

# Kirkpatrick & Lockhart LLP

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## VIA FEDERAL EXPRESS

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### RE: Docket No. 02P-0226/CP1 – Request for Full Waiver of Pediatric Studies

Dear Sir or Madam:

This letter supplements Kirkpatrick & Lockhart, LLP's ("petitioner's") May 16, 2002 Citizen Petition requesting Food and Drug Administration ("FDA") permission to file an abbreviated new drug application ("ANDA") for a methotrexate sodium oral solution, 5 mg/ml drug product. The reference listed drug ("RLD") for the proposed ANDA is Lederle Pharmaceutical's methotrexate sodium tablets (eq 2.5 mg base).

In accordance with 21 C.F.R. § 314.55(c)(2), the petitioner hereby requests a full waiver of the requirement to conduct pediatric studies with the proposed new dosage form of methotrexate sodium for all of the RLD's labeled indications. FDA has interpreted 21 C.F.R. § 314.55 as requiring the submission of pediatric studies for drug products that are the subject of a petition submitted under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("FDCA") requesting a change in active ingredient, dosage form, or route of administration.<sup>1</sup> See 63 Fed. Reg. 66632, 66641 (Dec. 2, 1998). Because petitioner's May 16, 2002 petition requested permission to file an ANDA for a new dosage form of methotrexate sodium, this agency policy is applicable to the proposed drug product.

The RLD is labeled for three distinct indications: (1) treatment of neoplastic diseases (i.e., cancer chemotherapy); (2) management of rheumatoid arthritis (including polyarticular-course juvenile rheumatoid arthritis ("JRA")); and (3) symptomatic control of severe, recalcitrant, disabling psoriasis that is unresponsive to other forms of therapy. For the reasons discussed below, a full waiver of the pediatric study requirement is warranted for each of these indications.

<sup>1</sup> The submission of this request does not constitute an admission that FDA has sufficient statutory authority to require pediatric studies in the context of petitions submitted under FDCA § 505(j)(2)(C).

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## 1. The Cancer Chemotherapy and JRA Indications

The currently approved RLD labeling states that the safety and effectiveness of the drug in pediatric patients has been established in "cancer chemotherapy and polyarticular-course juvenile rheumatoid arthritis." Therefore, petitioner requests a full waiver of the pediatric study requirement for the cancer chemotherapy and JRA indications on the basis that the labeling of currently approved methotrexate sodium drug products contain sufficient pediatric information concerning these two indications.

## 2. The Psoriasis Indication

With respect to the psoriasis indication, petitioner requests a full waiver of the pediatric study requirement on the basis that (1) the drug would not represent a meaningful therapeutic benefit to pediatric patients, and (2) the extremely limited number of pediatric psoriasis patients that suffer from a sufficiently severe form of the disease renders a pediatric study of this indication highly impractical. See 21 C.F.R. § 314.55(c)(2)(i), (ii). As evidenced by the substantial "black-box" warning contained in the methotrexate sodium labeling, the drug is known to result in significant, and potentially lethal, side-effects. Physicians are warned that the drug should only be used by "physicians whose knowledge and experience include the use of antimetabolite therapy." The drug is known to have caused fatal toxic reactions. One of the primary concerns with the use of methotrexate to treat chronic conditions (such as psoriasis) is the known potential of the drug to cause hepatotoxicity, fibrosis, and cirrhosis after prolonged use.

When using methotrexate to treat a fatal form of cancer or an extremely debilitating form of rheumatoid arthritis, the potential benefits of the drug often outweigh the associated risks. However, the risk/benefit balance is very different when treating a skin condition such as psoriasis, even in its most severe forms. This balance is further shifted away from methotrexate use when one considers that liver biopsies, both pre-therapy and during therapy, are recommended when using the drug for psoriasis. Thus, the RLD labeling instructs physicians to use methotrexate for only most severe and recalcitrant forms of psoriasis, and even then only after all other treatment options have been exhausted and the psoriasis diagnosis has been confirmed by biopsy and/or dermatologic consultation.

Therefore, our client is of the opinion that the number of pediatric psoriasis patients with a form of the disease that most practicing dermatologists would agree warrants methotrexate therapy is extremely small. The relevant data from IMS Health, Inc. ("IMS") and discussions with a prominent practicing pediatric dermatologist confirm this opinion. The IMS data demonstrate that, for the 2001 calendar year, 6% of the total oral methotrexate drug uses were for the treatment of psoriasis (indicated on in the IMS table as "other psoriasis"). See IMS Table for "Methotrexate Oral Solid" enclosed as Exhibit 1. The IMS data further demonstrate that there were 59,000 "appearances" for oral methotrexate in patients aged 19 or under (i.e., uses for all indications). See id. If one conservatively assumes that the 6% rate for psoriasis treatment with oral methotrexate is consistent across all age groups, it can be concluded that only 3,540 psoriasis patients under 19 years of age are treated with oral methotrexate per year (i.e., 6% of

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59,000).<sup>2</sup> Thus, while oral methotrexate is being used to treat psoriasis at a fairly significant level (i.e., 99,000 uses per year), the drug is apparently being used very rarely for pediatric psoriasis patients.<sup>3</sup> Our client discussed methotrexate prescribing practices with a prominent pediatric dermatologist who confirmed that neither she nor her mentors used methotrexate to treat pediatric psoriasis. See Letter from Dr. A. Sheth, Director and Assistant Professor of Pediatric Dermatology, Children's Hospital Medical Center, Cincinnati to [Name redacted] dated June 28, 2002 (enclosed as Exhibit 3).

We acknowledge that the difference in the adult versus pediatric methotrexate psoriasis prescribing practices could be due to number of factors. However, our client believes that the most prevalent factors are: (1) the lack of sufficient severity of most pediatric psoriasis cases (when one considers the potential side effects of methotrexate therapy); (2) the reluctance on the part of many physicians to begin methotrexate therapy at an early age in light of the significant cumulative hepatotoxic effects of the drug; and (3) the extensive and invasive liver biopsies that are required when using the drug for psoriasis treatment. As result, our client has concluded that the "severe, recalcitrant, disabling" psoriasis for which methotrexate is indicated occurs in very few pediatric patients in the United States. Thus, a pediatric study in this population that would yield statistically meaningful results would likely be extremely difficult, if not impossible, to conduct. Additionally, and more importantly, such a controlled clinical study in pediatric patients would raise significant ethical issues in light of the invasive biopsies that would be required and the marginal potential benefit to the pediatric patients.

Furthermore, even if a pediatric study for the psoriasis indication could be conducted, our client believes that it would not provide a meaningful therapeutic benefit to the pediatric community. It is important to note that the RLD labeling already contains a considerable amount of data concerning the safety of methotrexate in pediatric patients (i.e., JRA and neoplastic diseases). The sparse use of methotrexate to treat pediatric psoriasis does not appear to stem from a lack of information. On the contrary, it appears to flow from an acknowledgement on the part of practicing physicians of the known risks associated with the drug and the significant testing (i.e., liver biopsies) that are required for psoriasis treatment. Therefore, providing physicians with additional pediatric information is unlikely to result in more pediatric patients being treated with methotrexate because such information is unlikely to sufficiently tip the risk/benefit balance so as to result in additional methotrexate use.

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<sup>2</sup> Petitioner notes that the actual number of "pediatric" psoriasis patients treated with oral methotrexate is probably considerably lower. The IMS data do not allow analysis of the generally recognized "pediatric" population of birth to 16 years of age. When the data for the 17 to 19 year olds are excluded, one would expect number of actual number "pediatric" psoriasis patients receiving oral methotrexate to be considerably less than 3,540.

<sup>3</sup> Petitioner also notes that there were 21,000 "visits" to pediatricians that resulted in a diagnosis of "other psoriasis," yet there are **no** recorded "appearances" of methotrexate by pediatricians. Compare IMS Table for "Other Psoriasis" (Exhibit 2) with IMS Table for "Methotrexate Oral Solid" (Exhibit 1).

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Lastly, petitioner notes that requiring pediatric studies for this petition would deny the public access to a methotrexate sodium formulation that could be beneficial to pediatric JRA and neoplastic disease patients. Methotrexate sodium is approved for pediatric use in the treatment of JRA and neoplastic diseases. The IMS data suggest that the drug is being prescribed in significant numbers to pediatric patients for the treatment of JRA (i.e., 19,000 uses, see Exhibit 1). It would follow that a methotrexate sodium oral solution formulation would be beneficial to a considerable number of JRA pediatric patients, especially those in the younger age groups. Yet, petitioner's petition cannot be granted if the agency determines that an additional pediatric study is required. See FDCA § 505(j)(2)(C)(i). If this occurs, our client will be forced to discontinue its plans to market a methotrexate sodium oral solution due to the excessive costs associated with conducting a pediatric clinical study in an extremely small patient population and submitting a new drug application ("NDA") for its proposed formulation. In such a case, the pediatric study requirement will actually serve to prevent, rather than encourage, the development of a pediatric formulation.

For the above stated reasons, the petitioner believes that a full waiver of the pediatric study requirement is justified under 21 C.F.R. § 314.55(c)(2)(i) and (ii).

Please direct any correspondence or communications concerning this request to the undersigned at the above address or at telephone number (202) 778-9296.

Respectfully Submitted,



Michael H. Hinckle

Enclosure(s)

cc: Martin Shimer, FDA, Office of Generic Drugs