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Health Canada Endorsed Important Safety Information on ursodiol (ursodeoxycholic acid, UDCA; sold as ursodiol C, URSO®, URSO DS®)

Dominion Pharmacal

01/12/2011

Dear Healthcare Professional:

Subject: Association of high-dose ursodiol (ursodeoxycholic acid, UDCA) [URSO®, URSO DS® , Dom-URSODIOL C, phl-URSODIOL C, pms-URSODIOL C, TEVA-URSODIOL] with serious hepatic adverse events

The manufacturers of ursodiol (Aptalis Pharma Canada Inc., Dominion Pharmacal, Pharmascience Inc., Pharmel Inc., Teva Canada Ltd.), in consultation with Health Canada, would like to inform you of important new information regarding ursodiol (ursodeoxycholic acid, UDCA) [URSO®, URSO DS® , Dom-URSODIOL C, phl-URSODIOL C, pms-URSODIOL C, TEVA-URSODIOL].

Ursodiol (ursodeoxycholic acid, UDCA) is indicated for the management of cholestatic liver diseases.

Health professionals should be aware that the Canadian Product Monographs (PMs) for ursodiol products have been updated in October, 2011 to reflect data from a long-term clinical trial in primary sclerosing cholangitis (PSC) finding an increase in serious liver adverse events in patients taking an unapproved ursodiol dose (twice the recommended dose).

- The recommended ursodiol dose is 13-15 mg/kg/d for adults with cholestatic disease.
- In a clinical trial in patients with PSC , long-term use of twice the recommended dose of ursodiol (i.e., of 28-30 mg/kg/d) was associated with improvement in serum liver tests but did not improve survival, and was associated with higher rates of serious adverse events (including death or liver transplantation) compared to placebo.
- Improved serum liver tests do not always correlate with improved liver disease status.

In a 5-year randomized, double-blind, clinical trial, 150 PSC patients were treated with placebo or twice the recommended dose of ursodiol.* Serum AST and ALP concentrations decreased more in the ursodiol than the placebo treated group ($p<0.01$), but improvements in liver function tests were not associated with decreased endpoints. The risk was 2.1-fold greater for death, liver transplantation or minimal listing criteria in the high-dose ursodiol group ($p<0.05$). Serious adverse events (including varices, cirrhosis, and cholangiocarcinoma) were more common in the ursodiol than the placebo group (63% versus 37%; $p < 0.01$).

The Product Monographs for ursodiol have been revised to describe the clinical trial, and advise that improved serum liver tests (e.g. AST, ALP) do not always correlate with an improved liver disease status. The PMs continue to recommend monitoring of GGT, alkaline phosphatase, AST, ALT and bilirubin every month for three months after start of therapy, and every six months thereafter. Treatment should be discontinued if the levels of these parameters increase.

This information has been summarized for patients in a related public communication, which may be accessed at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2011/index-eng.php.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Any case of serious hepatic adverse events or other serious or unexpected adverse reactions in patients receiving ursodiol should be reported to the manufacturer (Aptalis Pharma Canada Inc., Dominion Pharmacal, Pharmascience Inc., Pharmel Inc., Teva Canada Ltd.) or Health Canada.

Aptalis Pharma Canada Inc.,
Dominion Pharmacal,
Pharmascience Inc.,
Pharmel Inc.,
Teva Canada Ltd.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

To change your mailing address or fax number, contact the Market Authorization Holder (Industry).

original signed by

Guy Rousseau, PhD
Executive Director, Regulatory Affairs
Aptalis Pharma Canada Inc.

**** References:***

Lindor, K.D., et. al. Hepatology, 2009, 50, pp 808-814. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis.