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IMPORTANT SAFETY INFORMATION FOR LAMOTRIGINE

Dear Healthcare Professional:

GlaxoSmithKline Inc. (GSK), following discussions with Health Canada, would like to inform you of important new safety information concerning the antiepileptic, LAMICTAL® (lamotrigine).

- **A recently completed clinical pharmacology study has demonstrated that concomitant use of hormonal contraceptives with Lamictal may significantly decrease serum lamotrigine levels. There have also been a limited number of post-marketing reports of break-through seizures occurring with the concomitant use of Lamictal and hormonal preparations. Significant adjustments in the maintenance dose of Lamictal may be required in some patients**
- **Patients should be advised not to start or stop their oral contraceptives without consulting their physician**
- **In the same study, Lamictal had a modest effect on levonorgestrel plasma concentrations and a minimal effect on ethinylestradiol concentrations. However, a limited number of reports have been received of unexpected pregnancies and of menstrual bleeding disorders (e.g. breakthrough bleeding) occurring with the concomitant use of Lamictal and hormonal preparations. Women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g., break-through bleeding) while receiving Lamictal in combination with these medications.**
- **The effect of other hormonal contraceptive preparations or hormone replacement therapy (HRT) on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may be similar to oral contraceptive preparations, and as such, dosage adjustments may be necessary.**

A recently completed clinical pharmacology study, in healthy human volunteers, investigating the interaction between lamotrigine 300 mg once daily and an oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel has documented that:

- An oral contraceptive preparation administered in combination with lamotrigine significantly decreased serum levels of lamotrigine (on average, 52% decrease in AUC and 39% decrease in Cmax)
- During the "pill-free" week of the oral contraceptive there was a gradual increase in trough lamotrigine serum concentrations, by approximately two fold by the end of the "pill-free" week.

- Lamotrigine had a modest effect on levonorgestrel plasma concentrations (on average, 19% decrease in AUC and 12% decrease in Cmax). The effect on ethinylestradiol concentrations was minimal.

- An increase in serum FSH and LH concentrations and a marginal increase in serum estradiol concentrations were observed during the period of co-administration of the oral contraceptive and lamotrigine
- There was no hormonal evidence of ovulation as evidenced by progesterone serum concentrations.
- GlaxoSmithKline has received a limited number of reports of break-through seizures, unexpected pregnancies and of menstrual bleeding disorders (e.g. breakthrough bleeding) occurring with the concomitant use of Lamictal and hormonal preparations.

The CLINICAL PHARMACOLOGY, PRECAUTIONS, DOSAGE AND ADMINSTRATION, and the INFORMATION FOR CONSUMER sections of the Product Monograph will be revised to reflect the results of this study. A summary of the major changes are outlined below.

- The Clinical Pharmacology and Precaution sections will be revised to include the drug interactions noted above.

- The DOSAGE AND ADMINISTRATION section will be revised to reflect the following recommendations for the use of Lamictal in women taking oral contraceptives:

  Starting Lamictal in Women Taking Oral Contraceptives
  No change to the recommended titration guidelines for Lamictal should be necessary based solely on the use of oral contraceptives. Please refer to the Lamictal Product Monograph for recommended guidelines for initiating therapy with Lamictal.

  Adjustments to the Maintenance Dose of Lamictal

  Taking or Starting Oral Contraceptives: The maintenance dose of Lamictal may need to be **increased** by as much as two-fold in women starting or currently taking oral contraceptives and who are **not** also taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

  Stopping Oral Contraceptives: The maintenance dose of Lamictal may need to be **decreased** by as much as 50% below the maintenance dose if oral contraceptives are stopped in patients who are not also taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

  Women and Other Hormonal Contraceptive Preparations or Hormone Replacement Therapy:
  Although not formally evaluated, similar adjustments may be needed for women receiving Lamictal in combination with other hormonal contraceptive preparations or hormone replacement therapy.

- The CONSUMER INFORMATION section will be revised to include the following:

  Women should be advised to notify their physician if they plan to start or stop use of oral contraceptives or other hormonal preparations. They should also be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g., break-through bleeding) while receiving Lamictal in combination with these medications.

GSK continues to work closely with Health Canada to monitor adverse event reporting and to ensure that up-to-date information regarding the use of lamotrigine is available.

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. Healthcare professionals are asked to report any suspected adverse reactions in patients receiving Lamictal (lamotrigine) directly to GSK or Health Canada at the following addresses:

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

Any suspected adverse reaction can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

For other inquiries: please refer to the contact information above.

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

Your professional commitment in this regard is important to 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 Medical Information via GSK Customer service at 1-800-387-7374.

Sincerely,

Ravinder Kumar, Ph.D.
Vice-President, Regulatory Affairs & Pharmaceutical Development
GlaxoSmithKline Inc.