

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-152/S-009/S-010**

**MEDICAL REVIEW**

APR 22 1997

## REVIEW AND EVALUATION of CLINICAL DATA

**NDA:** 20-152

**SPONSOR:** BRISTOL-MYERS SQUIBB

**DRUG:** SERZONE (Nefazodone HCl) Tablets

**INDICATION:** TREATMENT OF MAJOR DEPRESSION

**MATERIAL SUBMITTED:** LABELING CHANGE

**DATE SUBMITTED:** April 10, 1997

**DATE RECEIVED:** April 11, 1997

### I. REVIEW:

The sponsor has offered a compromise along the lines suggested at our telephone conference regarding the contraindication of Nefazodone and Triazolam. The two changes are listed below:

### CONTRAINDICATIONS

Coadministration of terfenadine, astemizole or cisapride with SERZONE (nefazodone hydrochloride) is contraindicated (see **WARNINGS** and **PRECAUTIONS** Sections).

SERZONE is contraindicated in patients with known hypersensitivity to nefazodone or other phenylpiperazine antidepressants.

The coadministration of triazolam and nefazodone causes a significant increase in the plasma level of triazolam (see **WARNINGS** and **PRECAUTIONS** Sections), and a 75% reduction in the initial triazolam dosage is recommended if the two drugs are to be given together. Because not all commercially available dosage forms of triazolam permit a sufficient dosage reduction, the coadministration of triazolam and SERZONE should be avoided for most patients including the elderly.

### WARNINGS

*Triazolam*

When a single oral 0.25-mg dose of triazolam was coadministered with nefazodone (200 mg BID) at steady state, triazolam half-life and AUC increased 4-fold and peak concentrations increased 1.7-fold. Nefazodone plasma concentrations were unaffected by triazolam.

***Coadministration of nefazodone potentiated the effects of triazolam on psychomotor performance tests.*** If triazolam is coadministered with SERZONE, a 75% reduction in the initial triazolam dosage is recommended. \_\_\_\_\_

\_\_\_\_\_ Because not all commercially available dosage forms of triazolam permit sufficient dosage reduction, coadministration of triazolam with SERZONE should be avoided for most patients, including the elderly. In the exceptional case where coadministration of triazolam with SERZONE may be considered appropriate, only the lowest possible dose of triazolam should be used (see CONTRAINDICATIONS and PRECAUTIONS Sections).

II: RECOMMENDATIONS:

I recommend we accept this labeling change as indicated.

*Earl D. Hearst M.D. 4/22/97*

Earl D. Hearst, M.D.  
Medical Reviewer

*4-22-97*  
*[Signature]*

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### I. REVIEW:

The sponsor had agreed to our suggestion that the reporting of priapism and seizures be included in the respective sub-sections under **PRECAUTIONS** and in addition they have listed these events again under Postintroduction Clinical Experience. I have highlighted the changed section below.

#### *Seizures*

During premarketing testing, a recurrence of a petit mal seizure was observed in a patient receiving nefazodone who had a history of such seizures.

In addition, one nonstudy participant reportedly experienced a convulsion (type not documented) following a multiple-drug overdose (see **OVERDOSAGE** Section). Rare occurrences of convulsions (including grand mal seizures) following nefazodone administration have been reported since market introduction. A causal relationship to nefazodone has not been established (see **ADVERSE REACTIONS** Section).

#### *Priapism*

While priapism did not occur during premarketing experience with nefazodone, rare reports of priapism have been received since market introduction. A causal relationship to nefazodone has not been established (see **ADVERSE REACTIONS** Section). If patients present with prolonged or inappropriate erections, they should discontinue therapy immediately and consult their physicians. If the condition persists for more than 24 hours, a urologist should be consulted to

determine appropriate management.

**Postintroduction Clinical Experience**

Postmarketing experience with SERZONE has shown an adverse experience profile similar to that seen during the premarketing evaluation of nefazodone. Voluntary reports of adverse events temporally associated with SERZONE that have been received since market introduction that are not listed above and for which a causal relationship has not been established include rare occurrences of convulsions (including grand mal seizures) and priapism (see PRECAUTIONS Section).

II. I recommend we accept these labeling changes.

*Earl D. Hearst M.D.* 4/22/97

Earl D. Hearst, M.D.  
Medical Reviewer

4-22-97

*J. Long*

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