

**LACHMAN CONSULTANT SERVICES, INC.**  
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE, WESTBURY, NY 11590  
(516) 222-6222 • FAX (516) 683-1887

May 14, 2002

**(OVERNIGHT COURIER 5/14/02)**

Dockets Management Branch, HFA-305  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Dear Sir or Madam:

**CITIZEN PETITION**

Lachman Consultant Services, Inc. (LCS) submits this petition in quadruplicate pursuant to 21 CFR 10.20 and 10.30 of the regulations and under Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act to request that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application may be submitted for Levorphanol Tartrate Tablets, USP 1 mg and 3 mg.

**A. Action Requested**

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that Levorphanol Tartrate Tablets, USP 1 mg and 3 mg are suitable for submission in an Abbreviated New Drug Application. The listed drug product upon which this petition is based is LEVO-DROMORAN<sup>®</sup> (Levorphanol Tartrate) Tablets, 2 mg (ICN Pharmaceuticals, Inc.). The petitioner therefore seeks a change in strength from that of the listed drug (from 2 mg to include both a 1 mg and a 3 mg strength tablet).

**B. Statement of Grounds**

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a new drug that differs in dosage strength from that of a listed drug provided the FDA has approved a petition that proposed the filing of such an application. This petition involves a change in strength for the proposed drug from that of the reference listed drug. The listed drug upon which this petition is based, LEVO-DROMORAN<sup>®</sup> Tablets, 2 mg (Levorphanol Tartrate Tablets (2 mg)), is manufactured by ICN Pharmaceuticals, Inc. The Agency's listing of this product is found on page 3-216 of the 22<sup>nd</sup> Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Attachment 1).

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Currently the approved 2 mg strength of LEVO-DROMORAN<sup>®</sup> (Levorphanol Tartrate) Tablets is indicated for use in the management of moderate to severe pain or as a preoperative medication where an opioid analgesic is appropriate. The labeling for the reference listed drug product indicates that doses of this medication should be individualized depending upon the “degree of pain to be relieved, the clinical setting, the physical condition of the patient, and the kind and dose of concurrent medication”. According to the labeling of the RLD, Levorphanol Tartrate is 4 – 8 times as potent as morphine and conversion of a patient on oral morphine should be at 1/15<sup>th</sup> – 1/12<sup>th</sup> the dose of oral morphine. Significant cautions are given regarding appropriate dosage titration and a warning that any dosage adjustment should be made only after 72 hours of dosing, to assure the patient has reached steady state on Levorphanol Tartrate due to its long half life and to, therefore, avoid excessive sedation due to drug accumulation. In addition, the Clinical Pharmacology Section of the labeling cautions that:

“as with all drugs of this class, patients at the extremes of age are expected to be more susceptible to adverse effects because of a greater pharmacodynamic sensitivity and probable increased variability in pharmacokinetics due to age or disease”.

The approved labeling further states:

“The **usual** recommended starting dose for oral administration is 2 mg. This may be repeated in 6 to 8 hours, as needed, provided the patient is assessed for signs of hyperventilation and excessive sedation. The dose may be increased up to 3 mg every 6 to 8 hours, after adequate evaluation of the patient’s response. Higher doses may be appropriate in opioid tolerant patients. Dosage should be adjusted according to the severity of the pain; age, weight, and physical status of the patient; the patient’s underlying diseases; use of concomitant medications; and other factors. Total oral daily doses of more than 6 to 12 mg in 24 hours are generally not recommended as starting doses in non-opioid tolerant patients; lower total daily doses may be appropriate” (emphasis added.)

“The approved 2 mg listed product is available as a scored tablet, that provides dosage selection options for the physician. Due to the varied response of a patient in pain and the clear labeled warnings regarding specific attention to the patient’s pain, age, disease state and other concomitant medication in individualizing a patient’s dose, it appears that a 1 mg tablet may be a viable and reasonable option for use in certain patients requiring a potent opioid narcotic. Since medical practice dictates that doses of potent narcotics are highly patient-dependent and should be individualized accordingly, the availability of a 1 mg

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dose for patients that are particularly sensitive to potent narcotics or are elderly would provide the practitioner with more options to select a dosage strength most appropriate for the specific patient. To further support this position the geriatric section of the labeling of the reference listed drug indicates that: "The initial dose of Levo-Dromoran should be reduced by 50% or more in the infirm elderly patient..."

The labeling therefore clearly contemplates a 1 mg starting dose for certain patients.

A 1 mg starting dose of Levorphanol is also consistent with a conversion from the labeled recommended doses of morphine products. For instance, Levo-Dromoran labeling, as mentioned above, indicates that patients should be converted at 1/15<sup>th</sup> – 1/12<sup>th</sup> the current oral dose of morphine. With oral morphine products available with doses ranging from between 5 mg – 30 mg it is clear that a 1 mg Levorphanol product would have utility as either a starting dose for certain patients or as a titration dose for others.

The 1 mg product as mentioned above, would have utility in aiding the patient to make certain incremental dose adjustments in accordance with their physician's instructions without having to break the small 2 mg tablets in half, which might be difficult for the elderly or infirmed. Availability of a 1 mg tablet may also decrease the chance for medication errors that could result from asking patient to break tablets in half. A 1 mg tablet would also allow the physician to prescribe a sufficient number of the 1 mg tablets, such that the patient could use the remainder of their 2 mg tablets to achieve the desired dose, and thereby decreasing the potential for diversion of the unused 2 mg tablets.

Labeling recommendations for dosage increases up to 3 mg are clearly contemplated in the labeling of the approved reference listed drug product upon which this petition is based. In addition, it is clear that typical dosing may necessitate certain total daily doses that would be facilitated by the availability of a 3 mg tablet.

The proposed 3 mg tablet strength would not represent a new higher starting dose for the product, but simply a more convenient higher strength for the physician to use in titrating their patients to an appropriate individualized dose. The 3 mg strength of Levorphanol Tartrate Tablets, USP would be used in adjusting dosage levels that maximize clinical response. The availability of a 3 mg tablet would enable dosing in a 1 mg increment from the usual recommended starting dose (2 mg) without requiring the patient to break tablets. This flexibility enables patients and practitioners to more precisely and conveniently individualize patient dosage to provide for a patient's optimum therapeutic benefit. It would provide for a more convenient direct

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administration of an individualized dose (i.e. 3 mg) for those patients who require that higher dose to achieve the desired therapeutic effect. Patients, especially the elderly or infirmed, may find it difficult to break tablets. In addition, the utility of a single 3 mg tablet may prove to increase compliance with a prescribed regimen, while at the same time reducing the potential for dosing errors.

The proposed 3 mg tablet strength would provide the physician with another tool for individualizing dosing for this particular drug product. The approval of a higher single dose for this drug product would be consistent with the dosing recommended in the labeling of the approved listed drug product. A decision to approve a petition seeking a higher strength product than that currently approved where the labeling clearly contemplates such a dose is consistent with other petition approvals where the Agency has previously considered and approved petitions for higher strength dosage units (e.g., the Agency's approval of a petition to allow for a 7.5 mg and 10 mg oxycodone component in combination with 325 mg of acetaminophen when the highest previous strength of oxycodone approved was 5 mg (see petition approval letter for Docket 97P-0347 (Attachment 2)).

It is acknowledged that Levorphanol Tartrate Tablets do have abuse potential. The labeling for both the reference listed drug, LEVO-DROMORAN<sup>®</sup> Tablets 2 mg and for the proposed Levorphanol Tartrate Tablets, USP (1 mg and 3 mg) contain similar caution statements related to drug abuse and dependence issues. Therefore, the proposed Levorphanol Tartrate Tablets, USP (1 mg and 3 mg) should not raise any concerns that the Agency has not already evaluated. Furthermore, the introduction of the proposed Levorphanol Tartrate Tablets, USP (1 mg and 3 mg) into the marketplace would not be expected to promote any greater potential for misuse of the product.

A copy of the reference listed drug labeling and draft labeling for the proposed Levorphanol Tartrate Tablets, USP (1 mg, 2 mg and 3 mg) are enclosed (Attachments 3 and 4, respectively). The uses, dosage, and indications for the proposed product are the same as those for LEVO-DROMORAN<sup>®</sup> Tablets, 2 mg, the reference listed drug.

Pursuant to 21 CFR 314.55 (a), the proposed change in strength does not constitute a request to file an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Therefore, the petitioner believes that the proposed product does not fall under the requirement for an assessment of safety and efficacy in pediatric patients.

The petitioner believes that the addition of the proposed dosage strengths (i.e. from a 2 mg tablet to include a 1 mg and 3 mg tablet) does not present any questions of safety or effectiveness and requests that the Agency approve the petition.

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### **C. Environmental Impact**

The action requested in this petition qualifies for a categorical exclusion under 21 CFR 25.31. Therefore, an environmental assessment is not required for the requested action.

### **D. Economic Impact**

Pursuant to 21 CFR 10.30 (b), economic impact information is to be submitted only when requested by the commissioner. Lachman Consultant Services, Inc. will promptly provide such information if so requested.

### **E. Certification**

Lachman Consultant Services, Inc. certifies that to its best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

  
Robert W. Pollock   
Vice President

RP/cc/m

Attachments:

1. Listing of LEVO-DROMORAN<sup>®</sup> TABLETS, 2 mg, page 3-216 of the 22<sup>nd</sup> Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations.
2. Copy of ANDA Suitability Petition approval letter for Docket No. 97P-0347/CP
3. Proposed package Insert - draft (Levorphanol Tartrate Tablets, USP (1 mg, 2 mg and 3 mg).
4. Package Insert for LEVO-DROMORAN<sup>®</sup> TABLETS, 2 mg.

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# ATTACHMENT 1

PRESCRIPTION DRUG PRODUCT LIST

3-216

<u>LEVONORGESTREL</u>				<u>LEVOTHYROXINE SODIUM</u>				
IMPLANT; IMPLANTATION				TABLET; ORAL				
LEVONORGESTREL				LEVOXYL				
BX	+	WYETH AYERST	75MG/IMPLANT	N20627 001	BX	JONES PHARMA	0.05MG	N21301 002
				AUG 15, 1996				MAY 25, 2001
NORPLANT II				N21301 003				
BX		POPULATION COUNCIL	75MG/IMPLANT	N20544 001	BX		0.075MG	MAY 25, 2001
				NOV 01, 1996	BX		0.088MG	N21301 004
NORPLANT SYSTEM IN PLASTIC CONTAINER				N21301 005				
	+	WYETH AYERST	36MG/IMPLANT	N20088 001	BX		0.1MG	MAY 25, 2001
				DEC 10, 1990	BX		0.112MG	N21301 006
INTRAUTERINE DEVICE; INTRAUTERINE				N21301 007				
MIRENA				MAY 25, 2001				
	+	BERLEX LABS	52MG	N21225 001	BX		0.125MG	MAY 25, 2001
				DEC 06, 2000	BX		0.137MG	N21301 008
TABLET; ORAL				N21301 009				
PLAN B				MAY 25, 2001				
	+	WOMENS CAPITAL	0.75MG	N21045 001	BX		0.15MG	N21301 010
				JUL 28, 1999	BX		0.175MG	MAY 25, 2001
<u>LEVONORGESTREL; *MULTIPLE*</u>				N21301 011				
<u>SEE ETHINYL ESTRADIOL; LEVONORGESTREL</u>				MAY 25, 2001				
				N21301 012				
				MAY 25, 2001				
				UNITHROID				
				STEVENS J				
				N21210 001				
				AUG 21, 2000				
				N21210 002				
				AUG 21, 2000				
				N21210 003				
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				N21210 004				
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