Bristol-Myers Squibb Company
P.O. Box 4500 Princeton, NJ 08543-4500

Dear Healthcare Professional:

CHANGES TO LABELING FOR DESYREL® (TRAZODONE HYDROCHLORIDE) TABLETS

Bristol-Myers Squibb Company (BMS) would like to advise you of important package insert changes concerning DESYREL® (trazodone hydrochloride) Tablets. DESYREL is indicated for the treatment of depression. We are writing to inform you that Bristol-Myers Squibb Company, in close cooperation with the U.S. Food and Drug Administration (FDA), has adopted new labeling for DESYREL.

The following label changes include modifications to the **CLINICAL PHARMACOLOGY** section:

> *Metabolism*
> *In vitro* studies in human liver microsomes show that trazodone is metabolized to an active metabolite, m-chlorophenylpiperazine (mCPP) by cytochrome P450 3A4 (CYP3A4). Other metabolic pathways that may be involved in metabolism of trazodone have not been well characterized.
> *Elimination*
> In some patients DESYREL may accumulate in the plasma.
> **Drug-Drug Interactions**
> See also **PRECAUTIONS: Drug Interactions**. *In vitro* drug metabolism studies reveal that trazodone is a substrate of the cytochrome P450 3A4 (CYP3A4) enzyme and trazodone metabolism can be inhibited by the CYP3A4 inhibitors ketoconazole, ritonavir, and indinavir. The effect of short-term administration of ritonavir (200 mg twice daily, 4 doses) on the pharmacokinetics of a single dose of trazodone (50 mg) has been studied in 10 healthy subjects. The C_{max} of trazodone increased by 34%, the AUC increased 2.4-fold, the half-life increased by 2.2-fold, and the clearance decreased by 52%. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered.
> Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg/day with trazodone 100 mg to 300 mg daily, carbamazepine reduced plasma concentrations of trazodone (as well as mCPP) by 76 and 60%, respectively, compared to pre-carbamazepine values.

Additionally, the **Drug Interactions** sub-section within the **PRECAUTIONS** section has been updated with the following information:

> *In vitro* drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with CYP3A4 inhibitors. Ritonavir, a potent CYP3A4 inhibitor, increased the C_{max}, AUC, and elimination half-life, and decreased clearance of trazodone after administration of ritonavir twice daily for 2 days. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered. It is likely that ketoconazole, indinavir, and other CYP3A4 inhibitors such as itraconazole or nefazodone may lead to substantial increases in trazodone plasma concentrations with the potential for adverse

effects. If trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered.
Carbamazepine reduced plasma concentrations of trazodone when co-administered. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking both drugs.

Healthcare professionals are strongly encouraged to report any serious adverse events that occur with the use of DESYREL to 1-800-321-1335 or to the FDA's MedWatch program by phone (1-800-FDA-1088), fax (1-800-FDA-0178), via the MedWatch website at www.FDA.gov/medwatch, or by mail (using postage-paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787.

A COPY OF THE FULL PRESCRIBING INFORMATION FOR DESYREL® (TRAZODONE HYDROCHLORIDE) TABLETS IS ENCLOSED. If you have further questions or require additional information, please contact the Bristol-Myers Squibb Medical Communications Department at 1-800-321-1335.

Sincerely,

Freda C. Lewis-Hall, M.D.
Senior Vice President
U.S. Medical Affairs
Bristol-Myers Squibb Company

Enclosure: Package Insert

