Annex IV

Scientific conclusions

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Scientific conclusions

Chronic obstructive pulmonary disease (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.

Inhaled corticosteroid (ICS) medicinal products are widely used in the treatment of COPD, as a mono-component or in combination with a long-acting beta$_2$ adrenergic agonist (LABA). The therapeutic effect of inhaled corticosteroids is considered to be the result of suppression of airway inflammation, 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.

A signal of increased risk of pneumonia in COPD patients with ICS-containing treatments was first identified in the TORCH study (Calverley et al., 2007) a large clinical study of three years treatment duration comparing the fluticasone propionate/salmeterol combination with its component parts and placebo in COPD patients. Since then 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 all together, 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.

The PRAC adopted a recommendation on 17 March 2016 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

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

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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, “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.

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Grounds for PRAC recommendation

- 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.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

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