WYETH-AYERST LABORATORIES

P.O. Box 8299, Philadelphia, PA 19101-8299 Division of American Home Products Corporation

June 1999

Dear Doctor:

Lederle Pharmaceuticals and Lederle Parenterals, Inc. are committed to providing information to physicians so that they can make informed prescribing and treatment decisions regarding Methotrexate Sodium (i.e., Rheumatrex® Dose Pack, Methotrexate Sodium Tablets, Methotrexate Sodium for Injection, and Methotrexate Sodium Injection). A summary of important new information as well as corresponding changes to the Methotrexate Sodium labeling is presented below.

We have received rare reports of bone and soft tissue necrosis following radiation therapy in patients receiving methotrexate.[1] The actual risk of this occurrence has not been established. Close observation for this potential complication is recommended.

There have also been rare reports of painful plaque erosions when methotrexate has been used for the treatment of psoriasis.[2] This should be considered when prescribing methotrexate for this indication.

Hepatotoxicity is a known potential adverse event associated with methotrexate therapy. It has been reported that the combination of methotrexate with other potentially hepatotoxic agents may increase the risk of hepatotoxicity.[3] The risk, if any, of such combination therapy has not been systematically evaluated. Care should be exercised when combining methotrexate with other medications that have hepatotoxic potential (for instance, azathioprine, retinoids, and sulfasalazine).

Urgent treatment of methotrexate overdose is sometimes necessary. Routine hemodialysis and hemoperfusion are ineffective in lowering methotrexate blood levels. A recent report indicates that high-flux dialysis equipment can acutely lower methotrexate blood levels.[4]

In light of the above information, the following statement has been added to the "Warnings" section of the Methotrexate Sodium prescribing information.

11. **Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.** [Note: We have amended the labeling to include "soft tissue necrosis" and "osteonecrosis" as adverse events in the "Adverse Reactions" section.]

The "General" subsection of the "Precautions" section has been revised to include the following underlined text:

Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate

corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer.

Similar language is also reflected in the "Overdosage" and "Guidelines For Methotrexate Therapy With Leucovorin Rescue" sections, respectively:

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28(6):846-854, 1996).

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.

The "Adverse Reactions in Psoriasis" section has been amended to include the following text:

Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35:835-838, 1996).

The "Drug Interactions" subsection has been modified to include the following paragraph:

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Finally, the "References" section of the labeling has been updated to include the following published guidelines regarding the handling of antineoplastic agents:

1. **Controlling occupational exposure to hazardous drugs (OSHA Work-Practice Guidelines). *Am J Health Syst Pharm* 1996; 53:1669-1685.**

We believe that your awareness of this information is important for a complete understanding of the benefits and risks of methotrexate therapy. If you are aware of any serious adverse events potentially associated with the use of methotrexate, please report such information to Lederle Pharmaceuticals at 1-800-934-5556 or to the Food and Drug Administration's MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, by modem at 1-800-FDA-7737, or by mail at MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

A copy of the revised Methotrexate Sodium prescribing information is included with this letter. If you have any questions regarding the information discussed in this letter, please contact:

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Sincerely,

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Enclosure: PI

REFERENCES:

1. Turner, SL et al: Radical external beam radiotherapy for 333 squamous carcinomas of the oral cavity--Evaluation of late morbidity and a watch policy for the clinically negative neck. *Radiotherapy & Oncology* 41: 21-29, 1996.

2. Pearce, HP and Wilson, BB: Erosion of psoriatic plaques: An early sign of methotrexate toxicity. *Am Acad Dermatol* 35: 835-838, 1996.

3. Data on file (spontaneous adverse event reporting system), Wyeth-Ayerst Laboratories.

4. Wall, SM et al: Effective clearance of methotrexate using high-flux hemodialysis membranes. *Am J Kidney Dis* 28(6): 846-854, 1996.