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January 22, 2004

IMPORTANT SAFETY INFORMATION REGARDING A DRUG INTERACTION BETWEEN FLUTICASONE PROPIONATE (FLONASE®/FLOVENT®/ADVAIR®) AND RITONAVIR (NORVIR®/KALETRA®)[1]

Concomitant use of ritonavir (NORVIR®, KALETRA®) can greatly increase fluticasone propionate (FLONASE®, FLOVENT®, ADVAIR®) plasma concentrations leading to systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Concomitant use of fluticasone propionate and ritonavir should be avoided, unless the benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Dear Health Care Professional,

GlaxoSmithKline Inc., in consultation with Health Canada, would like to inform you of the results of a drug interaction study conducted with FLONASE® (fluticasone propionate) aqueous nasal spray and NORVIR® (ritonavir, Abbott Laboratories).

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

The study also showed that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. However, there have been a few case reports, during worldwide post-marketing use, of adrenocortical suppression associated with the use of azole antifungals and inhaled fluticasone propionate. Therefore, care is advised when co-administering potent CYP3A4 inhibitors (e.g. ketoconazole) as there is potential for increased exposure to fluticasone propionate.

Corticosteroids metabolized primarily by CYP3A4 would potentially be affected by this interaction with ritonavir.

[1] Ritonavir is a protease inhibitor used in the treatment of HIV/AIDS.

The information regarding this drug interaction will be incorporated into the FLONASE® (fluticasone propionate) aqueous nasal spray, FLOVENT® (fluticasone propionate) inhalation aerosol and dry powder for inhalation and ADVAIR®(salmeterol xinafoate/fluticasone propionate) inhalation aerosol and dry powder for inhalation Product Monographs. This information has been incorporated into the Product Monograph for NORVIR® (ritonavir, Abbott Laboratories) and is to be incorporated into the Product Monograph for KALETRA® (lopinavir/ritonavir 4:1, Abbott Laboratories).

The identification, characterization, and management of drug-related adverse events are dependent on the active participation of health care professionals in adverse drug reaction reporting programs. Health care professionals are asked to report any suspected adverse reactions in patients receiving FLONASE® (fluticasone propionate) aqueous nasal spray, FLOVENT® (fluticasone propionate) inhalation aerosol and dry powder for inhalation or ADVAIR®(salmeterol xinafoate/fluticasone propionate) inhalation aerosol and dry powder for inhalation directly to GlaxoSmithKline or to the Marketed Health Products Directorate:

GlaxoSmithKline Inc.
7333 Mississauga Road N
Mississauga, Ontario
L5N 6L4
Tel: 1-800-387-7374

Canadian Adverse Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C1
Ottawa, Ontario K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
cadrmp@hc-sc.gc.ca

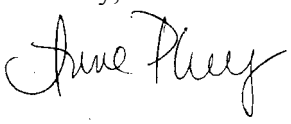
The ADR Reporting Form can be found in *The Canadian Compendium of Pharmaceutical and Specialties,* or on the TPD website, along with the ADR Guidelines at:

http://www.hc-sc.gc.ca

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Any questions from health care professionals may be directed to our Medical Information department via GlaxoSmithKline Customer Service at 1-800-387-7374.

Sincerely,



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GlaxoSmithKline Inc.