17 March 2016
EMA/330021/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Inhaled corticosteroids (ICS) containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease (COPD)

INNs: beclomethasone, budesonide, flunisolide, fluticasone propionate, fluticasone furoate

Procedure number: EMEA/H/A-31/1415

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
aHR	Adjusted Hazard Ratio
aOR	Adjusted odds ratio
BDF	Budesonide/formoterol
BMI	Body Mass Index
CAP	Community Acquired Pneumonia
CI	Confidence Interval
cAMP	cyclic adenosine monophosphate
COPD	Chronic Obstructive Pulmonary Disease
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FEV_1	Forced Expiratory Volume in 1 second
FF	Fluticasone Furoate
FF/VI	Fluticasone Furoate/ Vilanterol
FP	Fluticasone Propionate
FPS	Fluticasone/salmeterol
GCS	Glucocorticosteroids
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICS	Inhaled Corticosteroids
INN	International Nonproprietary Names
LABA	Long Acting $Beta_2$ Agonist
LoQ	List of Questions
LoOI	List of Outstanding Issues
MAH	Marketing Authorisation Holder
PRAC	Pharmacovigilance Risk Assessment Committee
OR	Odds ratio

RCT	Randomised Clinical Trials
RR	Rate Ratio
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System organ classes

1. Information on the procedure

Inhaled corticosteroid (ICS) medicinal products are widely used in the treatment of chronic obstructive pulmonary disease (COPD), as a mono-component or in combination with a long-acting $beta_2$ adrenergic agonist (LABA).

ICS-containing treatments are known to increase the risk of pneumonia in COPD patients. This signal was first identified in the TORCH study (Calverley et al., 2007) a large clinical study of 3 years treatment duration comparing the fluticasone propionate/salmeterol combination with its component parts and placebo in COPD patients. Since other products containing ICS have been subject to review, and it was considered that data on the risk of pneumonia with these products in the COPD population should be reviewed altogether, so that the risk of pneumonia in this patient population could be further characterised.

On 27 April 2015 the European Commission therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of ICS containing medicinal products indicated in the treatment of COPD and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

COPD is characterised by persistent, usually progressive, airflow limitation associated with an enhanced inflammatory response in the airways and the lungs. Exacerbations and comorbidities contribute to the overall severity in individual patients [Global Initiative for Obstructive Lung Disease (GOLD), 2015]. Symptoms of COPD include dyspnoea, chronic cough and chronic sputum production. Episodes of acute worsening of these symptoms (exacerbations) often occur.

ICS medicinal products are widely used in the treatment of COPD, as a mono-component or in combination with a LABA. The therapeutic effect of inhaled corticosteroids is considered to be the result of suppression of airway inflammation (Martinez et al 2013, Martinez and Vercelli 2013), but the airway effects of ICS in COPD are complex and the mechanism of action is not completely understood (Finney et al., 2014, Jen et al., 2012). However ICSs are an important therapeutic option for certain patient groups as established in some treatment guidelines (GOLD report, 2015).

ICS-containing products authorised across the EU for the treatment of COPD includes the active substances beclomethasone, fluticasone propionate, fluticasone furoate, budesonide and flunisolide. All these products are restricted to 'prescription only' status. Estimates based on the data provided suggest a patient exposure in the tens of millions across ICS as a class.

Whilst the majority of the products have been authorised through national procedures, some have been authorised through centralised procedure. These include BiResp Spiromax, Budesonide Formoterol Teva, DuoResp Spiromax, Relvar Ellipta, Revinty Ellipta and Vylaer Spiromax.

2.2. Risk of pneumonia with ICS containing products in COPD patients

Several potential explanations have been proposed for the mechanisms by which ICS may induce an increased pneumonia risk in COPD patients. However the evidence is limited and mainly founded on speculative theoretical mechanisms. No biological mechanism has been conclusively demonstrated by

studies to date which largely involved in vitro or animal studies with limited generalisability to clinical populations of patients with COPD. This is also complicated by the underlying disease process itself which is complex and carries its own risks of pneumonia comorbidity.

Increasing age is a predisposing factor for community acquired pneumonia (CAP) (Mullerova et al., 2012), as are severity of the underlying disease and low body mass index (BMI). Lifestyle factors associated with an increased risk of CAP include smoking, alcohol abuse, living in large households, having regular contact with children and poor dental hygiene. The presence of comorbid conditions, including chronic respiratory and cardiovascular diseases, cerebrovascular disease, Parkinson's disease, epilepsy, dementia, dysphagia, HIV and immunocompromised states or chronic renal or liver disease increases the risk of CAP by twofold to fourfold (Torres et al., 2013). Moderate and severe lung disease (percentage predicted FEV1: 50–80%) and moderate to severe COPD exacerbations have also been identified as independent risk factors for CAP in patients with COPD (Mullerova et al., 2012).

Since the results of the TORCH study that revealed an increased risk of pneumonia with the use of ICS in patients with COPD have been published in 2007, a number of large meta-analyses of pooled data have been conducted. As part of this review, marketing authorisation holders (MAHs) were asked to provide all available data on the risk of pneumonia with their ICS-containing products in COPD patients and to comment on the impact thereof on the benefit-risk balance of their products.

This report discusses the main clinical evidence, from both randomised controlled trials and observational studies.

2.2.1. Randomised controlled clinical trials

Several meta-analyses of randomised clinical trials (RCT) have been conducted in attempt to estimate the effect of ICS on pneumonia incidence rates. These are summarised in the below table.

Table 1. Summary of the randomised controlled trials reviewed.

Study	Study type (pneumonia-related outcome)	Included	Main results
Calverley et al 2007 TORCH study	Randomised controlled trial (pneumonia adverse events)	6,184 patients (1,544 placebo, 1,542 salmeterol, 1,552 fluticasone, 1,546 combination)	% of patients with pneumonia: placebo 12.3%, salmeterol 13.3%, fluticasone 18.3%, combination 19.6%; p<0.001 for fluticasone-containing treatment vs placebo
Crim et al 2009	post hoc analysis of the TORCH data (time to first pneumonia; risk factors)	6,184 patients (1,544 placebo, 1,542 salmeterol, 1,552 fluticasone, 1,546 combination)	HR vs placebo: Fluticasone HR 1.53; 95% CI 1.24-1.89 Combination HR 1.64; 95% CI 1.33-2.02 Risk factors: age ≥55, FEV_1 <50% predicted, COPD exacerbations in

			year prior to study, worse dyspnoea score and BMI <25 kg/m^2.
Drummond et al 2008	meta-analysis (effects of ICS treatment on mortality and adverse effects in patients with stable COPD)	7 studies with pneumonia data (10,776 patients: 5,405 treatment, 5,371 control)	Incidence of pneumonia with ICS: RR, 1.34; 95% CI, 1.03-1.75: p=0.03
Sobieraj et al 2008	meta-analysis (pneumonia adverse events)	9 studies of ICS in COPD	Incidence of pneumonia with ICS: RR 1.68; 95% CI 1.28-2.21
Rodrigo et al 2009	meta-analysis (pneumonia adverse events)	18 randomised controlled trials	Risk of pneumonia with ICS: RR 1.63; 95% CI 1.35–1.98
Sin et al 2009	meta-analysis (pneumonia adverse events, pneumonia SAEs and time to pneumonia as AE)	7 randomised controlled trials using budesonide	Incidence of pneumonia with budesonide: AEs: HR 1.05; 95% CI 0.81 – 1.37 SAEs: HR 0.92; 95% CI 0.62-1.35
Singh & Loke 2010	meta-analysis (pneumonia adverse events)	24 randomised controlled trials (23,096 patients)	Risk of pneumonia with ICS: RR 1.57; 95% CI 1.41–1.75
Halpin et al 2011	meta-analysis (pneumonia adverse events, pneumonia SAEs – OR given for budesonide/ fluticasone comparison only)	8 fluticasone/ salmeterol trials, 4 budesonide/ formoterol trials	Pneumonia AE: budesonide/ formoterol vs fluticasone/salmeterol OR 0.47; 95% CI 0.28-0.80 Pneumonia SAE: budesonide/ formoterol vs fluticasone/salmeterol OR 0.41; 95% CI 0.19-0.86
Spencer et al 2011	Cochrane review (pneumonia adverse events and pneumonia SAEs)	7 randomised trials	Incidence of pneumonia AE with ICS: OR 1.38; 95% CI 1.10 to 1.73 Incidence of pneumonia SAE with ICS: OR 1.48; 95% CI 1.13 to 1.94
Nannini et al 2012	Cochrane review (pneumonia adverse events)	14 studies (11,794 severe COPD patients)	Incidence of pneumonia with ICS/LABA vs LABA: OR 1.55; 95% CI 1.20-2.01

Nannini et al 2013a	Cochrane review (pneumonia adverse events)	19 randomised studies (10,400 patients)	Risk of pneumonia with ICS/LABA vs placebo: OR 1.62; 95% CI 1.36-1.94
Kew and Seniukovich 2014	Cochrane review (non-fatal pneumonia SAEs requiring hospital admission, all pneumonia events)	43 studies	Risk of pneumonia (non-fatal SAE) with fluticasone: OR 1.78; 95% CI 1.50-2.12 Risk of pneumonia (non-fatal SAE) with budesonide: OR 1.62; 95% CI 1.00-2.62

Since the results of the TORCH study were published in 2007 a number of large meta-analyses of pooled data have been conducted. All have found an association between ICS as a class and an increased risk of pneumonia in COPD patients.

The three year TORCH study tends to dominate these meta-analyses; for example in the analysis of pneumonia data from 14 RCTs by Nannini et al. (2013a) exclusion of TORCH data caused the finding of increased pneumonia risk in the ICS group to lose statistical significance. A number of common criticisms can be levelled at the studies included in these meta-analyses, including difficulties with the accurate identification of pneumonia (particularly pre-TORCH studies), variations in participant populations and comparators, and differential withdrawal rates. Many trials were not specifically powered to detect pneumonia.

The most recent and most important of the Cochrane meta-analyses for the purposes of this assessment is that of Kew & Seniukovich (2014) who specifically focused on the effect of ICS on the risk of pneumonia in COPD. This meta-analysis included parallel-group randomised controlled trials of at least 12 weeks duration which compared budesonide or fluticasone versus placebo, or either ICS in combination with a LABA versus the same LABA as monotherapy. Forty three studies met the inclusion criteria, with more evidence for fluticasone (26 studies; n = 21,247) than for budesonide (17 studies; n = 10,150). Mean duration weighted by sample size was 18 months for fluticasone studies and 14 months for budesonide studies. Studies of both fluticasone propionate and furoate were included. Two of the included budesonide studies reported no data that could be used in the analyses and are not included in these numbers. Evidence from the budesonide studies was more inconsistent and less precise. No studies directly comparing fluticasone with budesonide met the inclusion criteria. Fluticasone increased non-fatal serious adverse pneumonia events (requiring hospital admission) (OR 1.78; 95% CI 1.50-2.12; n = 19,504). No evidence suggested that this outcome was reduced by delivering it in combination with salmeterol or vilanterol or that different doses, trial duration or baseline severity significantly affected the estimate. Budesonide also increased non-fatal serious adverse pneumonia events compared with placebo, but the effect was less precise and was based on shorter trials (OR 1.62; 95% CI 1.00-2.62; n = 6,472). In a pooled analysis of both fluticasone and budesonide data, the OR for non-fatal pneumonia SAEs was 1.76 (95% CI 1.50-2.07). An indirect comparison of budesonide versus fluticasone monotherapy was also conducted and is discussed in section 2.2.3 of this report.

Overall, a consistent association between ICS use and pneumonia is seen across the meta-analyses, with an increased risk of pneumonia of 40 – 70% in patients treated with ICS.

2.2.2. Observational studies

A large number of observational studies of the pneumonia risk in COPD patients treated with ICS-containing products have been conducted. Results from the majority of these studies are presented in the table below.

Table 2. Summary table of observational studies.

Study	Study type (outcome of interest)	Number of COPD patients	Main results*
Ernst et al 2007	Nested case-control study (pneumonia hospitalisation)	175,906 (23,942 hospitalised with pneumonia)	RR 1.70 (95% CI 1.63–1.77)
Almirall et al 2010	Case-control study (community acquired pneumonia)	94 with pneumonia, 33 controls	OR 3.26 (95% CI 1.07– 9.98)
Joo et al 2010	Nested case-control study (pneumonia hospitalisation)	145,586 (13,995 pneumonia)	Current ICS use: aOR 1.38 (95% CI 1.31-1.45)
Snider et al 2012	Nested case-control study (pneumonia)	83,455 (13,778 pneumonia, 36767 controls)	OR 1.11 (95% CI 1.05–1.18) for ICS in past year; OR 1.26 (95% CI 1.16–1.36) for current use
Janson et al 2013	Retrospective pairwise cohort study (pneumonia)	2734 each for fluticasone/salmeterol and budesonide/formoterol; 2115 in matched groups	Pneumonia event rate: 11.0 events per 100 Pt years (95% CI 10.4-11.8) for fluticasone 6.4 events per 100 Pt years (95% CI 6.0-6.9) for budesonide
Lin et al 2013	Retrospective chart review (pneumonia)	2630 (402 pneumonia)	aHR 1.60 (95%CI 1.30–1.96)
Eurich et al 2013	Nested case-control study (pneumonia)	2652	aOR 1.72 (95% CI 1.17–2.55)
Suissa et al 2013	Nested case-control study (pneumonia)	163,514 (20,344 pneumonia)	RR 1.69 (95% CI 1.63-1.75)
Yawn et al 2013	Retrospective cohort analysis	135,445	HR 1.51 (95% CI 1.42–1.61)

Flynn et al 2014	Record linkage analysis (pneumonia hospitalisation)	4305 (3243 exposed to ICS, 550 pneumonia)	HR 1.42 (95% CI 1.07-1.88
DiSantostefano et al 2014	New user cohort study (pneumonia)	11,555 ICS/LABA & ICS, 6492 controls	Pneumonia hospitalisation: HR 1.55 (95% CI: 1.14-2.10) Any pneumonia: HR 1.49 (95% CI: 1.22-1.83)
Mapel et al 2010	Nested case control study (pneumonia)	5245	ICS/LABA (90 days prior to case): aOR 0.58 (95% CI 0.30-1.12) ICS alone (90 days prior to case): aOR 1.29 (95% CI 0.96-1.73)
Festic et al 2014	Prospective cohort study (pneumonia hospitalisation)	5584 (495 on ICS, 1234 pneumonia hospitalisation)	aOR 1.40 (95% CI 0.95-2.09)
Gershon et al 2014	Longitudinal cohort study (pneumonia hospitalisation)	8712 LABA/ICS, 3160 LABA only	HR 1.01 (95% CI 0.93-1.08)
Lee et al 2013	Case-crossover study	186,018 pneumonia	ICS alone: aOR 1.73 (95% CI 1.64–1.83) ICS/LABA: aOR 0.63 (95% CI: 0.61–0.66)

*Odds or hazard ratio for pneumonia incidence or pneumonia hospitalisation with/without ICS unless otherwise stated. aOR = adjusted odds ratio.

Overall the evidence from observational studies is in agreement with the RCT findings that use of ICS predisposes to an increased risk of pneumonia in COPD patients, though there are several conflicting studies (Mapel et al 2010, Festic et al 2014, Gershon et al 2014, Lee et al 2013). The studies vary widely in many aspects of their methodology including study type, cohort size, patient selection and the degree to which confounders such as disease severity were accounted for. A number of studies, notably three out of the four conflicting studies presented above (Festic et al 2014, Gershon et al

2014, Lee et al 2013), considered hospitalisation for pneumonia rather than all pneumonia events. It is therefore likely that only the more severe pneumonia events would be captured in these studies.

Nevertheless, in the majority of studies the estimated increase in the risk of pneumonia with ICS fell into the range of 40-70% (see summary table above).

2.2.3. Intra-class comparison of the risk of pneumonia

No clinical trials examined directly ICS-containing products head to head and conclusions regarding differences in the pneumonia risk with different ICSs have been drawn from indirect comparison in meta-analyses/systematic reviews or from observational studies, mostly between fluticasone and budesonide.

The results of these studies were variable, with some suggesting an increased risk of pneumonia with fluticasone compared to budesonide (Halpin et al., 2011; Janson et al., 2013; Suissa et al., 2013; Kew and Seniukowich, 2014) and others finding no difference (Singh & Loke, 2010; Roberts et al., 2011; Nannini et al., 2012; Nannini et al., 2013a; Mapel et al., 2013; Kern et al., 2015).

Interpretation of data from these studies is complicated by the wide methodological variability, particularly in observational studies. For the meta-analyses/systematic reviews, there was generally unequal duration and numbers between the budesonide and fluticasone groups - there were generally far fewer patients on budesonide. Doses sometimes differed between the studies used, some studies assessed these as separate subgroups (Kew & Seniukovich, 2014) but others did not. Studies included in the systematic reviews were generally not designed to investigate the risk of pneumonia as a primary outcome, were not powered to assess this risk and the treatment groups were not necessarily matched or similar.

The most recent and comprehensive Cochrane meta-analysis by Kew and Seniukovich (2014) found non-fatal serious adverse pneumonia events were increased by 78% and 62% for fluticasone and budesonide respectively. An indirect comparison of budesonide versus fluticasone monotherapy showed no significant difference in pneumonia SAEs. However, in an indirect comparison, the risk of any pneumonia event (i.e. less serious cases treated in the community) was higher with fluticasone than with budesonide (OR 1.86, 95% CI 1.04 to 3.34); this was the only significant difference reported between the two drugs. Interestingly, when Calverley et al (2007) (TORCH) was excluded in a sensitivity analysis, the difference was larger in magnitude but was much less precise and not statistically significant. TORCH was one of the studies with the longest duration and with a relatively large number of subjects compared to some of the other studies; this was considered to be a possible factor in the relatively high proportion of patients with pneumonia in this study, especially as there is no trial of a comparable size or duration with budesonide. It had the largest weighting in all ICS meta-analyses. As discussed by Kew and Seniukovich (2014), the results from the TORCH study were considered to skew event rates, as evidenced by the effect of its exclusion in the sensitivity analysis.

In response to the questions raised in the context of this referral procedure, a MAH provided a meta-analysis of 11 clinical trials in which budesonide was administered in COPD patients which found no increased risk of pneumonia SAEs with budesonide compared to control overall, although no comparison with fluticasone was made. However, a statistically significant increase in pneumonia SAE risk was found in certain sub-groups - in particular the subgroups containing studies >12 months duration, patients <55 years, and 640 µg dose versus placebo. This latter result is similar to the result by dose observed in the Kew and Seniukovich (2014) study. It is to be noted that no statistical measure of heterogeneity was presented; in addition, any pneumonia events occurring more than 14 days after treatment cessation will have been missed in this study design.

Overall, the PRAC therefore concluded that there is no conclusive clinical evidence for intra-class differences in the magnitude of the risk among inhaled corticosteroid products.

2.2.4. Influence of the dose and of concomitant medications on the risk of pneumonia

Dose response effect

In the meta-analysis of eight RCTs (involving studies of FP, budesonide and triamcinolone as either monotherapy or combination therapy) by Drummond et al (2008), subgroup analysis revealed that there was a significantly higher risk of pneumonia in the subgroup receiving the highest ICS dose (>1,000 mcg/day beclomethasone equivalents) (RR, 1.46; 95% CI, 1.10-1.92: p=0.008; I2=78%) but not the low dose (<800 mcg/day beclomethasone equivalents) or medium dose (800 – 1,000 mcg/day beclomethasone equivalents) subgroups. The high dose sub-group included 4,749 patients versus only 254 and 402 for the low and medium dose subgroups respectively.

In their large database case-control study, Suissa et al. (2013) identified a dose dependent increase in the risk of serious pneumonia with all ICS ranging from 24% for the lower doses (RR 1.24; 95% CI 1.13 to 1.36) to 86% with the highest doses of ICS, equivalent to fluticasone 1,000 mcg per day or more (RR 1.86; 95% CI 1.77 to 1.94). The dose response was considered to be particularly associated with fluticasone, with doses of 1,000 µg of fluticasone per day associated with a 122% increase in risk, however no statistical significance was seen between the low and medium doses. No dose–response effect was identified with budesonide. The findings were similar to those of the previous nested case-control study by Ernst et al (2007), which used the same health database.

ICS use was also associated with a dose-related increase in risk of pneumonia in the retrospective cohort analysis by Yawn et al (2013) with adjusted hazard ratios versus no use (95% confidence interval) of 1.38 (1.27–1.49) for low-dose users, 1.69 (1.52–1.88) for medium-dose users, and 2.57 (1.98–3.33) for high-dose users (P < 0.01 versus no use and between doses).

Although the systematic review by Kew and Seniukovich (2014) did not find that different doses of fluticasone (500 and 1,000 mcg) had any effect on pneumonia risk, combining all studies and organising by fluticasone dose did not reveal significant subgroup differences between doses (I^2 = 0%, P value 0.90). Higher-dose fluticasone propionate was the most widely studied and hence has the most precise estimate, but the pooled effect was not statistically different from the other dose subgroups. However, Kew and Seniukovich (2014) concluded that a significant difference between the two commonly used doses of budesonide was noted. The 640 mcg dose was associated with a larger effect than 320 mcg relative to placebo, however large heterogeneity was noted in the I^2 analysis for the budesonide studies (subgroup differences: I^2 = 74%, P value 0.05).

A systematic review by Yang et al. (2012) found that in the six long term (duration >6 months) studies that reported pneumonia as an adverse event, the rate of pneumonia was increased in the ICS group compared to placebo. However, a statistically significant association was only found in the studies using ICS > 1,000 µg budesonide equivalent/day, whereas there was no statistically significant association in the ICS < 1,000 µg budesonide equivalent/day group.

In the meta-analysis of 18 randomised controlled trials (12,446 subjects) comparing ICS/LABA combinations with LABA monotherapy by Rodrigo et al (2009), no dose effect was seen for fluticasone, with an increase in the risk of pneumonia with both moderate doses (500 mcg/d; RR, 1.75; 95%CI 1.16-2.64; I2 30%) and high doses (1,000 mcg/d; RR 1.64; 95% CI 1.32-2.06; I2 22%). No separate analysis was performed for budesonide. The study by Cheng et al. (2014) also showed no statistical significance in incidence of pneumonia between patients treated with high dose fluticasone propionate,

An observational retrospective cohort study of 9,893 patients (Janson et al., 2013) did not find a dose-related response in patients treated with either fluticasone/salmeterol or with budesonide/formeterol combinations (hazard ratio 1.00, 95% confidence interval 0.64 to 1.57; P=0.99). It is noted that there were only two thresholds used to discriminate between dosing with the low daily dose equivalent to budesonide <640 µg or fluticasone <1,000 µg and the high daily dose above or equal to these thresholds, this limits granularity of the analysis as differences with intermediate dosing would have been lost and there may have been significant variation in dosing within those two groups.

Crim et al. (2015) analysed data within identical, replicate, multicentre, double-blind, parallel-group trials comparing three strengths of fluticasone furoate/vilanterol (FF/VI). 50, 100, or 200 mg of FF combined with 25 mg of VI were administered once daily. 3,255 eligible subjects were randomized (1:1:1:1) to one of the four treatment regimens for 52 weeks. Crim et al (2015) could not confirm a dose related increase in the pneumonia risk associated with FF/VI.

Finally, in the systematic review conducted by Nannini et al. (2012), the trials using higher dose budesonide, BDF 320/9 µg twice daily, showed an increase in the odds of pneumonia that was not statistically significant (OR 1.08; 95% CI 0.60 to 1.97), and this was similar to the results from trials using lower dose budesonide, BDF 160/9 µg twice daily (OR 1.10; 95% CI 0.53 to 2.26). For fluticasone, studies using a lower dose of ICS, FPS 250/50 µg twice daily instead of 500/50 µg twice daily still showed a significant increase in the risk of pneumonia even on the lower dose of fluticasone (OR 2.19; 95% CI 1.35 to 3.53). Similarly in the meta-analysis of ICS/LABA versus placebo involving 19 studies (10400 patients; Nannini et al 2013a) although an increase in the risk of pneumonia was noted with combined inhalers compared with placebo treatment (OR 1.62; 95% CI 1.36-1.94) no dose effect was seen.

A number of meta-analyses and observational studies have found evidence of a statistically significant dose-response effect for ICS as a class or for fluticasone (Drummond et al., 2008, Ernst et al., 2007, Suissa et al., 2013, Yawn et al., 2013); others saw a trend which did not reach statistical significance (Rodrigo et al., 2009; Cheng et al., 2014). On the other hand, other studies by Janson et al (2013), Crim et al (2015) and Nannini et al (2012) saw no dose-response effect. The most recent Cochrane meta-analysis by Kew and Seniukovich (2014) found no dose-response relationship for fluticasone, but did find one for budesonide. There are, as expected, general limitations of these studies which require cautious interpretation of the data. Issues such as residual confounding, reliance on retrospective data, early departure of the subject from the database used, lack of information about indication of prescription, the absence of randomisation, difficulties in stratifying by severity of COPD disease from available information on the database and reliance on information from dispensed prescriptions with no information on whether the medications were taken or absorbed as prescribed limit the generalisability of the data to ICS using COPD patients. As with many studies of pneumonia in COPD, no definitions of pneumonia were used in these studies, and mostly relied on information from clinicians. It is also noted that although the recommended doses in the SmPCs for these products do not exceed a daily fluticasone equivalent dose of 1,000 µg, some studies considered a “high” dose of fluticasone to exceed this threshold. The extent of usage of a higher than recommended dose of ICS in clinical practice is not known.

While the concept of a dose-response for pneumonia risk has biological plausibility and there is some supportive clinical evidence, this has not been demonstrated conclusively across all studies.

Concomitant medications effect

Although there is a range of medications from different therapeutic classes that may be administered in COPD patients along with inhaled corticosteroids, such as beta agonists, the aminophyllines, inhaled

anticholinergics/muscarinic antagonists and systemic oral corticosteroids, the products assessed in this review are considered to be commonly administered with a long acting beta agonist (LABA) either separately or as part of a fixed dose combination.

LABAs have been shown to inhibit inflammatory and immune cell function; this includes inhibition of neutrophil activation, neutrophil-endothelial cell adhesion, neutrophil respiratory burst as well as the capacity to release pro-inflammatory cytokines from macrophages aimed at combatting bacterial infection as seen in in vitro studies (Otonello et al., 1996, Johnson & Rennard, 2001). Stimulation of β2-adrenoceptors leads to increase of intracellular signalling molecule cAMP (cyclic adenosine monophosphate), and cAMP elevation is considered to result in inhibition of macrophage activation, including phagocytosis (Aronoff et al., 2005).

It has been proposed that an ICS/LABA combination can predispose to an increased risk of pneumonia compared to either active substance alone. The mechanism for this is however unclear. Some in vitro studies have shown synergistic or additive inhibitory effects on the production of inflammatory cytokines and cell adhesion molecules with a combination of LABA and glucocorticosteroids (GCS). This has been shown for both fluticasone/salmeterol and budesonide/formoterol (Silvestri et al., 2001, Spoelstra et al., 2002). It has also been hypothesised that the combination allows ICS to achieve locally high concentrations in the lung, increasing the risk of pneumonia due to their local immunosuppressive effects (Rodrigo et al., 2009, Suissa et al., 2007).

It has also been suggested from in vitro data that there are effects of LABA other than bronchodilation which may act against lower respiratory tract infections. Salmeterol at therapeutic doses was shown to stimulate cilia and improve ciliary beat function in vitro (Yaghi et al., 2012, Piatti et al., 2005). LABAs have also been considered to reduce vascular permeability with a possible reduction in exudation into the alveolar space (Proud et al., 1998). However, once again, any potential mechanisms, whether protective or predisposing have not been demonstrated in clinical studies.

There is a paucity of data with regards to the potential effects of other classes of medication prescribed for a COPD indication. Studies evaluating the association between LABA/GCS tend to adjust for concomitant medications considered to increase the risk of pneumonia such as central nervous system medications (i.e. sedatives, hypnotics, barbiturates, benzodiazepines, anticonvulsants, and anti-Parkinson therapy) and immunosuppressant/ disease modifying drugs (Joo et al., 2010). In addition, pneumococcal or influenza vaccination may also reduce the risk of developing pneumonia in patients with COPD, a factor which does not appear to have been taken into account in observational studies (Crim et al., 2015).

3. Overall conclusions

Since the results of the TORCH study were published in 2007, a number of large meta-analyses of pooled data have been conducted. Although a number of common criticisms can be levelled at the studies included in these meta-analyses, including difficulties with the accurate identification of pneumonia (particularly pre-TORCH studies), variations in participant populations and comparators, differential withdrawal rates, and trials not specifically powered to detect pneumonia, a consistent association between ICS use and increased risk of pneumonia in COPD patients was seen across the meta-analyses. Overall the evidence from observational studies was in agreement with the randomised clinical trials (RCT) findings and it was therefore considered that the evidence continues to support the conclusion that treatment with ICS increases the risk of pneumonia in COPD patients.

No clinical trials directly examined the risk of pneumonia with ICSs head to head, and only indirect comparison in meta-analyses/systematic reviews or from observational studies is available, mainly

between budesonide and fluticasone. Results from older meta-analyses and from observational studies were also variable, with some suggesting an increased risk of pneumonia with fluticasone compared to budesonide and others finding no difference. Overall, due to the variability in the clinical data and multiple uncertainties with study methodologies, there is no conclusive clinical evidence for intra-class differences in the magnitude of the risk among inhaled corticosteroid products.

The PRAC therefore concluded that pneumonia (in COPD patients) should be added as a common adverse drug reaction in the product information of all ICS-containing products and that for products with an existing risk management plan (RMP), "increased risk of pneumonia in COPD patients" should be considered an Important Identified Risk.

It was acknowledged that any risk of pneumonia with ICS should be considered in context, as pneumonia is an intrinsic comorbidity to COPD with certain predisposing factors making some COPD patients more susceptible to this risk than others. Further, it was recognised that there are difficulties associated with the differential diagnosis of pneumonia or an exacerbation of COPD. To mitigate the risk of pneumonia, the PRAC considered that a warning should be included in the product information for healthcare professionals and patients to remain vigilant for the possible development of pneumonia in patients with COPD, taking into consideration the overlap of the symptoms of pneumonia with those of exacerbation of COPD.

Finally, the PRAC considered the ICS dose-response effect or the influence of LABA and other concomitant medications on the risk of pneumonia in COPD patients. Some evidence suggests an increased risk of pneumonia with increasing steroid dose. It is considered mechanistically plausible that a higher dose of corticosteroid could cause a greater degree of immunosuppression in the lung and lead to a higher risk of pneumonia, but this has not been demonstrated conclusively across all studies. It was considered that this should be reflected in the product information. Due to a paucity of data regarding the potential effects of other classes of medication prescribed for COPD, no conclusions could be drawn regarding the influence of concomitant medications on the risk of pneumonia in COPD patients.

In conclusion, the PRAC considered that the benefit-risk balance of ICS-containing products remained favourable, provided the proposed changes to the product information are implemented.

4. Risk management

The PRAC considered that for products with an existing RMP, "increased risk of pneumonia in COPD patients" should be considered an Important Identified Risk.

In addition, the PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to adequately reflect the risk of pneumonia as a class effect of inhaled corticosteroids in patients with COPD, with no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. These changes include amendments to sections 4.4 and 4.8 of the SmPC.

Pneumonia (in COPD patients) was added as a common adverse event and a warning was included to inform physicians and patients of the possible development of pneumonia in patients with COPD and highlighting the need to remain vigilant considering the overlap of the symptoms of pneumonia with those of exacerbation of COPD.

The package leaflet was amended accordingly.

5. Grounds for Recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for inhaled corticosteroids (ICS)-containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease (COPD);
- The PRAC reviewed the data submitted by the marketing authorisation holders in relation to the increased risk of pneumonia in patients with COPD in association with ICS-containing medicinal products;
- The PRAC concluded that the evidence provided supports a causal association between the use of ICS-containing products and an increased risk of pneumonia in COPD patients;
- The PRAC also concluded that there is no conclusive clinical evidence for intra-class differences in the magnitude of the risk among ICS-containing products;
- The PRAC considered that some evidence of an increased risk of pneumonia with increasing steroid dose exists, although this has not been demonstrated conclusively across all studies;
- The PRAC was of the view that the increased risk of pneumonia should be included in the product information of all ICS-containing products indicated in the treatment of COPD, with a warning for healthcare professionals and patients to remain vigilant for the possible development of pneumonia in patients with COPD, taking into consideration the overlap of the symptoms of pneumonia with those of exacerbation of COPD.

In view of the above, the Committee considers that the benefit-risk balance of ICS-containing medicinal products remains favourable in the treatment of COPD subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for ICS-containing medicinal products indicated in the treatment of COPD.

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