limited impact on quality of life and symptoms was found [9]. The numbers needed to treat for a beneficial outcome were estimated to 20, whereas the numbers needed to harm were estimated to 15.

Due to the questionable benefit and the increased risk of adverse effects, the Danish National Board of Health recommended that initiation with roflumilast is reserved for specialist use in respiratory medicine only.

As clinical trial populations often are highly selected, it is important to assess 'real-world' patterns of usage. This has not previously been done for roflumilast.

Our study aimed to assess the utilization pattern of roflumilast in Denmark as its market release in 2010 in relation to incidence, prevalence and duration of roflumilast usage.

Methods

We performed an observational register-based study, aiming to assess roflumilast usage in Denmark from 1 January 2010 to 31 December 2016 with use of information from nationwide Danish registers.

Data sources. Due to the unique civil registration number and the Danish National Health Service providing tax-supported health care for the entire Danish population, it is possible to conduct true population-based register-linkage studies covering the entire population [10].

Author for correspondence: Daniel Pilsgaard Henriksen, Department of Respiratory Medicine, Odense University Hospital, J.B. Winsløvs Vej 19, 2., 5000 Odense C, Denmark (e-mail: dphenriksen@health.sdu.dk).

The following registers were used as follows:

The National Prescription Registry (NPR) contains data on all redeemed drugs prescribed to all Danish citizens [11] from 1995 to present and includes information regarding the type of drug, date of dispensing and the number of defined daily doses redeemed. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) code, developed by the World Health Organization [12]. The quantity in each prescription is expressed by the defined daily dose (DDD) measure [12]. Data about dosing information and indication for prescription are not available; nor with information regarding drugs dispensed at hospital level. However, only 2.4% of the total amount of roflumilast is sold to hospitals [13].

The Danish National Patient Registry contains data on all contacts to Danish hospitals since 1977 [14]. Discharge diagnoses are coded according to International Classification of Diseases, tenth revision (ICD-10) since 1994.

The Danish Civil Person Register contains data on date of birth, death and migration to and from Denmark [10].

Study drugs. Roflumilast (ATC R03DX07) is the only PDE4 inhibitor marketed in Denmark. The DDD for roflumilast is 500 µg daily according to the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD index [12]. Each individual was defined as a 'current user' on a given day if he/she had redeemed a prescription for roflumilast with sufficient doses to cover that specific day. The duration of each roflumilast prescription was defined as the number of tablets dispensed (i.e. assuming a consumption of one tablet per day), while adding 25% to the duration to account for irregular prescription refills and/or primary non-compliance (i.e. a patient redeeming 30 DDDs was calculated as being treated for 37.5 days). The addition of 25% to the duration is based on an assumption of 80% compliance, which is often seen in traditional compliance research [15,16].

Ethics. According to Danish law, studies based solely on register data do not require approval from an ethics review board [17]. The study was approved by the Danish Data Protection Agency (Application no. 2008-58-0035).

Analysis. Baseline characteristics of individuals initiating roflumilast in the period of 2010 to 2017 were presented as absolute numbers and percentages for categorical values and medians with interquartile ranges (IQRs) for continuous values. For our analyses of redeemed medication excluding roflumilast, we assumed that if a prescription was redeemed within the last 12 months before initiating roflumilast, the patient was a user of the given medication.

For each calendar year (2010 to 2016), we calculated the total amount of DDD of roflumilast redeemed per individual. Comparisons of continuous variables were performed using the Wilcoxon rank-sum test.

Annual prevalence proportions, that is, the number of current users per 100,000 in the population from 2010 to 2017 were calculated using the entire population living in Denmark as of 1 January each relevant year as the denominator.

The duration of treatment was described using the proportion of patients covered (PPC) method [18]. All individuals were followed from their first prescription corresponding to incident users. The proportion of patients being alive and still using roflumilast was estimated over time. If a patient stopped the treatment with a following re-initiation, the patient was again considered a current user when redeeming a new prescription. The overall PPC was calculated as well as stratified by sex and comorbidity.

We calculated the median duration of treatment stratified by sex and year of roflumilast initiation.

We used logistic regression analysis to assess the association of demographic risk factors and early roflumilast discontinuation in two models: a crude model and an adjusted model where we adjusted for the pre-defined clinically relevant confounders' sex, age and comorbidity. Roflumilast discontinuation was defined as users redeeming only one prescription for roflumilast with at least 1-year observation period.

To define the comorbidity burden of the patients, we used the Charlson Comorbidity Index (CCI) [19]. In brief, a selected number of diseases are given a weighted number, and a higher CCI score is an indicator of severe comorbidity due to a high number of comorbidities.

Stata version 14.1 (StataCorp, College Station, TX, USA) was used for all data analyses.

Results

Demographic characteristics.

In total, 1573 individuals (47% males) redeemed at least one prescription for roflumilast during the study period. The median age of the females initiating roflumilast was 69 years (interquartile range (IQR) 63–76) and for males 71 years (IQR 65–77). The majority of patients ($n = 730$) initiating roflumilast had a CCI of 1 (46%), whereas 25% ($n = 391$) were defined as having severe comorbidity (CCI 3+).

During the study period, 10,500 prescriptions for roflumilast were filled, totalling 463,740 DDDs (fig. 1).

We found that 77.4% ($n = 1,218$) of the patients received oral corticosteroids 12 months preceding roflumilast initiation, while 53.8% had prescriptions of LABA, long-acting muscarinic antagonists (LAMA) and ICS (table 1).

During a total follow-up of 4710 years, 705 patients (45%) redeemed one prescription for roflumilast, while 22% and 38% redeemed 2–4 and 5+ prescriptions, respectively. Patients redeemed a median of 60 DDDs (IQR 30–360), regardless whether patients were male or female ($p = 0.68$).

The point prevalence was generally stable, increasing slightly from January 2011 (3.1 per 100,000 persons) to January 2014 (4.3 per 100,000 persons) and decreasing slightly thereafter. In December 2016, the point prevalence was 3.8 per 100,000 persons (fig. 2).

The incidence rate was at its highest in 2011 (7.5 per 100,000 person-years) for both males (6.6 per 100,000 person-years) and females (8.4 per 100,000 person-years) and decreased thereafter by 73% to 2.0 per 100,000 person-years. The decrease in incidence rates from 2011 to 2016 was more pronounced among females (decrease of 75% from 8.4 to 2.1 per 100,000 person-years) compared with males (decrease of 71% from 6.6 to 1.9 per 100,000 person-years) (fig. 3).

Duration of use.

Overall, 30% were still users 1 year after initiating roflumilast (fig. 4). Patients with low comorbidity burden showed a comparable proportion of patients still in roflumilast treatment compared with patients with high comorbidity burden (PPC 365 days: CCI 0: 22% versus CCI 3+: 29%). We found no difference in the sex-specific duration of use.

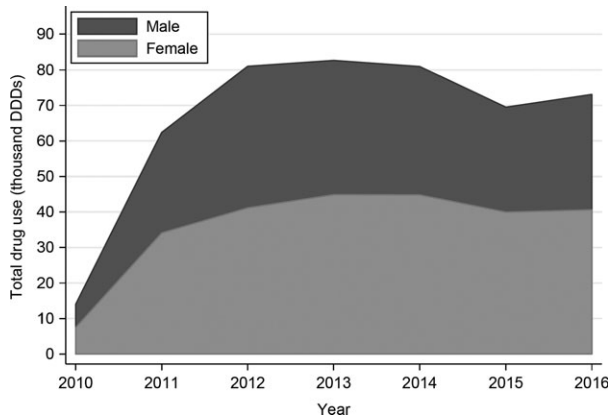


Fig. 1. Total consumption of roflumilast, 2010–2016.

Early discontinuation was associated with age 65 + years (adjusted OR 1.71 [95% CI 1.33–2.21]). A COPD-related admission up to 1 year prior to roflumilast initiation was associated with a continuous treatment with roflumilast (adjusted OR 0.62 [95% CI 0.49–0.80]) (table 2).

During the years 2011 to 2015, the median treatment duration was 109 days (IQR 38–468). An increase was observed each year from 2011 to 2015, from 66 days (IQR 38–423) in 2011 to 114 (IQR 38–438) in 2015 ($p = 0.004$).

Discussion

This is the first study to report the usage of roflumilast in a nationwide setting. We found a 73% decrease of new users initiating roflumilast from 2011 to 2016, and nearly half of all patients initiating roflumilast only redeemed one prescription. Further, only 28% were still in treatment after 12 months. However, the number of users in treatment was consistent throughout the study period and consistent with regard to different patient characteristics.

Our study showed that only 55% of the patients redeemed more than one prescription, and that about 28% were users for 12 months or more. The low compliance has previously been demonstrated in similar settings, as a real-life study of 55 patients in Spain from 2014 found that 50.9% of roflumilast-treated patients remained on the treatment for more than 1 year [20].

There are several possible explanations for the relatively low compliance. Firstly, clinical trials describe a number of adverse effects that are associated with poor compliance, especially affecting the gastrointestinal system (nausea, diarrhoea and weight loss) [21].

As the adverse effects manifest before the benefits of the anti-inflammatory action, the likelihood of high compliance is decreased. This could be a plausible explanation of why a Danish study from 2017 concluded that only 22.6% of patients

Table 1.

Characteristics of patients initiating roflumilast treatment in the period of 2010 to 2016.

	All	Age 18 to 64 years	Age 65 + years
Total	(n = 1,573)	(n = 433)	(n = 1,140)
Sex			
Female	835 (53.1%)	250 (57.7%)	585 (51.3%)
Male	738 (46.9%)	183 (42.3%)	555 (48.7%)
Age groups			
18-64 years	433 (27.5%)	433 (100.0%)	n < 10
65 + years	1,140 (72.5%)	n < 10	1,140 (100.0%)
Charlson Comorbidity Index (CCI)			
0	69 (4.4%)	23 (5.3%)	46 (4.0%)
1	730 (46.4%)	236 (54.5%)	494 (43.3%)
2	383 (24.3%)	86 (19.9%)	297 (26.1%)
3+	391 (24.9%)	88 (20.3%)	303 (26.6%)
Admissions			
Asthma-related	10 (0.6%)	n < 10	n < 10
COPD-related	582 (37.0%)	159 (36.7%)	423 (37.1%)
Medicine ¹			
Only ICS	16 (1.0%)	n < 10	10 (0.9%)
Only LABA + ICS	152 (9.7%)	56 (12.9%)	96 (8.4%)
Only LABA	n < 10	n < 10	n < 10
Only LAMA	19 (1.2%)	n < 10	12 (1.1%)
Only LAMA + ICS	11 (0.7%)	n < 10	n < 10
Only LABA + LAMA	26 (1.7%)	n < 10	19 (1.7%)
Only LABA + LAMA + ICS	1,315 (83.6%)	341 (78.8%)	974 (85.4%)
Medicine based on active ingredient ¹			
ICS (either ICS or LABA + ICS)	1,494 (95.0%)	405 (93.5%)	1,089 (95.5%)
LABA (either LABA or LABA + ICS or LABA + LAMA)	1,497 (95.2%)	405 (93.5%)	1,092 (95.8%)
LAMA (either LAMA or LAMA + LABA)	1,371 (87.2%)	357 (82.4%)	1,014 (88.9%)

LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

¹Within 1 year prior to roflumilast initiation.

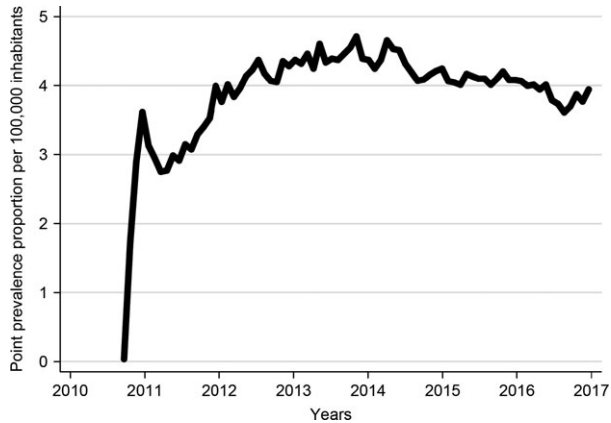


Fig. 2. Point prevalence of roflumilast usage, with data sampled each day from 2010 to 2017.

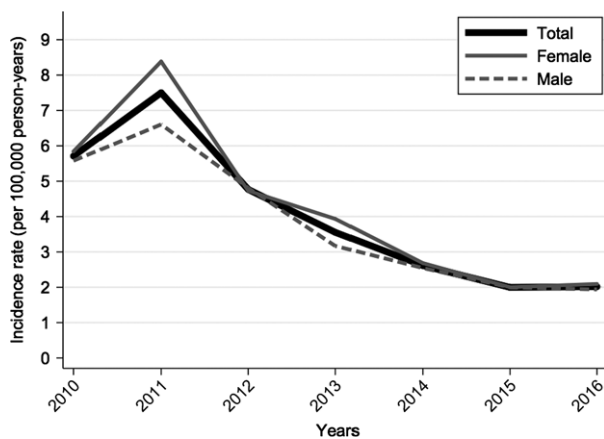


Fig. 3. The overall and sex-specific incidence rate of redeemed roflumilast per 100,000 from 2010 to 2016.

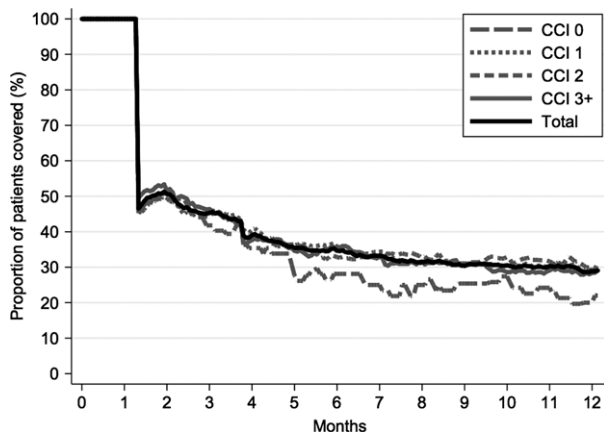


Fig. 4. Proportion of patients covered, showing the distribution among patients scoring different on the Charlson Comorbidity Index.

who met the criteria for roflumilast treatment were actually prescribed the drug [8]. Secondly, the drug is relatively expensive (2.28 Euro per DDD) [22], and thirdly, the Danish subsidy system requires the patients to have at least two exacerbations per year and to receive optimal treatment in

order to be reimbursed [23]. Furthermore, the subsidy lasts for 12 months, and the effect of the treatment must be described in detail to obtain a prolonged subsidy. The time-consuming process of writing prescriptions with subsidies combined with the high price and adverse effects may have an influence on the treatment persistence.

We assessed the association between demographic characteristics and early discontinuation of roflumilast and found that patients with severe comorbidity, a COPD-related admission, and patients prescribed oral corticosteroids within 1 year prior to roflumilast initiation were more likely to redeem more than one prescription for roflumilast.

Two separate meta-analyses [4,24] found that roflumilast is effective in reducing the number of exacerbations, and a full incremental analysis from the UK in 2012 concluded that roflumilast treatment is both clinical- and cost-effective in the treatment of patients 'continuing to exacerbate despite existing bronchodilator therapy' [25]. Identifying means to specifically select well-responders to the treatment may consequently reduce the number of hospital admissions and lower the costs associated with COPD exacerbations.

The Danish Ministry of Health requires treatment with ICS as a prerequisite for roflumilast subsidy [23]. In 2011, during the study period, a revised version of the GOLD guidelines was published, which recommended roflumilast treatment to patients with moderate and severe exacerbations treated with ICS (group D). However, we have not been able to derive the number of patients meeting these recommended indications for roflumilast prescription, as patients in GOLD group C can be treated with roflumilast as an 'alternative choice to standard first-line therapy with ICS and LABA or LAMA' [26]. Knowledge of the GOLD COPD stage of all patients treated with roflumilast could help further analyse the utilization pattern and better identify patients who may benefit from roflumilast treatment.

Strengths.

This study included all roflumilast redeemed to the Danish population outside hospitals during 7 years regardless of socio-economic or insurance status. The completeness of Danish Register of Medicinal Products Statistics allowed the analyses to be conducted without risk of recall bias or drop-out [11].

Limitations.

The study's main limitation was the lack of information regarding the exact duration of use. Therefore, we had to use the number of redeemed DDDs adding 25% to the duration of therapy based on a definition of 80% compliance. Patients redeeming only one package with 90 DDDs are likely to consume a lower percentage of the prescribed doses, compared with patients redeeming only one package with 30 DDDs. As 48.1% of the total DDDs sold came in packages with 90 DDDs, our calculations of treatment duration could be overestimated.

We only had information of outpatient pharmacy prescriptions, but only a negligible 2.4% of the total amount of roflumilast is sold to the hospitals [13].

Table 2.

Crude and adjusted odds ratios for early discontinuation of roflumilast among users with at least one-year observation period (n = 1264)

	Only one prescription redeemed	More than one prescription redeemed	Crude OR ¹	Adjusted OR ¹
Total	(n = 537)	(n = 727)		
Sex				
Female	286 (53.3%)	386 (53.1%)	REF	REF
Male	251 (46.7%)	341 (46.9%)	0.99 (0.79–1.24)	0.97 (0.78–1.22)
Age groups				
18–64 years	125 (23.3%)	246 (33.8%)	REF	REF
65 + years	412 (76.7%)	481 (66.2%)	1.69 (1.31–2.17)	1.71 (1.33–2.21)
Charlson Comorbidity Index (CCI)				
0	31 (5.8%)	28 (3.9%)	REF	REF
1	261 (48.6%)	355 (48.8%)	0.66 (0.39–1.13)	0.65 (0.38–1.12)
2	128 (23.8%)	175 (24.1%)	0.66 (0.38–1.16)	0.62 (0.35–1.09)
3+	117 (21.8%)	169 (23.2%)	0.63 (0.36–1.10)	0.59 (0.33–1.04)
Admissions				
Asthma-related	n < 10	n < 10	n < 10	n < 10
COPD-related	151 (28.1%)	282 (38.8%)	0.62 (0.49–0.78)	0.62 (0.49–0.80)
Medicine ²				
Only ICS	10 (1.9%)	n < 10	n < 10	n < 10
Only LABA+ICS	56 (10.4%)	68 (9.4%)	1.13 (0.78–1.64)	1.21 (0.83–1.77)
Only LABA	n < 10	n < 10	n < 10	n < 10
Only LAMA	n < 10	n < 10	n < 10	n < 10
Only LAMA + ICS	n < 10	n < 10	n < 10	n < 10
Only LABA + LAMA	13 (2.4%)	n < 10	n < 10	n < 10
Only LABA + LAMA + ICS	431 (80.3%)	624 (85.8%)	0.67 (0.50–0.90)	0.63 (0.47–0.86)
Medicine based on active ingredient ²				
ICS (either ICS or LABA + ICS)	505 (94.0%)	698 (96.0%)	0.66 (0.39–1.10)	0.63 (0.38–1.07)
LABA (either LABA or LABA + ICS or LABA + LAMA)	501 (93.3%)	703 (96.7%)	0.48 (0.28–0.81)	0.46 (0.27–0.79)
LAMA (either LAMA or LAMA + LABA)	459 (85.5%)	644 (88.6%)	0.76 (0.54–1.06)	0.71 (0.51–0.99)

OR, odds ratio; CI, confidence ratio; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

¹Adjusted for age, sex and comorbidity.²Within 1 year prior to roflumilast initiation.

Further, the relatively short period of study, the recent introduction of the drug and the limited number of patients receiving prescriptions make it difficult to analyse and predict any trend.

The COPD severity was not possible to assess, because we lacked information regarding the extent of airway obstruction (FEV1 and FVC) as well as clinical information (MRC). Instead, we reported the different combinations of LABA, LAMA and ICS, as well as COPD admissions up to roflumilast initiation.

In conclusion, almost half of the patients who initiated roflumilast in the period of 2010 to 2017 did not redeem a second prescription. The incidence rates decreased by 73% from 2011 to 2016 while a stable point prevalence was observed. The decreasing incidence and high level of early roflumilast discontinuation could be due to lack of benefit, a low awareness among physicians, secondary to a challenging prescribing procedure or adverse effects.

Funding

The research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclosures

AP reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim,

Servier and Leo Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this article. ØNUS, JRD and DPH declare no conflict of interests.

References

- 1 Fabricius P, Løkke A, Marott JL, Vestbo J, Lange P. Prevalence of COPD in Copenhagen. *Respir Med* 2011;**105**:410–7.
- 2 Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet Lond Engl* 2012;**380**: 2095–128.
- 3 Wedzicha JA, Calverley PM, Rabe KF. Roflumilast: a review of its use in the treatment of COPD. *Int J Chron Obstruct Pulmon Dis* 2016;**11**:81–90.
- 4 Rogliani P, Calzetta L, Cazzola M, Matera MG. Drug safety evaluation of roflumilast for the treatment of COPD: a meta-analysis. *Expert Opin Drug Saf* 2016;**15**:1133–46.
- 5 GOLD - the Global initiative for chronic Obstructive Lung Disease [Internet]. [henvist 6. marts 2016]. Tilgængelig hos: <http://www.goldcopd.com/guidelines-global-strategy-for-diagnosis-management.html>
- 6 Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ *et al*. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet Lond Engl* 2009;**374**:685–94.

- 7 Martinez FJ, Calverley PMA, Goehring U-M, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet Lond Engl* 2015;**385**:857–66.
- 8 Holm CP, Holm J, Nørgaard A, Godtfredsen N. COPD, stage and treatment in a large outpatient clinic. *Eur Clin Respir J* 2017;**4**:1267470.
- 9 Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;**9**:CD002309.
- 10 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**:541–9.
- 11 Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the danish national prescription registry. *Int J Epidemiol* 2016;**46**:798.
- 12 WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2017. 2017.
- 13 Schmidt M, Hallas J, Laursen M, Friis S. Data Resource Profile: danish online drug use statistics (MEDSTAT). *Int J Epidemiol* 2016;**45**:1401–2 g.
- 14 Lyng E, Sandegaard JL, Rebolj M. The danish national patient register. *Scand J Public Health* 2011;**39**(7 Suppl):30–3.
- 15 Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient non-compliance? *Hypertension* 1980;**2**:757–64.
- 16 Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc* 2011;**86**:304–14.
- 17 Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011;**39**(7 Suppl):12–6.
- 18 Hallas J, Støvring H, Pottegård A. Individual level drug utilization analyses. I: drug Utilization Research: methods and Applications. Chichester, West Sussex: John Wiley & Sons Inc, Hoboken, NJ: 2016.
- 19 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.
- 20 Muñoz-Esquerre M, Diez-Ferrer M, Montón C, Pomares X, López-Sánchez M, Huertas D *et al.* Roflumilast added to triple therapy in patients with severe COPD: a real life study. *Pulm Pharmacol Ther* 2015;**30**:16–21.
- 21 Yuan L, Dai X, Yang M, Cai Q, Shao N. Potential treatment benefits and safety of roflumilast in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016;**11**:1477–83.
- 22 Daxas® [Internet]. [henvist 20. juni 2017]. Tilgængelig hos: <http://pro.medicin.dk/Medicin/Praeparater/5843>
- 23 KOL: Daxas® [Internet]. [henvist 20. juni 2017]. Tilgængelig hos: <https://laegemiddelstyrelsen.dk/da/tilskud/individuelle-tilskud/enkelt-tilskud/vejledende-kriterier/kol-daxas/>
- 24 Luo J, Wang K, Liu D, Liang B-M, Liu C-T. Can roflumilast, a phosphodiesterase-4 inhibitor, improve clinical outcomes in patients with moderate-to-severe chronic obstructive pulmonary disease? A meta-analysis *Respir Res* 2016;**17**:18.
- 25 Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:183–99.
- 26 Taegtmeier AB, Leuppi JD, Kullak-Ublick GA. Roflumilast—a phosphodiesterase-4 inhibitor licensed for add-on therapy in severe COPD. *Swiss Med Wkly* 2012;**142**:w13628.