Important Safety Information on
CELEBREX *(celecoxib) capsules,
A Selective Cyclo-oxygenase-2 (COX-2) Inhibitor Non-Steroidal Anti-Inflammatory Drug (NSAID)

21 September 2005

Subject: **CELEBREX* (celecoxib) capsules**
Important Safety Information

Dear Healthcare Professional,

Pfizer Canada Inc., following discussions with Health Canada, would like to inform you of important new safety information for CELEBREX* (celecoxib) capsules. The Product Monograph for CELEBREX is being revised as outlined below.

The revisions to the CELEBREX Product Monograph are based on Health Canada's ongoing scientific review of the cardiovascular safety of selective COX-2 inhibitor non-steroidal anti-inflammatory drugs (NSAIDs).

Health Canada acknowledges that as a group, selective COX-2 inhibitor NSAIDs are associated with an increased risk of cardiovascular events, a risk that is similar to those associated with most NSAIDs and consequently, will issue guidance to manufacturers, establishing standards for the risk and benefit information that must be included in product labelling of NSAIDs.

1. INDICATIONS AND CLINICAL USE

The INDICATIONS AND CLINICAL USE section has been revised to include the following boxed statement:

Randomized clinical trials with NSAIDs, including CELEBREX, have not been designed to detect differences in cardiovascular adverse events in a chronic setting (See CONTRAINDICATIONS and CLINICAL TRIALS – Safety Studies).

The decision to prescribe CELEBREX should be based on the individual patient's overall risk (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Use of CELEBREX should be limited to the lowest effective dose for the shortest possible duration of treatment.

2. CONTRAINDICATIONS

The CONTRAINDICATIONS section has been updated to include the following boxed statements:

Coronary Artery Bypass Graft Surgery

CELEBREX is CONTRAINDICATED in the peri-operative setting of coronary artery bypass surgery (CABG). Although CELEBREX has not been studied in this patient population, another selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.

Pregnancy (3rd Trimester), Breastfeeding

- **CELEBREX is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and uterine inertia (prolong parturition).**
- **CELEBREX is CONTRAINDICATED for use in women who are breastfeeding because of the potential for serious adverse reactions in nursing infants.**

(See Pregnant Women and Breast Feeding)

3. WARNINGS AND PRECAUTIONS

The following boxed statements have been added:

Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV)

Caution should be exercised in prescribing CELEBREX to any patient with ischemic heart disease (including but not limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but not limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

One of three randomized clinical trials of about 3 years duration showed a dose-related increase in serious cardiovascular events (mainly myocardial infarction), detectable at doses of CELEBREX 200 mg twice daily or more, compared to placebo.

The following text has also been added regarding the risk of cardiovascular and thromboembolic events:

Caution should be exercised in prescribing CELEBREX to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (not an exhaustive list) (See Clinical Trials – Safety Studies):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 50 mL/min**

4. CLINICAL TRIALS

The *Clinical Trials* section has been updated to include a sub-section entitled *Cardiovascular Safety - Ongoing Clinical Trials* as follows:

Preliminary safety information from three long-term studies involving patients with Sporadic Adenomatous Polyps or who were predisposed to developing Alzheimer's disease treated with CELEBREX is available. In one of the three studies, the APC (Prevention of Sporadic Colorectal Adenomas with Celecoxib) study involving patients with adenomatous polyps, there was a dose-related increase in cardiovascular events (mainly myocardial infarction, MI) at CELEBREX doses of 200 mg BID and 400 mg BID compared to placebo. The relative risk (RR) for the composite endpoint (cardiovascular death, MI or stroke) was 3.4 (95% CI 1.4 – 8.5) for the higher dose and 2.5 (95% CI 1.0 – 6.4) for the lower dose of CELEBREX, compared to placebo. The absolute risk for the composite endpoint was 3.0% for the higher dose of CELEBREX, 2.2% for the lower dose of CELEBREX, and 0.9% for placebo.

Preliminary data from the other two long-term studies did not show an increased cardiovascular risk with CELEBREX 200 mg BID and 400 mg QD compared to placebo. Data from one of these studies, PreSAP (Randomized, Double Blind, Placebo –Controlled Study of the Efficacy and Safety of Celecoxib in the Prevention of Colorectal Sporadic Adenomatous Polyps), a 36-month study in patients with a history of sporadic adenomatous polyps, has not shown an increased cardiovascular risk with CELEBREX 400 mg QD compared to placebo. Data from the third study, ADAPT (Alzheimer's Disease Anti-Inflammatory Prevention Trial), involving patients who were predisposed to developing Alzheimer's disease (20 months average duration of treatment), has not shown an increased cardiovascular risk with CELEBREX 200 mg BID compared to placebo.

5. OTHER – PREGNANCY AND BREASTFEEDING

The following boxed statement has been added to the **WARNINGS AND PRECAUTIONS** section:

Risk in Pregnancy

Caution should be exercised in prescribing CELEBREX during the first and second trimesters of pregnancy. CELEBREX is CONTRAINDICATED for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition).

(See Contraindications, Pregnancy)

CELEBREX continues to be indicated for the relief of symptoms associated with osteoarthritis and adult rheumatoid arthritis. CELEBREX may also be used for the short-term (one week or less) management of moderate to severe pain in adults caused by conditions such as sprains, surgery or tooth extractions.

Physicians should consider this information in evaluating the risks and benefits of CELEBREX in individual patients treated for OA, RA or acute pain.

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 programmes. Healthcare professionals are asked to report any suspected adverse reactions in patients receiving CELEBREX* to the following addresses:

Pfizer Canada Inc.
Drug Safety
P.O. Box 800
Pointe-Claire- Dorval, Quebec
H9R 4V2
1 800 463-6001

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

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.

<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html>
<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html>

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 use of drugs.

For further reference, please see Health Canada's news release:
http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2005/2005_75_e.html

The full copy of the Product Monograph can be found at: http://www.pfizer.ca

If you require any further information on CELEBREX* (celecoxib) please contact Pfizer Medical Information at 1-800-463-6001.

Sincerely,

original signed by

Bernard Prigent, M.D., MBA
Vice-President and Medical Director
Pfizer Canada Inc.

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