NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by the European Commission:

Product Name(s), Strength(s) and Pharmaceutical Form(s)	To be determined
Therapeutic class	inhaled corticosteroid containing products indicated in the treatment of chronic obstructive pulmonary disease (COPD)
Marketing Authorisation Holder(s)	To be determined

Inhaled corticosteroid (ICS) containing medicinal products are authorised both centrally and nationally. They 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[1], a large clinical study of 3 years treatment duration comparing the fluticasone propionate/salmeterol combination with its component parts and placebo in COPD patients. This study was considered in a 2010 review of the risk of pneumonia in COPD patients by the CHMP Pharmacovigilance Working Party that concluded that the treatment with an ICS, either alone or in combination with a LABA, increases the risk of pneumonia in COPD patients.

Since the previous conclusions other products containing ICS have been subject to review. New clinical trials, publications and meta-analysis[2,3,4,5,6] considered individually in the context of national and European reviews for individual active substances may have led to differential reflection of the risk of pneumonia in the COPD population in the product information.

[1] Calverley PMA, Anderson JA, Bartolome C et al. Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease (TORCH) N Engl J Med 2007;356:775-789
[2] Chen D, Restrepo MI, Fine MJ, Pugh MJ, Anzueto A, Metersky ML, et al. Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia. Am J Respir Crit Care Med. 2011;184:312–6.
[3] Dransfield MT,Bourbeau WE, Jones PW et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials Lancet Respir. Med. 1(3), 210 (2013)
[4] Kew KM & Seniukovich A Inhaled steroids and risk for pneumonia for chronic obstructive pulmonary disease. Cochrane Database of Systemic Reviews 2014, Issue 3:CD010115.
[5] Sin D, Tashkin D, Xuekui Zhang X, et al. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. 2009 Lancet 374(9691):712–719. A patient level meta-analysis suggesting that inhaled budesonide may not increase the risk of pneumonia.
[6] Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68:1029–36.

It is considered that data on the risk of pneumonia with these products ICS containing products authorised in the Union in the treatment of COPD as monocomponent or in combination such as fluticasone; fluticasone/salmeterol; fluticasone/vilanterol; budesonide; budesonide/formoterol; beclomethasone; beclomethasone/formoterol; flunisolide/salbutamol in the COPD population should be reviewed altogether so that the risk of pneumonia in this patient population can be further characterised.
In view of the elements described above, the European Commission considers that it is in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee pursuant to Article 31 of Directive 2001/83/EC and requests that it reviews all available data in order to further characterise the risk of pneumonia for all ICS containing medicinal products and gives its recommendation as to whether marketing authorisations of these products should be maintained, varied, suspended, or withdrawn.

As the procedure encompass centrally authorised products, pursuant to Article 31(1) of Directive 2001/83/EC the final recommendation shall be referred to the Committee for Medicinal Products for Human Use to issue the opinion.

[redacted]

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