

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-140

MEDICAL and STATISTICAL REVIEW(S)

CLINICAL and Statistical REVIEW

Application Type NDA
Submission Number 20-140
Submission Code C

Letter Date June 29, 2007
Receipt Date July 10, 2007
Old Regulatory Clock Date January 7, 2008 (Initial)
March 7, 2008 (After major amendment)

Clinical Reviewer Name Nancy S. Scher, MD
Statistical Reviewer Name Shenghui Tang, PhD
Review Completion Date February 25, 2008

Established Name Levoleucovorin calcium
(Proposed) Trade Name ISO-Vorin for Injection
Therapeutic Class Folic acid derivative
Applicant Spectrum Pharmaceuticals

Priority Designation S

Formulation Sterile freeze dried powder 50 mg/vial
Dosing Regimen 7.5 mg (approximately 5 mg/m²) IV q6h x
10 doses starting 24 hours after beginning methotrexate infusion
(based on a methotrexate dose of 12 gm/m² IV over 4 hours)

Indication After high-dose methotrexate therapy in
osteosarcoma and to diminish the toxicity and counteract the effects of impaired methotrexate
elimination and of inadvertent overdosage of folic acid antagonists.

Intended Population Children and adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The application is recommended for approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special risk management activities have been recommended as of this time except for a change in proprietary name. The applicant submitted a Risk Management Plan to reduce the potential for dosing errors by using "tall man" lettering for the proprietary product name, ISO-vorin, and enhancements to product labeling to avoid confusion with the currently marked *d,l*-racemic leucovorin products. FDA recommended against use of the name ISO-vorin. The use of an alternate proprietary name, agreed to by the applicant, should help avoid product confusion and resultant dosing errors. The applicant has proposed the names _____ which

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1.2.2 Required Phase 4 Commitments

No phase 4 commitments are required.

1.2.3 Other Phase 4 Requests

No other phase 4 requests have been required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Levoleucovorin calcium (*l*-leucovorin), also known as levofolinic acid, is a folate analog. It is the stereoisomer of *d,l*-leucovorin calcium, which has been licensed in the US since 1952. Only the "l" form of leucovorin is pharmacologically active. No new clinical trial data were submitted with this application. The following synopsis refers to the trial data submitted in 1991, which FDA determined, and the Oncologic Drugs Advisory Committee concurred, provided evidence of safety and efficacy for *l*-leucovorin for the indications.

Indication and population studied: Children and young adults ages 6-21 were treated with levoleucovorin, in the adjuvant and metastatic settings, following therapy with high-dose methotrexate (HDM) for osteosarcoma. The indications are:

- After high-dose methotrexate therapy in osteosarcoma
- To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

Number of pivotal efficacy and safety trials: Patients were treated using (multidrug) regimens from 5 different pediatric trials for osteosarcoma, which included HDM as one component, and which utilized 3 different levoleucovorin rescue protocols. "Matched historical controls" treated with *d,l*-leucovorin were selected from the respective studies for comparison.

Number of patients enrolled in the primary trials: There were 16 patients with osteogenic sarcoma treated with levoleucovorin after 58 courses of HDM. There were 28 historical controls who received 101 courses of HDM followed by *d,l*-leucovorin rescue.

Overall number of patients in the safety database and extent of exposure: There were 16 patients ages 6-21 who received 58 courses of HDM therapy for osteogenic sarcoma. The mean number of levoleucovorin doses per course was 18.2 and the mean total dose per course was 350 mg. The original sponsor, Lederle Laboratories, submitted a 120-day safety update to NDA 20-140 and 20-141 (levoleucovorin tablets) on May 16, 1991. The update provided data for 48 additional courses of therapy for 8 patients in the original study group, as well as data for 9 new patients treated with a total of 50 courses of therapy. Including all patients treated, the applicant reports that the mean number of doses of levoleucovorin per course is 15.8 and the mean total dose per course is 291 mg. For the new patients reported in the update, 6 patients were ages 10-19; 2 patients were younger than age 10, and 1 patient was age 20-29.

1.3.2 Efficacy

No new clinical trial data were provided for this submission. In 1991 the FDA Clinical Reviewers and the Oncological Drugs Advisory Committee determined that there were sufficient data to support the safety and efficacy of levoleucovorin for the proposed indications. The efficacy of levoleucovorin rescue following high-dose methotrexate was based on the demonstration that levoleucovorin prevented the severe toxicity certain to occur in the absence of adequate "rescue." Conclusions could not be made regarding the comparative efficacy of *l*-leucovorin and the historical controls treated with *d,l*-leucovorin due to the small number and low evaluability rate of the latter. (See Section 6.) Non Approvable letters were issued in 1992 and 1993 because of CMC deficiencies. These issues are now resolved for the intravenous formulation of levoleucovorin.

1.3.3 Safety

No new clinical trial data were provided for this submission. The efficacy of levoleucovorin rescue following high-dose methotrexate (HDM) was based on the demonstration that

levoleucovorin prevented the severe toxicity known to occur in the absence of adequate “rescue.” (See section 6.) For the current submission, the applicant provided a safety update based on international post marketing experience for calcium levoleucovorin from the World Health Organization (WHO) Uppsala Postmarketing database (See Appendix 10.3). The applicant submitted a review of the medical literature to provide additional support for safety. Although there were numerous reports of levoleucovorin in combination with 5-fluorouracil for colorectal carcinoma, the applicant was able to provide only three published studies reporting the use of levoleucovorin with HDM for osteosarcoma. (See Section 7.2.2.3.)

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is 7.5 mg (approximately 5 mg/m²) intravenously every 6 hours for 10 doses starting 24 hours after beginning methotrexate infusion (based on a methotrexate dose of 12 gm/m² IV over 4 hours). Since only the “*T*” isomer of leucovorin is pharmacologically active, levoleucovorin is dosed at one-half the usual dose of the racemic mixture, *d,l*-leucovorin. Serum creatinine and methotrexate levels are to be measured daily and levoleucovorin, hydration and urinary alkalization are to be continued until the methotrexate level is below 5 x 10⁻⁸ M (0.05 micromolar). For delayed methotrexate elimination and/or evidence of acute renal injury, the dose of levoleucovorin should be adjusted. (See Section 8.1 of this review which contains a table with details from the product label.)

1.3.5 Drug-Drug Interactions

- Drug-drug interactions were not studied during the development plan.
- There is evidence from the medical literature that folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children. It is not known whether folinic acid has the same effects. However, since folic and folinic acids share some common metabolic pathways, caution should be taken when administering folinic acid in combination with anticonvulsant drugs.
- Levoleucovorin increases the toxicity of 5-fluorouracil.

1.3.6 Special Populations

- There are no special dosing considerations identified for race, gender, age for adults or for children. Clinical studies of levoleucovorin in the treatment of osteosarcoma evaluated a pediatric population, and did not include subjects aged 65 and over to determine whether they respond differently from younger subjects.
- There have been no studies done with regard to dose modifications for hepatic or renal insufficiency. No dosing modifications would be anticipated for the proposed indication.
- Animal reproduction studies have not been conducted with levoleucovorin. It is also not known whether levoleucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Levoleucovorin should be given to a pregnant woman only if clearly needed and is classified Pregnancy Category C.

- It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when levoleucovorin is administered to a nursing mother

APPEARS THIS WAY ON ORIGINAL

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name: Levoleucovorin calcium (Levofolinic acid)
Proposed Trade Name: ISO-Vorin for injection (Late in the review, alternate names were proposed:)

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Applicant: Spectrum Pharmaceuticals
157 Technology Drive
Irvine, CA 92618

Chemical Class: New formulation

Pharmacological Class: Folate analog

Formulation: Sterile freeze dried powder 50 mg/vial

Proposed Indication:

- After high-dose methotrexate therapy in osteosarcoma
- To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

Proposed Dosage and Administration: 7.5 mg (approximately 5 mg/m²) intravenously (IV) every 6 hours for 10 doses starting 24 hours after beginning methotrexate infusion (based on a methotrexate dose of 12 gm/m² IV over 4 hours). Since only the “l” isomer of leucovorin is pharmacologically active, levoleucovorin is dosed at one-half the usual dose of the racemic mixture, d,l-leucovorin. Serum creatinine and methotrexate levels are to be measured daily and levoleucovorin, hydration and urinary alkalinization are to be continued until the methotrexate level is below 5 x 10⁻⁸ M (0.05 micromolar). For delayed methotrexate elimination and/or evidence of acute renal injury, the dose of levoleucovorin should be adjusted. (See Section 8.1 of this review which contains a table with details from the product label.)

2.2 Currently Available Treatment for Indications

Although *levoleucovorin* calcium (*l*-leucovorin) is not marketed in the United States (US), leucovorin calcium, as a racemic mixture (*d*-, *l*-leucovorin calcium), is available commercially both for parenteral use and as oral tablets. The racemic mixture is a 1:1 mixture of “d” and “l” forms but only the “l” form is pharmacologically active. Therefore, the recommended dose range for the pure *l*-isomeric form (ISO-vorin) is 50% of the dose range for the racemic mixture marketed in the US. *Leucovorin* calcium injection is marketed by Hospira (NDA #008107) and under several generic labels in the US. Leucovorin calcium tablets are marketed by Xanodyne Pharmacal (NDA #018459) and under several generic labels in the US. In Europe, *levoleucovorin* calcium (also known as calcium levofolinate) is marketed by multiple companies,

including under the trade name ISO-Vorin by Wyeth in Spain, United Kingdom (UK) and France. Schering markets *L*-leucovorin calcium as Folanemin/Levofolene in Italy.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient of ISO-Vorin, *levoleucovorin* calcium (*L*-leucovorin) is not marketed in the United States (US). Leucovorin calcium, as a racemic mixture (*d*-, *L*-leucovorin calcium), has been marketed in the US since 1952. Leucovorin is also known as folinic acid. Leucovorin calcium is marketed by several companies, and is commercially available both as parenteral preparations and oral tablets.

2.4 Important Issues With Pharmacologically Related Products

There are no important issues with pharmacologically related products. However, it should be noted that the dosing for levoleucovorin calcium is half that for the racemic mixture (*d*-, *L*-leucovorin calcium) marketed in the US since 1952. Spectrum has proposed a Risk Management Plan to reduce the potential for dosing errors. FDA has recommended that the applicant not use ISO-vorin as the proprietary name in order to reduce product confusion and dosing errors.

2.5 Presubmission Regulatory Activity

Spectrum Pharmaceuticals submitted this Amendment to NDA 20-140, which was originally submitted on December 14, 1990, by Lederle Laboratories (Lederle). On July 1, 1991, the application was presented to the Oncological Drugs Advisory Committee (ODAC). The committee voted 6-2 that "the limited clinical data [were] sufficient to confirm that ISO-vorin injection is safe and effective when used in the rescue of high dose methotrexate." On January 3, 1992, FDA issued a "not approvable" (NA) letter for NDA 20-140

_____ due to CMC deficiencies. (No pharmacology/toxicology or clinical deficiencies were cited.) Lederle responded to the FDA on January 22, 1993, regarding the deficiencies. Following several changes of ownership, on June 29, 2007, Spectrum submitted an Amendment to NDA 20-140 containing the following: Revised ISO-vorin for Injection draft labeling; Chemistry, Manufacturing and Controls (CMC) information for drug product and drug substance; a Risk Management Plan to reduce the potential for dosing errors; and a safety update based on international post marketing experience for calcium levoleucovorin.

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Table 1: Regulatory History (Reviewer Table)

12/14/1990	NDA 20-140 submitted to FDA by Lederle.
12/18/1990	FDA approved orphan drug status in the treatment of advanced metastatic colorectal adenocarcinoma in combination with 5-fluorouracil. (Application #90-485)
07/01/1991	ODAC voted 6-2 that ISO-Vorin is safe and effective for high dose methotrexate (MTX) rescue.
08/01/1991	FDA approved orphan drug status for use in conjunction with high dose MTX in the treatment of osteosarcoma. (Application #90-484)

01/03/1992	FDA issued Not Approvable (NA) letter (for injection and for tablets) due to CMC and labeling deficiencies.
01/9/1993	Lederle notified FDA of intent to Amend NDA 20-140 (and 20-141).
01/22/1993	Lederle submitted letter to FDA regarding deficiencies.
12/13/1993	FDA issued NA letter to Lederle citing CMC deficiencies.
04/22/1998	Following purchase of Lederle by Wyeth Pharmaceuticals, Lederle withdrew _____ and US rights reverted to Merck Eprova AG (Switzerland).
12/04/2003	Merck Eprova licensed US rights for <i>L</i> -leucovorin products to Targent, Inc.
11/29/2004	Letter of authorization provided from Merck Eprova to FDA for right of Targent to reference _____ and NDAs 20-140 and 20-141.
07/18/2005	Pre-NDA meeting canceled by Targent, following review of FDA's written responses to sponsor's questions. FDA agreed the NDA resubmission would include a new CMC section, revised labeling, and a safety update. FDA also advised Targent to propose a Risk Management Plan to reduce the potential for dosing errors.
04/19/2006	NDA ownership transferred from Targent to Spectrum.
06/29/2007	Spectrum submitted Amendment to NDA 20-140 to FDA.

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2.6 Other Relevant Background Information

Multiple companies market levoleucovorin calcium in Europe, where the established name is calcium levofolinate. The initial approval was in Italy in 1991, and it has been marketed in Japan since 1999. The product is marketed by Wyeth Pharmaceuticals, Inc., under the trade name ISO-Vorin in Spain, the UK, France, and in several other countries of the European Union. Spectrum owns the right to market ISO-Vorin in North America. Merck Eprova manufactures the drug substance for ISO-Vorin marketed in Europe and for the Spectrum product. The Wyeth product is indicated "to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy...Calcium Levofolinate Rescue." It is also indicated for advanced colorectal cancer to provide "enhanced 5-Fluorouracil (5-FU) cytotoxic activity...(to)...give greater efficacy compared to 5-FU given alone."

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

On January 3, 1992, and December 13, 1993, FDA issued Not Approvable letters for the NDA, citing CMC deficiencies. The current resubmission (Amendment to NDA 20-140) contains responses to the cited deficiencies. The CMC primary reviewers are Dr. Mark Sassaman (drug substance) and Dr. Sarah Pope (drug product). Please see their separate review(s) for details.

Dr. Robert Mello is the Microbiology reviewer. Please see his separate review for details. The data did not support an _____ post constitution hold time. Significant growth for *P. aeruginosa*

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started between the 12 and 18 hour time periods, not observed with the 0.9% saline controls. Based on the data, Dr. Mello required a hold time of not more than 12 hours following reconstitution of the drug product and further dilution with 0.9% saline. Since no data were provided for dilution with 5% Dextrose Injection, such dilutions may be held for not more than 4 hours.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology/toxicology data were provided for this re-submission. Dr. Hans Rosenfeldt is the primary Pharmacology/Toxicology reviewer. Please see his separate review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

No new clinical trial data were submitted for this response to deficiencies. For the current review, sources include the original FDA Clinical Reviews by Drs. Robert Justice and John Johnson and the July 1991 ODAC minutes, which were in agreement that levoleucovorin injection was safe and effective for the proposed indication. Some of the original clinical trial data were audited (e.g. peak plasma methotrexate levels) for the current review, and the original Lederle Clinical Study Reports for NDA 20-140 and 20-141 were reviewed. Additional sources include literature reports and the World Health Organization (WHO) Uppsala Vigibase (international) postmarketing data. Consultation was requested from the FDA Office of Surveillance and Epidemiology (OSE) to review the safety database for the leucovorin calcium (*d,l*-leucovorin) products marketed in the US and advise on the review of the WHO international postmarketing data for levoleucovorin. Ms Susan Lu, R.Ph. reviewed the FDA AERS database for *d,l*-leucovorin and provided comments on the results of "Data Mining." (See Section 7.1.17) Dr. Allen Brinker reviewed the WHO findings for levoleucovorin and provided comments. (See Appendix 10.3)

4.2 Tables of Clinical Studies

No new clinical trial data were submitted for this application. The following table summarizes the primary sources of clinical data evaluating safety and efficacy of *l*-leucovorin from the NDA submitted by Lederle Laboratories, the original sponsor, in December 1990. The subjects were pediatric patients treated with high-dose methotrexate (HDM) for osteogenic sarcoma. The patients were enrolled into or treated according to protocols conducted by the Pediatric Oncology Group (POG), MD Anderson Cancer Center (TIOS-III), and St. Jude Children's Hospital (OS-86). See section 6.1.1 for additional detail.

Table 2: Sources of Clinical Efficacy Data Submitted to NDA in 1990 (Reviewer Table)

Protocols	Patient Number	Age Range in Years	Formulation <i>L</i> -Leucovorin	Dose <i>L</i> -Leucovorin	Methotrexate Regimen
POG	10	10-21	Tablets and IV	7.5 mg q6h x10 at 20 hours after end of HDM	12 g/m ² IV over 4 hours
TIOS-III	3	4-15	IV	7.5 mg q3h x18 at 12 hours after end of HDM	12.5 g/m ² IV over 6 hours
OS-86	3	7-17	Tablets and IV	7.5 mg q6h x10 at 20 hours after end of HDM	12 g/m ² IV over 4 hours

4.3 Review Strategy

No new clinical trial data were submitted for this application. The NDA was Not Approvable in 1992 and 1993 due to CMC deficiencies. The FDA Review Team and ODAC determined (in 1991) that the clinical data were sufficient to support approval. For the current submission (Amendment), the following materials were reviewed by the medical officer:

- The regulatory history of the application
- Archival submissions to NDA 20-140 (IV formulation) and NDA 20-141 (tablet), including Clinical Study Reports and audit of selected data and case report forms (CRFs) from the original NDA submission
- Clinical Reviews from the original NDA submissions (1991)
- ODAC Minutes from July 1, 1991
- Correspondence between the applicant (and previous NDA-holders) and FDA in Division Files
- NDA electronic submissions including WHO Uppsala post-marketing safety data for levoleucovorin
- FDA AERS database for (*d,l*-) leucovorin calcium marketed in the US
- Applicant's electronic labeling proposals
- Labels for related products (leucovorin calcium [US] and calcium levofolinate [Wyeth, Europe])
- Articles from the published literature for levoleucovorin as further support for efficacy and safety.

The goal of the current clinical review was to evaluate the basis for the determination in 1991 by FDA and ODAC that the clinical data were sufficient to support approval and to verify that there is adequate information to support development of a product label.

4.4 Data Quality and Integrity

No new clinical trial data were submitted for this application.

4.5 Compliance with Good Clinical Practices

No new clinical trial data were submitted for this application.

4.6 Financial Disclosures

No new clinical trial data were submitted for this application.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new clinical pharmacology data were submitted. Dr. Sophia Abraham is the primary Clinical Pharmacology reviewer. Please see her separate review.

5.2 Pharmacodynamics

No new clinical pharmacology data were submitted.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indications are as follows:

- After high-dose methotrexate therapy in osteosarcoma
- To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

6.1.1 Methods

The data evaluated by the clinical reviewers for the original submission in 1990 were limited and somewhat heterogeneous. The trials for treatment of osteogenic sarcoma in pediatric populations utilized 5 different complex chemotherapy regimens, of which HDM was one component. The controls were matched, historical controls treated with *d,l*-leucovorin. Since *l*-leucovorin is the active stereoisomer, the dose of *l*-leucovorin was ½ the dose of the racemic mixture, *d,l*-leucovorin. There were 3 Pediatric Oncology Group (POG) trials: # 8759 in patients with metastatic, unresectable, or recurrent disease, who had received prior therapy; #8651 adjuvant or neoadjuvant, initial therapy of patients with non-metastatic disease; #8107 post-operative adjuvant therapy or after relapse and surgery, also in patients who had not received prior chemotherapy. The TIOS-II study was for pediatric osteosarcoma patients at MD Anderson, either newly diagnosed or previously treated, if they had not previously received “aggressive”

chemotherapy. The OS-86 study was performed at St. Jude Children's Hospital and enrolled pediatric patients with potentially resectable or unresectable primary lesions, or with metastatic disease, who had received no prior chemotherapy.

There were three different leucovorin rescue protocols across these five trials. The POG and St. Jude trials (#OS-86) used a combination of IV and oral *L*-leucovorin. The MD Anderson trial (TIOS-III) utilized IV *L*-leucovorin. (See Table 2, section 4.2.)

Across the trials, there were 16 patients with osteogenic sarcoma treated with *L*-leucovorin (11 adjuvant, 5 metastatic) with 58 courses of HDM. This was compared with 28 "matched historical controls" who received 101 courses of HDM followed by *d,L*-leucovorin rescue.

6.1.2 General Discussion of Endpoints

Following discussions with FDA in 1988 and 1989, the sponsor developed a plan to evaluate the clinical efficacy of *L*-leucovorin in the rescue of patients with osteosarcoma from high-dose methotrexate toxicity. Patients treated with *L*-leucovorin would be compared with retrospectively selected, historical controls, previously treated in the same studies but having received *d,L*-leucovorin for rescue from HDM. The use of *L*-leucovorin for rescue from methotrexate toxicity would address the issues of both efficacy and safety simultaneously. Efficacy was to be demonstrated by the effectiveness of *L*-leucovorin in preventing the severe toxicity expected following administration of high dose methotrexate in the absence of "rescue." The incidence and severity of toxicities were to be compared for the two treatment groups for leukopenia, thrombocytopenia, mucositis, and liver function abnormalities.

6.1.3 Study Design

No new clinical trial data were provided for this submission. See sections 6.1.1 and 6.1.2 for discussion of some aspects of study design for the trials submitted in 1990, as well as the original Clinical Review from 1991.

The dose of *L*-leucovorin was evaluated at ½ the dose of *d,L*-leucovorin, because *L*-leucovorin is the pharmacologically active stereoisomer. Some patients were treated exclusively with IV *L*-leucovorin or IV *d,L*-leucovorin (the patients treated according to the TIOS-III protocol), and the remaining patients were treated with a combination of IV and oral leucovorin, either *L*-leucovorin or *d,L*-leucovorin, respectively, according to treatment group. The dosing schedule for HDM and for leucovorin for patients according to the TIOS-III trial differed from that of the other two trials. (See table 2, section 4.3).

Selection of historical controls. Investigators retrospectively identified patients who had been treated with HDM and *d,L*-leucovorin rescue at the same institution, utilizing the same protocols used for patients subsequently treated with *L*-leucovorin under the auspices of Lederle Laboratories (the initial sponsor). Data were retrospectively transcribed from the records of the patients treated with *d,L*-leucovorin onto the Lederle case report forms (CRFs). An attempt was made to select two patients recently treated with *d,L*-leucovorin for comparison with every one

patient treated with *l*-leucovorin, matching patients who had received a similar number of courses of therapy.

For each of the 5 chemotherapy protocols in osteogenic sarcoma under which patients were treated, there were similar requirements for laboratory monitoring. Serum methotrexate blood levels were required at 24, 48, and 72 hours after completion of HDM infusion for the POG and TIOS-III trials. For patients treated according to the OS-86 trial, methotrexate levels were required at 12, 20, 24, 34, 44, and 68 hours post completion of HDM infusion. Each protocol had pre-specified instructions to increase the dose/duration of leucovorin therapy if methotrexate levels were undesirably high at any of these times. The schedule of routine laboratory assessments to evaluate the efficacy and safety of leucovorin rescue was the same for all 5 trials. Patients were required to have baseline and day 7 assessment of CBC (includes differential and platelet count), blood chemistry (liver and renal function, electrolytes, glucose), and urinalysis. History and physical examinations were also to be done on the day of therapy and on day 7 following treatment with HDM.

6.1.4 Efficacy Findings

No new clinical trial data were provided for this submission. The current review provides some additional data and analyses which were not cited in the original review, and provides an overview of the efficacy findings. Please see the original Clinical Review from 1991 for further details.

Exposure

The following table is modified from table 6 of the 1990 CSR for NDA 20-140. It demonstrates the sponsor's assessment of the extent of drug exposure in patients treated with *l*-leucovorin compared with the matched historical controls treated with *d,l*-leucovorin.

Table 3: Drug Exposure in Patients Treated with *l*-Leucovorin or *d,l*-Leucovorin (Reviewer Table)

Protocol Treatment Group	Number of Patients	Number of Courses	Mean Total Dose/Course (Range) Mg
POG			
<i>l</i> -leucovorin	10	30	148 (60-487)
<i>d,l</i> -leucovorin	16	47	254 (135-2515)
TIOS-III			
<i>l</i> -leucovorin	3	22	657 (150-1150)
<i>d,l</i> -leucovorin	6	42	1262 (135-3100)
OS-86			
<i>l</i> -leucovorin	3	6	233 (75-809)
<i>d,l</i> -leucovorin	6	12	317 (136-1122)

Two *d,l*-leucovorin treated subjects were selected as historical controls from the TIO-III (MD Anderson) and OS-86 (St. Jude) studies for comparison with subjects treated with *l*-leucovorin at

the same institutions. For the POG studies, it appears that a lesser number of historical controls were selected for comparison than the 2:1 number specified in the protocol. As expected, the mean exposure to *d,l*-leucovorin was higher than that for *l*-leucovorin, since the pre-specified dosing ratio in mg was 2:1. The observed mean dose per course was 350 mg +/- 42 mg of *l*-leucovorin (range, 60-1150 mg) and 681 +/- 87 mg of *d,l*-leucovorin (range, 135-3100 mg).

Reviewer comment: *As expected, the mean exposure to d,l-leucovorin was higher than that for l-leucovorin, since the pre-specified dosing in mgs was 2:1 for the racemic mixture compared with the l-isomer. As expected, the exposure per course to both products was higher in the TIOS-III trial, compared with exposure for patients in the other trials. (TIOS-III required l-leucovorin 18 doses per course compared with 10 doses per course for POG and OS-86.) For each treatment group, the range is quite variable. This is consistent with the known heterogeneity of the study population. In addition, patients in all protocols were administered higher doses and more doses for evidence of delayed methotrexate excretion.*

The next table is modified from NDA 20-141 (1990) CSR table 12, and shows the distribution of the number of doses of leucovorin administered per course by treatment group.

Table 4: Number of Doses of Leucovorin per Course by Treatment Group (Reviewer Table)

Number of Doses per Course	<i>l</i> -Leucovorin: Number (%) of Courses	<i>d,l</i> -Leucovorin Number (%) of Courses
8-9	4 (7)	3 (3)
10	9 (16)	30 (30)
11-15	9 (16)	22 (22)
16-20	19 (33)	21 (21)
>20	17 (29)	25 (25)

The next table is modified from CSR Table 13 and demonstrates, by treatment group, the distribution of the number of courses of HDM with leucovorin rescue administered per patient.

Table 5: Number of Courses of HDM and Leucovorin per Patient by Treatment Group (Reviewer Table)

Number of Courses	<i>l</i> -Leucovorin: Number (%) of Patients	<i>d,l</i> -Leucovorin: Number (%) of Patients
1	4 (25)	7 (25)
2	4 (25)	7 (25)
3	1 (6)	2 (7)
4	1 (6)	1 (4)
5	1 (6)	2 (7)
6	3 (19)	7 (26)
7	1 (6)	0
8	0	0
9	1 (6)	2 (7)

Reviewer comment: *Although the distribution of the number of courses of therapy administered to the l- vs. d,l- leucovorin treatment groups was similar (as expected for matched groups), the number of doses of leucovorin per course appears somewhat variable for both treatment groups. The mean number of doses per course was 18.2 +/- 1.03 (range, 4-45) for the l-leucovorin group and 16.2 +/- .60 (range, 9-31) for the d,l-leucovorin group. The sponsor indicated in the 1990 CSR that a lower percentage of l-leucovorin patients (9%) than d,l-leucovorin patients (25%) received oral leucovorin only.*

Audit of Methotrexate (MTX) Levels from Case Report Forms (CRFs)

Subjects were required to have serum MTX levels assessed at 24, 48, and 72 hours after completion of HDM infusion for patients treated according to the POG and TIOS-III protocols. For patients treated according to the OS-86 protocol, peak methotrexate levels were required and again at 12, 20, 24, 34, 44, and 68 hours post completion of HDM infusion. CRFs were available for patients treated with l-leucovorin in the osteosarcoma trials. We performed an audit of MTX levels available in these CRFs to verify that the intensity of MTX therapy would have required “rescue” to prevent life-threatening and lethal toxicity. Peak levels were available for many patients. Twenty-four hour levels were drawn on all patients. The data reflect that the intensity of MTX therapy was such that patients would have experienced severe toxicity in the absence of effective leucovorin rescue.

Efficacy Assessment

The primary efficacy endpoint was a safety endpoint. Patients treated with l-leucovorin were compared with retrospectively selected, historical controls, previously treated according to the same protocols for osteogenic sarcoma, but having received d,l-leucovorin for rescue from HDM. (L-leucovorin was administered at one half the dose of d,l-leucovorin.) Efficacy was assessed by comparing the effectiveness of l-leucovorin with that of d,l-leucovorin in preventing the severe toxicity expected following administration of high dose methotrexate in the absence of “rescue.” The incidence and severity of toxicities were also to be compared for the two treatment groups for leukopenia, thrombocytopenia, mucositis, and liver function abnormalities.

Safety data were to be collected for 1 week after administration of HDM or until any toxicity had resolved. Across 5 different chemotherapy trials, utilizing three different leucovorin rescue protocols (see section 4.2 and section 6.1.1), there were 16 patients with osteogenic sarcoma treated with l-leucovorin (11 adjuvant, 5 metastatic) for a total of 58 courses of HDM. These patients were compared with 28 “matched historical controls” who received 101 courses of HDM followed by d,l-leucovorin rescue.

Sponsor Assessment

There were no deaths attributable to HDM therapy. The sponsor’s assessment was that although adverse events were common in both treatment groups, there were very few serious adverse events (SAEs) observed. Typhlitis and stomatitis occurred in one patient with delayed MTX excretion, for a (course) incidence of SAEs of 1.7% in the l-leucovorin group. During 101

courses of *d,l*-leucovorin in 28 patients, SAEs of stomatitis, sepsis, and bacterial infection occurred, each in a single course, for a (course) incidence of 3%. The following table is taken from the sponsor's 1991 CSR and summarizes the adverse events observed in the *l*-leucovorin group.

Table 6: *L*-leucovorin Treatment Group Adverse Events (1991 CSR, Sponsor Table 7)

Body system/ adverse experience	Number (%) of patients with adverse experiences (N = 16)	Number (%) of courses with adverse experiences (N = 58)
Gastrointestinal		
Diarrhea	1 (6.3)	1 (1.7)
Dyspepsia	1 (6.3)	1 (1.7)
Gastritis (cyphilitis)	1 (6.3) ^a	1 (1.7) ^a
Nausea	3 (18.8)	3 (5.2)
Stomatitis	6 (37.5) ^a	10 (17.2) ^a
Vomiting	6 (37.5)	14 (24.1)
Respiratory		
Dyspnea	1 (6.3)	1 (1.7)
Skin and appendages		
Dermatitis	1 (6.3)	1 (1.7)
Other		
Confusion	1 (6.3)	1 (1.7)
Neuropathy	1 (6.3)	1 (1.7)
Renal function abnormal	1 (6.3)	3 (5.2)
Taste perversion	1 (6.3)	1 (1.7)
Total	9 (56.3)	25 (43.1)

^a Severe in one patient or one course.
Symbol: N, total number of patients or courses.
(Data are from Summary Tables 10 and 16, Attachment 1 in the Integrated Summary of Safety Information, Section 8 of this submission.)

The next table is also taken from the 1991 CSR and compares the distribution of White Blood Cell (WBC) Counts for the two treatment groups.

Table 7: Distribution of WBC Counts Compared by Treatment Group (Sponsor Table 9)

WBC count (μL)	Number (%) of courses with specified range of WBC count, by treatment	
	<i>l</i> -Leucovorin (N = 58)	<i>d,l</i> -Leucovorin (N = 101)
≤2500	9 (20)	19 (25)
2501 - 5000	19 (43)	31 (41)
5001 - 10,000	16 (36)	26 (34)
Unknown	14	25

^a Values were the lowest value obtained 5 to 15 days after the beginning of each course.
Symbol: N, total number of courses.
(Data are from Summary Table 23A, Attachments 1 and 2 in the Integrated Summary of Safety Information, Section 8 of this submission.)

Patients received myelosuppressive chemotherapy other than HDM, so that leukopenia in both treatment groups may have related to other chemotherapy administered close in time (before or subsequent) to the HDM therapy.

Reviewer comment: *It is of note that WBC's obtained between 5 and 15 days after beginning a course of therapy were unknown for 14% of the l-leucovorin courses and for 25% of the d,l-leucovorin courses.*

The next table is also taken from the 1991 CRS. It demonstrates the Distribution of platelet counts, comparing the l-leucovorin treatment group with the d,l-leucovorin retrospective control group.

Table 8: Distribution of Platelet Counts by Treatment Group (Sponsor Table 10)

Platelet count (μL)	Number (1) of courses with specified range of platelet count, by treatment	
	l-Leucovorin (N = 56)	d,l-Leucovorin (N = 101)
≤ 75,000	2 (5)	2 (3)
76,000 - 100,000	1 (2)	1 (1)
101,000 - 400,000	37 (86)	55 (74)
> 400,000	3 (7)	16 (22)
Unknown	15	27

^a Values were the lowest value obtained 5 to 15 days after the beginning of each course.

Symbol: N, total number of courses.

(Data are from Summary Table 26A, Attachments 1 and 2 in the Integrated Summary of Safety Information, Section 8 of this submission.)

One patient in the l-leucovorin group (POG study) had platelet counts below 75,000/μL (lowest value 4,000/μL) during cycles 2 and 3, requiring platelet transfusions, but with normal platelet counts for course 4 and above 100,000/μL for course 5. For the d,l-leucovorin treated patients, one experienced thrombocytopenia of 54,000 /μL in the first course and a second patient experienced a platelet count of 25,000/μL during the first course, both with normal platelet counts upon subsequent testing.

Reviewer comment: *It is of note that platelet counts that were to be obtained between 5 and 15 days after beginning a course of therapy were unknown for 15% of the l-leucovorin courses and for 27% of the d,l-leucovorin courses.*

The sponsor concluded that l-leucovorin is effective in providing rescue from the severe AEs and myelosuppression associated with HDM. The sponsor concluded that l-leucovorin is effective in both the adjuvant and metastatic setting and in patients previously treated with cisplatin, who may have some renal insufficiency.

Assessment of Clinical Reviewers in 1991

For details of this assessment, see the original 1991 Clinical Review. The reviewers noted that although the data submitted in the NDA included all patients and every course of therapy for *l*-leucovorin, many of the treatment courses were inevaluable because follow-up was incomplete. Since it was not possible to document that adverse events were followed to resolution, they could not be sure that reported toxicities were the most severe grade experienced during a course. The reviewers stated that “only 9 of the 16 patients treated with *l*-leucovorin were fully evaluable for the toxicities of leukopenia, thrombocytopenia, mucositis and liver function abnormalities,” and “only 20 courses were fully evaluable for all of these toxicities.” However, they concluded that, “despite these deficiencies, review of the submitted data revealed no severe side effects from or lack of efficacy of *l*-leucovorin when used for methotrexate rescue.”

FDA concluded that the clinical trial data did not permit direct comparisons between *d,l*-leucovorin and *l*-leucovorin. In a July 1991 presentation to ODAC, Dr. Robert Justice stated that the use of historical controls, in small number, and with a “low evaluability rate, make it impossible to reach any conclusions about the relative efficacy of *d,l*-leucovorin and *l*-leucovorin.”

6.1.5 Clinical Microbiology

Dr. Robert Mello was the microbiology reviewer. See Section 3.1 of this review and his separate review for details.

6.1.6 Efficacy Conclusions

The efficacy of levoleucovorin rescue following high-dose methotrexate was based on the demonstration that levoleucovorin prevented the severe toxicity certain to occur in the absence of adequate “rescue.” Conclusions could not be made regarding the comparative efficacy of *l*-leucovorin and the historical controls treated with *d,l*-leucovorin due to the small number and low evaluability rate of the latter. There were data for 16 patients with osteogenic sarcoma treated with *l*-leucovorin (11 adjuvant, 5 metastatic) for a total of 58 courses of HDM. These patients were compared with 28 “matched historical controls” who received 101 courses of HDM followed by *d,l*-leucovorin rescue. These patients were treated with one of five different chemotherapy regimens, of which HDM was only one component. The HDM was frequently sandwiched between other myelosuppressive or nephrotoxic chemotherapy drugs. Patients were treated with one of 3 different leucovorin rescue regimens, two of which could include leucovorin tablets as well as IV leucovorin. Nine per cent of patients in the *l*-leucovorin treatment group were treated with oral leucovorin only, as were 25% of patients in the *d,l*-leucovorin group. In spite of the heterogeneity of the treatment populations and the limited number of patients and courses that were said to be fully evaluable by the 1991 Clinical Reviewers (9 and 20, respectively), they concluded, along with ODAC, that the data were sufficient to demonstrate safety and efficacy for *l*-leucovorin.

At a meeting of ODAC on July 1, 1991, the FDA clinical reviewer stated that FDA and Lederle (the original sponsor) had agreed on three steps in product development. (See section 8.5.)

These were:

- To provide evidence that the *d*-isomer did not contribute significantly to the efficacy of leucovorin rescue
- To demonstrate that the new products were bioequivalent for *L*-leucovorin
- To provide clinical evidence that the products could provide effective rescue after therapy with high dose methotrexate. However, FDA agreed a large randomized trial comparing rescue with *L*- and *d,L*-leucovorin would not be required if the first 2 conditions were satisfied.

In 1991 ODAC determined that the first 2 conditions had been met, and the clinical data were sufficient to demonstrate safety and efficacy. (Subsequent non-approvable determinations were based on CMC deficiencies.)

Reviewer comment: *The fact that most patients in both treatment groups were treated with a combination of both IV and oral leucovorin, makes it difficult to separate out the data for IV L-leucovorin from the combined data for both formulations. However, the bioavailability of an intravenous preparation is more predictable than that of an oral preparation. Therefore, any bias introduced by using oral L-leucovorin, in contrast to IV, would be expected to diminish rather than enhance the efficacy observed.*

The current application provides additional support for efficacy/ safety from literature reports of the use of *L*-leucovorin in Europe, where it has been licensed for the indication since 1991, and from the postmarketing safety database of the World Health Organization (WHO) International Drug Monitoring center in Uppsala, Sweden. (See Section 7.2.2.3 for discussion of literature reports and see Appendix 10.3 for discussion of WHO data.) The FDA safety database (AERS DataMart) was also assessed in order to compare safety reports for the leucovorin calcium (*d,L*-leucovorin) products marketed in the US. (See Section 7.1.17 for discussion of "Data Mining.")

The data from clinical trials and the WHO postmarketing safety data are adequate to permit writing of a product label for levoleucovorin calcium.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

No new clinical trial safety data were submitted. The efficacy endpoint of the clinical trials was a safety endpoint, *i.e.*, to demonstrate the absence of the severe toxicity expected with HDM if rescue were not adequate. The original development plan was to compare the safety profile of *L*-leucovorin treated patients with historical controls treated with *d,L*-leucovorin following HDM for osteosarcoma. In 1991, the original Clinical Reviewers determined, and ODAC concurred, that the historical controls were too few and not adequately evaluable to make conclusions

regarding comparative efficacy between the treatment groups. However, the Reviewers and ODAC were able to conclude that the data were sufficient to demonstrate safety and efficacy for *l*-leucovorin. Please see Sections 4.2 and 6.1 for overview and details regarding the clinical trials.

This section captures some safety information not contained in the original review. This includes a summary of the 120-day safety update from 1991, which documents additional exposure to levoleucovorin, including new patients and additional courses of therapy for the existing patients (see Section 7.2.9). Appendix 10.3 contains an analysis of the World Health Organization (WHO) Uppsala international postmarketing safety data submitted by the applicant in the current Amendment to support the safety of levoleucovorin. In Section 7.1.17, there is a discussion of the US postmarketing experience with *d,l*-leucovorin from the FDA AERS database. Section 7.2.2.3 provides a review of the medical literature with reference to the safety (and efficacy) of *l*-leucovorin for rescue from HDM therapy in patients with osteogenic sarcoma.

7.1.1 Deaths

No new clinical trial data were provided for this submission. The sponsor indicated that no patients died related to therapy with HDM and levoleucovorin rescue.

7.1.2 Other Serious Adverse Events

No new clinical trial data were provided for this submission.

7.1.3 Dropouts and Other Significant Adverse Events

No new clinical trial data were provided for this submission.

7.1.4 Other Search Strategies

No new clinical trial data were provided for this submission.

7.1.5 Common Adverse Events

No new clinical trial data were provided for this submission. See Section 6.1.4.

7.1.6 Less Common Adverse Events

No new clinical trial data were provided for this submission.

7.1.7 Laboratory Findings

No new clinical trial data were provided for this submission.

7.1.8 Vital Signs

No new clinical trial data were provided for this submission.

7.1.9 Electrocardiograms (ECGs)

No new clinical trial data were provided for this submission.

7.1.10 Immunogenicity

Postmarketing data for *d,l*-leucovorin (FDA) and WHO Uppsala Postmarketing data (see Appendix 10.3) show some occurrences of “allergic sensitization” and “possible allergic reaction,” respectively. The former included anaphylactoid type reactions and urticaria. Articles from the medical literature report anaphylactic shock in a man due to IV folinic acid (Benchalal 2002) and IgE-mediated anaphylaxis in a woman associated with oral ingestion of folic acid vitamin supplements. In the latter case, subsequent graded oral challenge with folinic acid (leucovorin) resulted in generalized urticaria, after 100 mg, but not after 10 or 50 mg (Dykewicz 2000).

7.1.11 Human Carcinogenicity

Levoleucovorin is a folate analog and would not be expected to have carcinogenic potential. However, no carcinogenicity or genotoxicity trials were done in the development program.

7.1.12 Special Safety Studies

No new clinical trial data or pharmacology/toxicology data were provided for this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Levoleucovorin is a folate analog and would not be expected to have abuse potential or cause withdrawal symptoms.

7.1.14 Human Reproduction and Pregnancy Data

It is not known whether levoleucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Levoleucovorin should be given to a pregnant woman only if clearly needed and is classified Pregnancy Category C.

7.1.15 Assessment of Effect on Growth

No new clinical trial or pharmacology/toxicology data were provided for this submission. The effect on growth was not studied.

7.1.16 Overdose Experience

There is no information from clinical trials, from the WHO Uppsala Monitoring Center Postmarketing database, or from the literature regarding overdose. Excessive doses of levoleucovorin could interfere with the chemotherapeutic efficacy of folic acid antagonists.

7.1.17 Postmarketing Experience

Levoleucovorin is not marketed in the US. See Appendix 10.3 for discussion of WHO Uppsala Monitoring Center international postmarketing database for levoleucovorin.

Although *levoleucovorin* calcium (*l*-leucovorin) is not marketed in the United States, leucovorin calcium, as a 1:1 racemic mixture (*d,l*-leucovorin calcium), is available commercially both for parenteral use and as oral tablets. Consultation was requested from the Office of Surveillance and Epidemiology to evaluate the adverse events that had been reported for the US marketed products. Ms Susan Lu, R.Ph., performed a data-mining search of the FDA AERS database for folinic acid for all events with $EB05 \geq 2$. EB05 and EB95 are the lower and upper 90% confidence limits for the EBGM (Empirical Bayes Geometric Mean) values, where EBGM is an estimate of the relative reporting rate of an event from a particular drug relative to other drugs and events in the database. A drug-event combination with an $EB05 \geq 2$ indicates 95% confidence that the drug-event combination occurs at least twice the expected rate compared with other drugs and events in the database.

The data-mining search of the FDA AERS postmarketing database for folinic acid for all events with $EB05 \geq 2$ identified 143 separate events. The only events which could be attributed to leucovorin per se include the labeled events of "allergic sensitization," including anaphylactoid type reactions and urticaria. The majority of reported events do not appear to be related to leucovorin, but, are likely due to underlying malignancy and/or treatment with chemotherapy.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

No new clinical trial data were provided for this submission. See Section 1.3.1, Section 6.1.1, 6.1.3, and 6.1.6.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No new clinical trial data were provided for this submission.

7.2.2.2 Postmarketing experience

See Section 7.1.17 (US postmarketing experience for *d,l*-leucovorin) and see Appendix 10.3 (WHO Uppsala database for international postmarketing experience for *l*-leucovorin).

7.2.2.3 Literature

The applicant provided numerous articles from the medical literature in which levoleucovorin was used concomitantly with 5-fluorouracil in the treatment of colorectal cancer. In response to the FDA's request for references specifically dealing with/citing the use of *l*-leucovorin in conjunction with HDM in osteosarcoma, the applicant again searched PubMed and CureHunter, using search terms "levofolinic acid" or "*l*-leucovorin." A search from January 1, 1991, through November 6, 2007, yielded 2 articles which provided clinical trial data of safety and efficacy (Goorin 1995, Jaffe 1993). Three additional articles were obtained when the search was run back from Dec., 31, 1990, with the earliest article from 1984, but these did not contribute to the evidence of safety and efficacy for the osteosarcoma indication.

The articles by Goorin (1995) and Jaffe (1993) reported on patients treated in the Lederle-supported trials and there is significant overlap with the clinical trial data submitted to the NDA. Jaffe reported on 3 osteosarcoma patients treated with 22 courses of HDM (12.5 g/m² over 6 hours) and rescued with *l*-leucovorin at MD Anderson from Nov. 1989 to March 1990. One patient was given 50 mg doses of *l*-leucovorin (instead of 7.5 mg) due to a history of previous delayed methotrexate excretion with previous *d,l*-leucovorin rescue. One subject required an increase in five *l*-leucovorin doses to 50 mg for the 4th course and subsequent courses due to delayed methotrexate excretion. The 3rd patient was given 25 mg doses based on previous experience with delayed methotrexate excretion. Data were also obtained from 6 historical controls treated with 42 courses of HDM with *d,l*-leucovorin rescue. In the control group, 2 patients were treated with 15 mg of *d,l*-leucovorin for all courses; the others were treated with higher doses for some courses. Both groups experienced liver function abnormalities attributed to methotrexate. *L*-leucovorin was felt to be effective in preventing severe toxicity known to be associated with HDM therapy.

The Goorin (1995) article reported on 15 osteosarcoma patients treated in or according to Pediatric Oncology Group (POG) trials from Oct. 1989 until Feb. 1993 at Dana Farber, Stanford, Medical College of Wisconsin and National Cancer Institute. These patients received HDM 12 gm/m² IV over 4 hours. Twenty-four hours after completion, they were treated with *l*-leucovorin 7.5 mg every 6 hours for 60 hours, or longer, depending on the methotrexate concentration at 72 hours. These 15 patients received 90 courses of HDM. They received a mean of 16.2 doses of *l*-leucovorin per course and a mean of 126 mg per course. (Note that this is less than the mean 291 mg per course of *l*-leucovorin reported for the patients in the licensing trial and included in the 120-day safety update to the NDA in 1991. The mean number of courses reported at the time of the 120-day update was similar to this report, 15.8 courses.) More than 20 doses of *l*-leucovorin were given in 19% of courses due to *delayed methotrexate excretion in 7 patients*. "There were no instances of severe, acute methotrexate toxicity." The

“severe adverse experience of 4% (4/90) compares favorably with the 10% experience of” a historical control group rescued with *d,l*-leucovorin.

Reviewer comment: *Although the authors of both papers, and the sponsor conclude that l-leucovorin at one half the dose of d,l-leucovorin, safely and effectively rescues patients from the toxicity of” ... HDM, it is clear that increased dose and duration of both l- and d,l-leucovorin were frequently used.*

Independent review of the medical literature by FDA did not yield additional clinical trial evidence of efficacy and safety with levoleucovorin following HDM for the treatment of osteogenic sarcoma. However, FDA literature search produced two case reports of allergic reactions associated with folate analogs. One well-documented report cited anaphylactic shock in a man due to IV folinic acid as part of a regimen of therapy with 5-fluorouracil, where other drugs were eliminated as the cause (Benchahal 2002). A second study demonstrated IgE-mediated anaphylaxis in a woman associated with oral ingestion of folic acid vitamin supplements. In the latter case, subsequent graded oral challenge with folinic acid (leucovorin) resulted in generalized urticaria, after 100 mg, but not after 10 or 50 mg (Dykewicz 2000).

7.2.3 Adequacy of Overall Clinical Experience

No new clinical trial data were provided for this submission.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new pharmacology/Toxicology data were provided for this submission. Based on the drug class and mechanism of action, no special animal or in vitro testing was required in the development plan.

7.2.5 Adequacy of Routine Clinical Testing

No new clinical trial data were provided for this submission.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Drug-drug interactions were not studied during the development plan.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No new clinical trial data were provided for this submission.

7.2.8 Assessment of Quality and Completeness of Data

No new clinical trial data were provided for this submission.

7.2.9 Additional Submissions, Including Safety Update

No new clinical trial data were submitted. The original sponsor, Lederle Laboratories, submitted a 120-day safety update to NDA 20-140 and 20-141 (levoleucovorin tablets) on May 16, 1991. The update provided data for 48 additional courses of therapy for 8 patients in the original study group, as well as data for 9 new patients treated with a total of 50 courses of therapy. Patients were treated with a combination of IV and oral levoleucovorin. These data were not cited in the original Clinical Review or by ODAC, although the current sponsor indicates the Update was included in the ODAC Briefing Document. Including all patients treated, the applicant reports that the mean number of doses of levoleucovorin per course was 15.8 and the mean total dose per course was 291 mg. For the new patients reported in the update, 6 patients were ages 10-19; 2 patients were younger than age 10, and 1 patient was age 20-29.

Reviewer comment: *The mean number of doses per course, 15.8, and the mean total dose per course, 291 mg, are higher than would be anticipated based on the schedule of rescue specified for patients treated according to POG and OS-86 protocols, 7.5 mg x 10 doses. The schedule for the TIOS-III trial, according to which a small number of patients was treated, required 7.5 mg of l-leucovorin x 18 doses. In addition, patients were administered higher doses and more doses for evidence of delayed methotrexate excretion. (See Section 6.1.4 for exposure data during the core studies and Section 7.2.2.3, discussion of Jaffe (1993) and Goorin (1995) literature reports.)*

The following synopsis by the original sponsor, Lederle, of the findings of the 120-day safety update was provided by the current applicant, in a submission dated February 1, 2008.

“The safety data presented in this section in the use of l-leucovorin in rescuing from high-dose methotrexate toxicity in patients with osteosarcoma are comparable to those previously submitted (NDA #20-140 and #20-141). Few severe adverse experiences were observed, and no life-threatening toxicity was reported in any of the patients. No new patients were withdrawn from these studies and no deaths occurred among the combined patients (new patients and patients in the submission). The distributions of WBC and platelet counts and serum transaminase, serum bilirubin, and serum creatinine values reported in this section are also comparable to those included in the submission. In conclusion, no unusual or unexpected toxicities were observed; these data provide additional evidence to support the safety of l-leucovorin in rescuing from high-dose methotrexate toxicity in patients with osteosarcoma.” (NDA Amendment dated May 31, 1991, page 173).”

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

No new clinical trial data were provided for this submission. See table 6, 7, 8 and discussion in Section 6.1.4. Also see section 6.1.6 Efficacy Conclusions). In 1991, FDA and ODAC determined that *L*-leucovorin was safe and effective for the indications.

7.4 General Methodology

No new clinical trial data were provided for this submission.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen is 7.5 mg (approximately 5 mg/m²) intravenously every 6 hours for 10 doses starting 24 hours after beginning methotrexate infusion (based on a methotrexate dose of 12 gm/m² IV over 4 hours). Levoleucovorin is dosed at one-half the usual dose of the racemic form, *d,l*-leucovorin. Serum creatinine and methotrexate levels are to be measured daily and levoleucovorin, hydration and urinary alkalinization are to be continued until the methotrexate level is below 5×10^{-8} M (0.05 micromolar). For delayed methotrexate elimination and/or evidence of acute renal injury, the dose of levoleucovorin should be adjusted. The following table is taken from the product label.

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Table 9: Guidelines for *L*-leucovorin Dosage and Administration

Clinical Situation	Laboratory Findings	Levoleucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours	7.5 mg IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 7.5 mg IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	75 mg IV q 3 hours until methotrexate level is less than 1 micromolar; then 7.5 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.

8.2 Drug-Drug Interactions

- Drug-drug interactions were not studied during the development plan.
- There is evidence from the medical literature that folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children. It is not known whether folinic acid has the same effects. However, since folic and folinic acids share some common metabolic pathways, caution should be taken when administering folinic acid in combination with anticonvulsant drugs.
- Levoleucovorin increases the toxicity of 5-fluorouracil.

8.3 Special Populations

- There are no special dosing considerations identified for race, gender, age for adults or for children. Clinical studies of levoleucovorin in the treatment of osteosarcoma evaluated a pediatric population, and did not include subjects aged 65 and over to determine whether they respond differently from younger subjects.
- There have been no studies done with regard to dose modifications for hepatic or renal insufficiency. No dosing modifications would be anticipated for the proposed indication.
- Animal reproduction studies have not been conducted with levoleucovorin. It is also not known whether levoleucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Levoleucovorin should be given to a pregnant woman only if clearly needed and is classified Pregnancy Category C.
- It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when levoleucovorin is administered to a nursing mother

8.4 Pediatrics

The clinical trials for levoleucovorin in osteosarcoma were performed in pediatric populations.

8.5 Advisory Committee Meeting

On July 1, 1991, the Oncological Drug Advisory Committee (ODAC) discussed Lederle's NDA 20-140 (IV) and NDA 20-141 (oral tablets) for levoleucovorin for "rescue after high dose methotrexate therapy in osteosarcoma, impaired methotrexate elimination and inadvertent overdosage of folic acid antagonists." The FDA and Lederle had agreed upon three steps in development:

- To provide evidence that the *d*-isomer did not contribute significantly to the efficacy of leucovorin rescue
- To demonstrate that the new products were bioequivalent for *L*-leucovorin
- To provide clinical evidence that the products could provide effective rescue after therapy with high dose methotrexate. However, FDA agreed a large randomized trial comparing rescue with *L*- and *d,l*-leucovorin would not be required if the first 2 conditions were satisfied.

After discussion, the committee addressed the following questions posed by FDA:

- Are the clinical data adequate to conclude that *L*-leucovorin is an active isomer and that the contribution of *d*-leucovorin to methotrexate rescue is insignificant? The vote was yes, 8 and no, 0.
- Are the bioequivalence and the bioavailability data sufficient to conclude that *L*-leucovorin administered at a half-dose of *d,l*-leucovorin results in a cumulative blood level of the *L*- form? The vote was yes, 8 and no, 0.
- If the answers to the above two questions are affirmative, is the limited clinical data sufficient to confirm that Isovorin injection is safe and effective when used in the rescue of high dose methotrexate? The vote was yes, 6 and no, 2. (ODAC also voted that the Isovorin tablets were safe and effective when used in the rescue of high dose methotrexate: Yes, 6 and no, 2.)

8.6 Literature Review

Review of the published literature provided limited additional safety and efficacy information regarding the use of levoleucovorin following treatment with HDM for osteosarcoma. (See Section 7.2.2.3.)

8.7 Postmarketing Risk Management Plan

The applicant submitted a Postmarketing Risk Management Plan. This was directed at avoiding dosing errors related to similarities in name between the marketed racemic mixture, Leucovorin, and levoleucovorin, proposed proprietary name, ISO-Vorin. DMETS

recommended the applicant propose alternate proprietary names, which are currently under review. Therefore, the proposed plan is no longer relevant.

8.8 Other Relevant Materials

- Consultation was requested from the Division of Medication Errors and Technical Support (DMETS), Office of Surveillance and Epidemiology. DMETS had concerns regarding nomenclature and packaging of the product. These concerns were communicated to the applicant, including the recommendation that the applicant propose an alternate proprietary name. The applicant has proposed alternate proprietary names, which are under review.
- Comments were received from DDMAC and were incorporated into the label as appropriate.

9 OVERALL ASSESSMENT

9.1 Conclusions

No new clinical trial data were provided with this submission. In 1991 the FDA Clinical Reviewers and the Oncological Drug Advisory Committee determined that there were sufficient data to support the Safety and Efficacy of levoleucovorin for the proposed indications. The efficacy of levoleucovorin rescue following high-dose methotrexate was based on the demonstration that levoleucovorin prevented the severe toxicity certain to occur in the absence of adequate "rescue." Conclusions could not be made regarding the comparative efficacy of *l*-leucovorin and the historical controls treated with *d,l*-leucovorin due to the small number and low evaluability rate of the latter. Non Approvable letters were issued subsequently because of CMC deficiencies. These issues are now resolved for the intravenous formulation of levoleucovorin.

In this Amendment, the applicant provided a safety update based on international postmarketing experience for calcium levoleucovorin from the World Health Organization (WHO) Uppsala Monitoring Center (UMC) database (Vigibase). (See Appendix 10.3) Review of the published literature provided limited additional safety and efficacy information regarding the use of levoleucovorin following treatment with HDM for osteosarcoma. (See Section 7.2.2.3)

9.2 Recommendation on Regulatory Action

The application is recommended for approval.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

FDA recommended that the applicant provide an alternate proprietary name to ISO-vorin, to diminish product confusion and resulting dosing errors. No other special risk management activities have been recommended as of this time.

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are required.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

Consultation was requested from the Division of Medication Errors and Technical Support (DMETS), Office of Surveillance and Epidemiology. DMETS had concerns regarding nomenclature and packaging of the product. These concerns were communicated to the applicant, including the recommendation that the applicant propose an alternate proprietary name. The applicant has proposed alternate proprietary names, which are under review.

A medication guide is not required, as levoleucovorin will be administered by health professionals.

Changes were made to the label for the purposes of conforming to 21CFR 201.56 and 201.57 and to improve clarity.

9.5 Comments to Applicant

There are no comments pertaining to specific deficiencies.

10 APPENDICES

10.1 Review of Individual Study Reports

No new clinical trial data were submitted.

10.2 Line-by-Line Labeling Review

See Approval Letter for final label.

10.3 Review of WHO Uppsala Monitoring Center Database Postmarketing Data

The applicant provided a safety update based on international postmarketing experience for calcium levoleucovorin from the World Health Organization (WHO) Uppsala Monitoring Center (UMC) database (Vigibase). The UMC maintains a database of spontaneous events reported from the national reporting system of approximately 77 countries since 1968. Levoleucovorin calcium (established name, calcium levofolinate) has been marketed in a number of countries in Europe, with initial approval in Italy in 1991. (See Sections 2.2 and 2.6) The UMC database provided a summary of adverse events where levofolinate was reported with any event, whether it had been administered concomitantly or was a suspected or interacting cause of such events. There were 252 such reports (525 events) that listed calcium levofolinate as a suspected, interacting or concomitant medication. The sponsor's consultant described the search of the database as follows: "Events were searched on the preferred term for the reported reaction which was assigned according to the WHOART coding system. Using this methodology, the UMC identified 108 reports (217 events) that listed calcium levofolinate as either a suspected or interacting medication...these 217 events were reported from Belgium, Canada, France, Italy, Portugal, Sweden, the USA and South Africa. Because levofolinate is not available commercially in the USA and Canada, reports from these countries are probably related to clinical trial exposure. ...the majority of these events were reported after 2004."

The majority of reports in the database concern patients who were treated with levoleucovorin concomitantly with 5-fluorouracil for colorectal cancer. Only seven cases were identified where levoleucovorin was known to be administered with a regimen of methotrexate. The reported events were dyspnea, pruritus, rash, temperature change and rigors. For 217 adverse reactions (108 reports) where levoleucovorin was a suspected or interacting, medication, there were 40 occurrences of "possible allergic reaction."

Reviewer comment: *There are no unusual or unexpected adverse reactions identified from the WHO spontaneous reports. The findings were discussed with Dr. Allen Brinker (Office of Surveillance and Epidemiology), who concurred, and noted that the WHO profile is based on a limited number of reports (n=108). The only events which are probably attributable to levoleucovorin are those of an allergic nature. This is similar to "data-mining" findings from the FDA AERS postmarketing database for d,l-leucovorin. (See Section 7.1.17) That analysis*

yielded only the labeled events of "allergic sensitization," including anaphylactoid type reactions and urticaria which could be attributed to leucovorin per se. For both databases and for both products, most events do not appear to be due to leucovorin, but are likely due to underlying malignancy and/or treatment with chemotherapy.

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NDA: 20-140
20-141

APPLICANT: Lederle Laboratories Division
American Cyanamid Company
N. Middletown Road
Pearl River, NY 10965

DATE RECEIVED: December 18, 1990

1. GENERAL INFORMATION

A. Name of drug:

(1) Generic -- 1-leucovorin calcium tablets and injection

(2) Trade -- Isovorin tablets and injection

B. Pharmacologic category: folic acid derivative

C. Formulation:

(5) Each — 50 and — mg vial of 1-leucovorin calcium for injection when reconstituted with — 5 and — ml, respectively, of sterile diluent yields an 1-leucovorin concentration of 10 mg/ml.

C. Proposed Indications: "ISOVORIN rescue is indicated after high-dose methotrexate therapy in osteosarcoma. ISOVORIN is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists."

b(4)

b(4)

D. Dosage and route of administration: "The recommendations for 1-leucovorin rescue are based on a methotrexate dose of 12 grams/m² administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information). 1-Leucovorin rescue at a dose of 7.5 mg (approximately 5 mg/m²) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion.

b(4)

"Serum creatinine and methotrexate levels should be determined at least once daily. ISOVORIN administration, hydration, and urinary alkalinization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5×10^{-8} (0.05 micromolar). The ISOVORIN dose should be adjusted or rescue extended based on the following guidelines:

"Normal methotrexate elimination: If serum methotrexate level is approximately 10 micromolar at 24 hours after administration, 2 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours, then ISOVORIN should be given 7.5 mg PO or IV q 6 hours for 60 hours (10 doses starting at 24 hours after the start of methotrexate infusion).

"Delayed methotrexate elimination: If serum methotrexate level remains above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration, then ISOVORIN should be given 7.5 mg PO or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.

"Delayed early methotrexate elimination and/or evidence of acute renal injury: If serum methotrexate level is 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration; or if there is a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more), then ISOVORIN should be given 75 mg IV q 3 hours, until methotrexate level is less than 1 micromolar; then 7.5 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar."

For the injectable form:

doses greater than 10 mg/m² are not recommended.

b(4)

Because of the Ca⁺⁺ content of the 1-leucovorin solution, no more than 16 ml should be injected intravenously per minute."

E. Rationale for the use of leucovorin: Methotrexate is a potent inhibitor of the enzyme dihydrofolate reductase (DHFR), a key enzyme in intracellular folate metabolism. In cells that are actively dividing, the synthesis of thymidylic acid (required for DNA repair and replication) involves oxidation of a tetrahydrofolate cofactor (5,10-methylenetetrahydrofolate) to dihydrofolic acid, an inactive form of folate. The catalytic activity of DHFR is required to convert dihydrofolic acid back to tetrahydrofolic acid, which can then be converted to other active forms of this cofactor. When DHFR is inhibited by methotrexate, inactive dihydrofolic acid accumulates while active tetrahydrofolate derivatives are depleted; this results in the inhibition of all of the metabolic processes which require reduced folate cofactors, including the synthesis of thymidylate.

Leucovorin is used clinically to diminish the predictable hematologic and clinical toxicity of methotrexate ("rescue"). Leucovorin is converted to 5,10-methylenetetrahydrofolate and then to other tetrahydrofolates, thus replenishing the pools of reduced folate cofactors which are depleted in cells exposed to antifolates.

Other mechanisms may contribute to the clinical efficacy of leucovorin in methotrexate rescue, as follows:

(1) Leucovorin competes with methotrexate for the membrane reduced-folate carrier, which is responsible for the active transport of both of these compounds into the cell. Since the intracellular level of methotrexate represents a balance between the rate of cellular uptake of this drug and the rate at which it exits the cell, reduced uptake of methotrexate by this mechanism could result in more rapid reduction in the intracellular methotrexate concentration.

(2) Leucovorin competes with methotrexate at the level of folyl polyglutamate synthase. This enzyme converts folates (and methotrexate) to polyglutamate derivatives, which are more active biologically than are the parent compounds.

(3) Leucovorin metabolites may displace methotrexate from DHFR, thus reactivating this enzyme and allowing it to rapidly catalyze the conversion of accumulated (inactive) dihydrofolic acid to tetrahydrofolic acid, causing rapid replenishment of active folate cofactor pools in the cell.

F. Related IND:

b(4)

2. MANUFACTURING CONTROLS (See Chemistry Review)

3. PHARMACOLOGY (See Pharmacology and Biopharmaceutics Reviews)

A. In vitro studies

The efficacy of the l- and d-isomers of leucovorin has been compared to the mixture of diastereoisomers in cell lines. Measures of efficacy include restoration of normal thymidylate biosynthesis in folate-deficient cells, rescue from methotrexate toxicity, enhancement of cytotoxicity or inhibition of thymidylate synthase in cells treated with 5-FU, and competition with methotrexate for membrane transport and folyl polyglutamate synthesis.

1. Folate-deficient cells

In folate-deficient cells, thymidylate biosynthesis can be restored to normal when l-leucovorin is present at concentrations ranging from 5×10^{-9} to 10^{-8} M; d,l-leucovorin is effective when the concentration of l-leucovorin is 2.5×10^{-8} M. The d-isomer is not effective even at the highest concentration tested, which was 10^{-5} M (Submitted monograph, J. Zittoun, '90). In other studies, the d-isomer either fails to promote the growth of folate-depleted human cells ("The expanding role of folates and fluoropyrimidines in cancer chemotherapy," Roswell Park, p.13, '88) or does so only at a concentration 100 times greater than that of l-leucovorin (Invest New Drugs 7:382, '89). Activity seen with the d-isomer at high doses is considered possibly due to contamination with l-leucovorin. The d-isomer supports the growth of folate-requiring microorganisms only at a concentration 600 times greater than that of l-leucovorin (Analyt Biochem 154:516, '86).

2. Methotrexate rescue

In cells treated with methotrexate, l- and d,l-leucovorin are effective in returning thymidylate synthesis to normal when concentrations are 100 times higher than those of methotrexate. d-Leucovorin is effective only when tested at a concentration 1000 times higher than that of methotrexate (Submitted monograph, J. Zittoun, '90). Other studies with methotrexate and leucovorin in murine tumor cells (Biochem Pharm 28:2993, '79) and human leukemia cells (Analytic Biochem 168:398, '88; Proc AACR 28:275, '87) indicate that the l-isomer of leucovorin accounts for the efficacy of d,l-leucovorin in rescue from methotrexate toxicity.

3. Potentiation of 5-FU

Cytotoxicity of 5-FU or 5-fluorouridine increases when cells are pre-incubated in l- or d,l-leucovorin, but d-leucovorin has no effect. Increased

inhibition of thymidylate synthase has also been demonstrated when cells treated with 5-FU are pre-incubated in l- or d,l-leucovorin; d-leucovorin does not enhance the inhibition (Submitted monograph, J. Zittoun, '90). In addition, other studies with fluoropyrimidines indicate that the l-isomer accounts for the potentiation of the inhibitory effect of fluorodeoxyuridine on the growth of human hepatoma cells and potentiates the inhibition of thymidylate synthase (Proc AACR 26:245, '85).

4. Competition with methotrexate for membrane transport

Leucovorin can compete with methotrexate for the membrane reduced-folate carrier; this appears to be almost entirely due to the l-component of d,l-leucovorin. The d-isomer is a relatively ineffective competitor for transport. In 3 animal cell lines, d-leucovorin was 20-fold less effective than l-leucovorin in inhibiting cellular methotrexate uptake (Biochem Pharmacol 28:2993, '79).

5. Competition with methotrexate for folyl polyglutamate synthesis

Leucovorin can compete with methotrexate at the level of folyl polyglutamate synthase, the enzyme that catalyzes the intracellular metabolism of folates and methotrexate to active polyglutamate derivatives. The d-isomer of leucovorin is a substrate for folyl polyglutamate synthase, but l-leucovorin is a much better substrate for this enzyme, having a 15-fold greater affinity (Proc AACR 25:312, '84).

6. Leucovorin displacement of methotrexate from DHFR

Although there is apparently no published information regarding the relative abilities of the l- and d-isomers of leucovorin to displace methotrexate from its binding site on DHFR, 5-methyltetrahydrofolate and polyglutamated reduced folates are more effective than unmodified reduced folates in the displacement process (Cancer Res 44:2325, '84). Since only the l-isomer of leucovorin is metabolized to 5-methyltetrahydrofolate, and since it is more efficiently polyglutamated, the presumption is that the l-isomer plays a much larger role than the d-isomer in displacing methotrexate from DHFR.

B. In vivo studies

A study in mice given leucovorin shows that l-leucovorin is more than twice as effective in diminishing the toxicity of methotrexate as an equal amount of d,l-leucovorin (Cancer Treat Rep 65:1117, '81). Toxicology

studies in mice (detailed in section 4C below) have demonstrated that the l-isomer of leucovorin is the pharmacologically active component in diminishing the toxicity of methotrexate. It was shown that the d-isomer does not contribute to the reversal of methotrexate toxicity and that the l-isomer can potentiate the toxicity of 5-FU in mice (Submitted monograph, Lederle).

4. TOXICOLOGY

A. Single-dose

1. Mouse -- oral. In one study, single gavage doses of 2500 mg/kg of l-leucovorin alone or 5000 mg/kg of d,l-leucovorin were administered to groups of 10 mice. All animals survived the 15-17 day study period. Clinical signs observed were squinting and decreased motor activity. There were no gross postmortem findings.

2. Mouse -- intravenous. Single intravenous doses of l-leucovorin alone or as d,l-leucovorin were given to groups of 5 mice/group. Toxic signs observed immediately after dosing were sedation, tremor, convulsion and death. There were no gross postmortem findings. The LD50 of l-leucovorin was 575 mg/kg when given alone and 370 mg/kg when given in combination with the d-isomer.

3. Rat -- oral. Single gavage doses of 2500 mg/kg of l-leucovorin alone or 5000 mg/kg of d,l-leucovorin were administered to groups of 10 rats. There was no mortality during the 15 day study period. Decreased motor activity was observed after dosing. There were no gross postmortem findings.

4. Rat -- intravenous. Single intravenous doses of l-leucovorin alone or as d,l-leucovorin were administered to groups of 5 rats. Toxic signs seen immediately after dosing were decreased motor activity, prostration, labored breathing, convulsion and death. There were no gross postmortem findings. The LD50 of l-leucovorin was 378 mg/kg when given alone, and 255 mg/kg when given as d,l-leucovorin.

B. Multiple-dose

1. Dog -- 1 month intravenous. Beagle dogs 3/group were dosed intravenously twice daily for 1 month at doses of 15, 30 or 60 mg/kg/day of l-leucovorin. Another group received 120 mg/kg/day of d,l-leucovorin. There were no drug-related findings.

C. Studies with methotrexate and leucovorin

1. Mouse -- po methotrexate with po leucovorin.

Gavage doses of methotrexate (200 or 400 mg/kg/day) were followed 4-5 hours later by gavage doses of l-leucovorin (100 or 200 mg/kg/day) for 5 days. All mice that received methotrexate alone died by day 10. No treatment-related mortality occurred in mice given the methotrexate/l-leucovorin combinations.

2. Mouse -- po methotrexate with ip leucovorin.

Oral doses of methotrexate 200 mg/kg followed 4 to 6 hours later by ip doses of l-leucovorin (3, 10, 30 or 100 mg/kg), d-leucovorin (100 mg/kg) or d,l-leucovorin (6, 20, 60 or 154 mg/kg) were given to 10 mice/group for 5 days. There were no survivors in the group that received methotrexate alone, but rescue from most animals who received either d,l- or l-leucovorin survived, without significant differences between these two groups in survival rates. The d-isomer was ineffective in preventing methotrexate mortality.

5. ANIMAL PHARMACOKINETICS

In dogs infused intravenously with d,l-leucovorin, the l-isomer of leucovorin had a half-life of 47 minutes compared to 143 minutes for the d-isomer. Renal clearance was the same for both isomers. Urinary excretion appeared to be the only route of elimination of the d-isomer. In addition to urinary excretion, the l-isomer is extensively metabolized to components that are associated with normal biosynthetic pathways. The apparent volume of distribution is about 58% of body weight for both isomers.

6. HUMAN PHARMACOKINETICS

The d-isomer of leucovorin is not metabolized to any significant degree by humans and is not taken up in tissues; pharmacokinetic data indicate that d-leucovorin remains largely within the central compartment and is eliminated unchanged by the kidneys (Cancer Res 44:3114, '84; J Chromatog 424:158, '88).

A. Absolute bioavailability

Thirty-three adult males completed a study in which the bioavailability parameters were compared between 15 mg oral and IV doses of l-leucovorin and between 30 mg oral and IV doses of d,l-leucovorin. Serum concentrations of total tetrahydrofolate were determined. The mean absolute bioavailability for the oral l-leucovorin tablet compared with the IV l-leucovorin formulation was 74.3% (90% CI 65.1% to 77.6%). The mean absolute bioavailability for the corresponding d,l-leucovorin tablet and IV formulations was 65.4% (90% CI 57.8% to 68.9%).

In an extension of this study 18 men received either 22.5 mg (3 7.5-mg tablets) or 30 mg (4 7.5-mg tablets) of l-leucovorin. Mean absolute bioavailabilities were 72.4% and 36.7%, respectively, suggesting a saturation of intestinal transport of l-leucovorin, similar to that which is seen with d,l-leucovorin.

B. Bioequivalence

Bioequivalence was measured in 35 adult males for the following comparisons: l-leucovorin 12.5 mg (5 2.5-mg tablets) vs. d,l-leucovorin 25 mg (5 5-mg tablets); and l-leucovorin 12.5 mg (1 12.5 mg tablet) vs. d,l-leucovorin 25 mg (1 25-mg tablet). Measured total tetrahydrofolate and 5-methyl tetrahydrofolate C_{max} and AUC_{0-24} averaged about 12% less with the l-leucovorin preparations, compared to the d,l- preparations. In a separate comparison of l-leucovorin 15 mg (2 7.5-mg tablets) and d,l-leucovorin 30 mg (2 15-mg tablets) there were no significant differences between C_{max} and AUC values.

C. Chart of bioequivalence and bioavailability data submitted by the company

Protocol number (N)	Treatment	Assay Method	Mean (SD) Pharmacokinetic Parameters				
			C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	K_{el} (h ⁻¹)
76-3-1 (33)	l-leucovorin 15 mg (IV injection)	RIA ^a	275(48)	0.8(0.8)	1817(338)	2135(400)	0.10(0.02)
		Micro ^b	1722(888)	0.2(0.2)	3175(812)	3308(833)	0.15(0.04)
	l-leucovorin 15 mg (Two 7.5-mg tablets)	RIA	287(45)	2.8(0.5)	1801(304)	2084(384)	0.12(0.02)
		Micro	383(84)	2.7(0.7)	2312(604)	2421(650)	0.15(0.04)
	d,l-leucovorin 30 mg (IV injection)	RIA	328(51)	0.8(0.2)	2173(301)	2417(332)	0.10(0.01)
		Micro	1817(480)	0.2(0.1)	3776(845)	3837(882)	0.14(0.02)
	d,l-leucovorin 30 mg (Two 15-mg tablets)	RIA	287(82)	2.8(0.8)	1820(304)	2103(362)	0.12(0.04)
		Micro	382(77)	2.5(1.0)	2358(575)	2485(604)	0.14(0.02)
76-4-1 (35)	l-leucovorin 12.5 mg (Five 2.5-mg tablets)	RIA	247(41)	2.8(0.4)	1745(331)	1852(383)	0.10(0.02)
		Micro	352(55)	2.1(0.4)	1842(326)	1904(339)	0.16(0.05)
	d,l-leucovorin 25 mg (Five 5-mg tablets)	RIA	278(78)	2.7(0.3)	1888(460)	2078(314)	0.10(0.03)
		Micro	388(84)	2.2(0.4)	2038(470)	2107(488)	0.16(0.08)
	l-leucovorin 12.5 mg (One 12.5-mg tablet)	RIA	248(39)	2.7(0.5)	1708(278)	1803(343)	0.10(0.02)
		Micro	365(88)	2.2(0.4)	1887(458)	1958(473)	0.16(0.05)
	d,l-leucovorin 25 mg (One 25-mg tablet)	RIA	281(71)	2.8(0.4)	1813(357)	2127(407)	0.10(0.02)
		Micro	387(75)	2.3(0.4)	2078(436)	2171(448)	0.14(0.08)

7. CLINICAL STUDIES

A. Background. The data submitted in the NDA come from 2 types of studies. First, l-leucovorin is compared with d,l-leucovorin for rescue from high-dose methotrexate in patients with osteosarcoma, which is intended to provide safety and efficacy information relevant to the proposed indications. The data come from studies using 5 different chemotherapy regimens, utilizing 3 different leucovorin rescue protocols. The rescue protocols are referred to as the POG study, the TIOS-III study, and the OS-86 study.

Second, data are submitted to present supportive safety data from clinical trials using l-leucovorin in combination with 5-FU for the treatment of gastrointestinal cancers. Since this use is outside the proposed indication, and has no bearing on the drug's safety and efficacy in methotrexate rescue, these data will not be discussed further.

B. Osteosarcoma studies -- design

1. POG study. Title: High-dose methotrexate with leucovorin rescue in pediatric osteosarcoma patients treated according to pediatric oncology group protocols 8759, 8651 and 8107 -- a comparison of efficacy/safety in patients treated with l-leucovorin and historical controls treated with d,l-leucovorin.

a. Objective. The objective was to determine the efficacy and safety of l-leucovorin (at one half the appropriate d,l-leucovorin dose) in comparison with the efficacy and safety of d,l-leucovorin in methotrexate rescue for the treatment of patients with osteosarcoma.

b. Rationale. The currently marketed preparations of leucovorin used for methotrexate rescue contain equal amounts of the d- and l- diastereoisomers. The l-isomer is thought to account for virtually all of the efficacy of d,l-leucovorin in methotrexate rescue, so l-leucovorin (at one half the d,l-leucovorin dose) was expected to have clinical effectiveness equal to that of d,l-leucovorin in methotrexate rescue.

c. Eligibility criteria. Patients were required to be between 10 and 30 years old with biopsy-proven, high-grade or metastatic osteosarcoma. Patients entered into POG protocols 8107 and 8651 had no prior therapy, while those entered into protocol 8759 had no previous treatment with ifosfamide. Protocols also specified that patients have normal renal and hepatic function, a WBC count >4000, a platelet count >100,000, and a performance status <2. In addition, prior to treatment

with high-dose methotrexate and leucovorin, all patients needed to have: an absolute neutrophil count >200 , WBC >1500 , platelets $>75,000$, serum creatinine increased $<50\%$ over baseline or creatinine clearance >50 ml/min/1.73 m² (>60 in protocol 8107), bilirubin <1.2 , SGOT <500 (for protocol 8107 SGOT and SGPT <450), no mucositis, and for protocol 8651 and 8759, no nonsteroidal antiinflammatory drugs for at least 1 week.

d. Procedure. The following chemotherapy regimens were used for the study, according to 3 separate protocols.

1. POG protocol 8651.

(a) Regimen. This protocol compared adjuvant and neoadjuvant chemotherapy in nonmetastatic osteosarcoma. Neoadjuvant chemotherapy was begun 10 weeks before surgery, and adjuvant therapy started as soon as possible (not later than 3 weeks) after surgery. The same chemotherapy regimen was used for both neoadjuvant and adjuvant therapy. The regimen is as follows:

Treatment	Dose	Week
HDMTX (neoadjuvant)	12 g/m ²	0,1
(adjuvant)		3,4
Doxorubicin (neoadjuvant)	75 mg/m ²	2
Cisplatin (adjuvant)	120 mg/m ²	5
HDMTX (neoadjuvant)	12 g/m ²	5,6
(adjuvant)		8,9
Doxorubicin (neoadjuvant)	75 mg/m ²	7
Cisplatin (adjuvant)	120 mg/m ²	10
HDMTX	12 g/m ²	13,14
Bleomycin	15 U/m ² /day x 2	15
Cyclophosphamide	600 mg/m ² /day x 2	
Dactinomycin	0.6 mg/m ² /day x 2	
HDMTX	12 g/m ²	18,19

Doxorubicin	30 mg/m ² /day x 3	20
HDMTX	12 g/m ²	23,24
Doxorubicin	75 mg/m ²	25,28
Cisplatin	120 mg/m ²	
Bleomycin	15 U/m ² /day x 2	31,34
Cyclophosphamide	600 mg/m ² /day x 2	
Dactinomycin	0.6 mg/m ² /day x 2	
HDMTX	12 g/m ²	37,38
Bleomycin	15 U/m ² /day x 2	39,42
Cyclophosphamide	600 mg/m ² /day x 2	
Dactinomycin	0.6 mg/m ² /day x 2	

Abbreviation: HDMTX - high-dose methotrexate with leucovorin rescue.

(b) Dosage and administration of high-dose methotrexate with leucovorin rescue. The regimen used was as follows: A maintenance infusion of sodium bicarbonate and KCl in 5% dextrose in water was administered at a rate of 250 mL/1m²/h for 2 hours, then at 125 mL/m²/h for 4 hours. At the start of the prehydration period, allopurinol was given orally at a dose of 300 mg and then continued at 100mg three times daily for 12 doses. Six hours after the start of the maintenance infusion, methotrexate (12 g/m² dissolved in 500 mL/m² of 5% dextrose in water with 40 mEq/L of sodium bicarbonate) was administered over a 4-hour period. At the end of the methotrexate infusion, the maintenance infusion was reinstituted at 125 mL/m²/h. Twenty hours after completion of the methotrexate infusion, leucovorin rescue was initiated (15 mg of d,l-leucovorin or 7.5 mg of l-leucovorin administered either orally, intravenously, or intramuscularly every 6 hours for 10 doses).

The serum concentrations of methotrexate were to be determined at 24, 48, and 72 hours after the end of the methotrexate infusion. In the case of mild toxicity (serum level of methotrexate above the shaded area of Fig 1 (page 13) but below the solid line accompanied by a serum creatinine increase of 25% to 50%), no intervention was required. In the event of moderate toxicity, ie, serum concentrations of methotrexate above the shaded area of Fig 1 but below the solid line and with an increase in serum creatinine of 50% to 100% and evidence of stomatitis or myelosuppression sufficient to cause a delay in treatment, leucovorin rescue was increased by an additional 15 mg (for d,l-) or 7.5 mg (for l-) every 6 h for 1 day. In the event of delayed late excretion of

methotrexate (serum concentration of methotrexate $> 0.2 \mu\text{M}$ at 72 h or $> 0.05 \mu\text{M}$ at 96 h), hydration and alkalinization were continued with leucovorin rescue until the concentration of methotrexate was $< 0.05 \mu\text{M}$. In the event of severe toxicity (serum concentration of methotrexate above the solid line in Fig 1 [$> 50 \mu\text{M}$ at 24 h or $> 5 \mu\text{M}$ at 48 h with an increase in serum creatinine $> 100\%$]), administration of leucovorin at 150 mg (for d,l-) or 75 mg (for l-) intravenously every 3 h was promptly instituted and continued until the serum concentration of methotrexate was reduced to below $1 \mu\text{M}$. Leucovorin was then administered at 15 mg (for d,l-) or 7.5 mg (for l-) every 3 h until the serum concentration of methotrexate was below $0.05 \mu\text{M}$.

(c) Evaluation of efficacy and safety of leucovorin rescue. The schedule of laboratory assessments was as follows:

Schedule of Assessments

Procedure	HDMTX	24h	48h	72h	Day 7
History and physical exam	x				x
Performance status	x				x
Details of prior treatment	x				x
Weight/body surface area	x				x
Hematology (CBC with differential, platelets)	x				x
Blood chemistry ^a	x				x
Urinalysis	x				x
Methotrexate concentration, serum creatinine, BUN		x	x	x	x

^aSGOT, SGPT, LDH, total bilirubin, direct bilirubin, BUN, serum creatine, serum electrolytes, blood glucose.

Any clinical or laboratory evidence of toxicity was followed by repeat assessments until resolved.

2. POG Protocol 8107.

(a) Regimen. This protocol was designed to evaluate the effect of the timing of the administration of chemotherapy on disease-free survival of patients with nonmetastatic osteosarcoma; chemotherapy was given either shortly after surgical removal of the primary tumor or after eventual relapse and surgery to remove metastases. The same chemotherapy regimen was used for both treatment groups and was as follows:

Treatment	Dose	Week
Bleomycin	15 U/m ² /day x 2	0
Cyclophosphamide	600 mg/m ² /day x 2	
Actinomycin D	0.6 mg/m ² /day x 2	
HDMTX	12 g/m ²	2,3, 4,5
Doxorubicin	30 mg/m ² /day x 3	6
HDMTX	12 g/m ²	9,10
Bleomycin	15 U/m ² /day x 2	11
Cyclophosphamide	600 mg/m ² /day x 2	
Actinomycin D	0.6 mg/m ² /day x 2	
HDMTX	12 g/m ²	13,14
Doxorubicin	30 mg/m ² /day x 3	15
Doxorubicin	50 mg/m ²	18,21
Cisplatin	100 mg/m ²	
Bleomycin	15 U/m ² /day x 2	24
Cyclophosphamide	600 mg/m ² /day x 2	
Actinomycin D	0.6 mg/m ² /day x 2	
HDMTX	12 g/m ²	27,28
Doxorubicin	50 mg/m ²	31,34
Cisplatin	100 mg/m ²	
Bleomycin	15 U/m ² /day x 2	37,40
Cyclophosphamide	600 mg/m ² /day x 2	
Actinomycin D	0.6 mg/m ² /day x 2	
HDMTX-LCV	12 g/m ² - 15 mg q 6h x 10	42,43

(b) Dosage and administration of high-dose methotrexate with leucovorin rescue. The regimen was the same as for POG protocol 8651.

(c) Evaluation of efficacy and safety of methotrexate rescue. The schedule of laboratory assessment was the same as for POG protocol 8651.

3. POG protocol 8759.

(a) Regimen. This protocol was designed to evaluate a combination chemotherapy regimen in the treatment of patients having metastatic, unresectable or recurrent osteosarcoma, and was as follows:

Treatment	Dose	Week
Ifosfamide-mesna	2400 mg/m ² /day x 5 480 mg/m ² /day x 5 (surgery at week 0)	-6, -3
HDMTX	12 g/m ²	1, 2
Doxorubicin Cisplatin	37.5 mg/m ² 60 mg/m ²	3
HDMTX	12 g/m ²	6, 7
Ifosfamide-mesna	2400 mg/m ² /day x 5 480 mg/m ² /day x 5	8
HDMTX	12 g/m ²	11, 12
Doxorubicin Cisplatin	37.5 mg/m ² 60 mg/m ²	13
HDMTX	12 g/m ²	16, 17
Ifosfamide-mesna	2400 mg/m ² /day x 5 480 mg/m ² /day x 5	18
HDMTX	12 g/m ²	21, 22
Doxorubicin Cisplatin	37.5 mg/m ² 60 mg/m ²	23
Ifosfamide-mesna	2400 mg/m ² /day x 5 480 mg/m ² /day x 5	26
Doxorubicin Cisplatin	37.5 mg/m ² 60 mg/m ²	29
Ifosfamide-mesna	2400 mg/m ² /day x 5 480 mg/m ² /day x 5	32
HDMTX	12 g/m ²	35, 36
Doxorubicin	30 mg/m ² /day x 3	37
Ifosfamide-mesna	2400 mg/m ² /day x 5 480 mg/m ² /day x 5	40

(b) Dosage and administration of high-dose methotrexate with leucovorin rescue. The regimen was the same as that used for POG protocol 8651.

(c) Evaluation of efficacy and safety of leucovorin rescue. The schedule of laboratory assessments was the same as that used for POG protocol 8651.

2. TIOS-III study. Title: High-dose methotrexate with leucovorin rescue in pediatric osteosarcoma patients treated according to MD Anderson Cancer Center Protocol TIOS-III.

a. Objective. Same as POG study.

b. Rationale. Same as POG study.

c. Eligibility criteria. Patients could be entered at any time during their sequence of chemotherapy treatments. Eligible were newly diagnosed patients with osteosarcoma and previously treated patients who did not appear to have had previous aggressive chemotherapy with cisplatin, doxorubicin, methotrexate or cyclophosphamide. Patients were excluded who were: over 16 or pregnant; or who had a serum bilirubin over 1.2, LDH and SGOT over 3x normal, WBC under 1000, platelets under 50,000, dehydration, creatinine clearance below 60/m², severe infection, present, suspected or anticipated methotrexate toxicity, ascites or pleural effusion.

d. Procedure

1. Regimen. In the TIOS-III study, patients eligible for limb conservation received induction therapy with 7 courses of intra-arterial cisplatin 150 mg/m² every 2 weeks. After completion of induction therapy, patients were treated according to Regimen E:

Treatment	Dose	Week
Doxorubicin	40 mg/m ²	1, 4, 7, 10, 13
Cyclophosphamide	600 mg/m ²	
Cisplatin	150 mg/m ²	17, 20, 23, 26, 29
Doxorubicin	40 mg/m ²	32, 35, 38, 41, 44
Cyclophosphamide	600 mg/m ²	
Cisplatin	150 mg/m ²	47, 50, 53, 56, 59

Doxorubicin	40 mg/m ²	62, 65, 68, 41, 44
Cyclophosphamide	600 mg/m ²	
HDMTX	12.5 g/m ²	71, 72
Cyclophosphamide	600 mg/m ²	73
HDMTX	12.5 g/m ²	76, 77
Cyclophosphamide	600 mg/m ²	78
HDMTX	12.5 g/m ²	81, 82, 83, 84

Reinforcement treatment with intra-arterial cisplatin every 6 months for 2 years was recommended as a holding action until patients became eligible for limb salvage.

2. Dosage and administration of high-dose methotrexate with leucovorin rescue. The regimen was as follows: A maintenance infusion of 5% dextrose in 1/4 normal saline with sodium bicarbonate and KCl was administered at a rate of 3 L/m²/24 hours and was continued until completion of leucovorin rescue. Beginning 4 to 6 hours after the start of the saline infusion, methotrexate (12.5 g/m² dissolved in 600 mL of 5% dextrose in water) was administered over a 6-hour period. Twelve hours after completion of the methotrexate infusion, leucovorin rescue was initiated (15 mg of d,l leucovorin or 7.5 mg of l-leucovorin, administered intravenously every 3 hours for 18 doses). The serum concentrations of methotrexate were determined at 24, 48, and 72 hours after the beginning of the methotrexate infusion. The expected values were as follows:

Time (hours)	Expected serum concentration of MTX (umole/L)
24	30-300
48	3-30
72	< 0.3

If the methotrexate concentration was >30 umole/L at 48 hours or > 0.3 umole/L at 72 hours, the following measures were instituted: (1) the rate of the saline infusion was increased to 4 L/m²/24 hours and (2) leucovorin was administered intravenously as 50 mg of l-leucovorin or 100 mg of d,l-leucovorin every 3 hours until the serum concentration of methotrexate was below 0.3 umole/L. This escalated dose of leucovorin was then used for the patient's subsequent courses of HDMTX-LCV.

3. Evaluation of efficacy and safety of leucovorin rescue. The schedule of laboratory assessments is the same as for the POG study.

3. OS-86 study. Title: High-dose methotrexate with leucovorin rescue in pediatric osteosarcoma patients treated according to St. Jude Children's Hospital protocol OS-86.

a. Objective. Same as POG protocol.

b. Rationale. Same as POG protocol.

c. Eligibility criteria. At any time during the course of their chemotherapy, patients could be entered onto the protocol specifying l-leucovorin in place of d,l leucovorin. Patients were required to have osteosarcoma, either potentially resectable or unresectable primary lesions or with metastatic disease. In addition, patients were to have had no prior chemotherapy, WBC >3500, platelets >150,000, normal liver function tests, creatinine <1.5, normal urinalysis, normal echocardiogram, and on days of treatment with methotrexate WBC >1000, platelets >75,000, bilirubin <1.2, SGOT and SGPT <450.

d. Procedure

1. Regimen. The OS-86 study specified 3 courses of ifosfamide followed by 3 courses of high-dose methotrexate-leucovorin, a course of doxorubicin, and subsequent courses of cisplatin and doxorubicin, ifosfamide, and high-dose methotrexate-leucovorin. Mesna was given with ifosfamide. The sequence of administration of chemotherapeutic agents was as follows:

Treatment	Dose	Week
Ifosamide-	1.6 g/m ² /day x 5	0,3,6
Mesna	400 mg/m ² /dose, 0,4,6 h after ifosamide	
HDMTX	12 g/m ²	7,8,9
Doxorubicin	30 mg/m ² /day x 3	10 (surgery at week 13 or 14)
Cisplatin	100 mg/m ²	15
Doxorubicin	37.5 mg/m ² x 2	

Ifosamide-	1.6 g/m ² /day x5	18
Mesna	400 mg/m ² /dose, 0,4,6 h after ifosamide	
HDMTX	12 g/m ²	19,20,21
Cisplatin	100 mg/m ²	22
Doxorubicin	37.5 mg/m ² x 2	
Ifosamide	1.6 g/m ² /day x 5	25
Mesna	400 mg/m ² /dose, 0,4,6 h after ifosamide	
HDMTX	12 g/m ²	26,27,28
Cisplatin	100 mg/m ²	29,32
Doxorubicin	37.5 mg/m ² x 2	

2. Dosage and administration of high-dose methotrexate with leucovorin rescue. Hydration fluids were administered intravenously as follows: 5% dextrose in water plus 40 mEq/L of NaHCO₃ and 20 mEq/L of KCl was administered at an infusion rate of 250 mL/m²/hour for 2 hours, followed by the same fluid at 125 mL/m²/hour for 4 hours. The urine pH was checked with each void and had to be > 6.5 for the patient to receive methotrexate. If the urine pH was < 6.5, 20 mEq of NaHCO₃ was given.

After the initial hydration procedure, methotrexate (12 g/m² dissolved in 500 mL/m² of dextrose in water plus 40 mEq/L of NaHCO₃) was infused over a 4-hour period. After administration of methotrexate, infusion of the dextrose-NaHCO₃ intravenous fluid was continued at 125 mL/m²/h for a minimum of 24 hours. Patients who could tolerate oral fluids could be discharged from the hospital at that time and were required to consume 2.4 L of fluid per m² over the following 24 hours.

Leucovorin rescue was initiated 20 hours after completion of the methotrexate infusion. A 7.5-mg dose of l-leucovorin or a 15-mg dose of d,l-leucovorin was administered orally or intravenously every 6 hours for 10 doses. In patients with stomatitis severe enough to delay subsequent chemotherapy courses, an additional four doses of leucovorin were administered, giving a total of 14 doses.

According to the OS-86 protocol, serum concentrations of methotrexate were to be determined at 0, 12, 20, 24, 34, 44, and 68 hours after the methotrexate infusion in order to determine whether changes were required in the dose or schedule of leucovorin.

Leucovorin Dosage Adjustments for Delayed Methotrexate Excretion

Serum concentration of methotrexate (uM)	<u>d,l-Leucovorin dosage^a</u>		
	Dose (mg/m ²)	Frequency (h)	Route
90 - 100	1000	3	IV
80 - 90	900	3	IV
70 - 80	800	3	IV
60 - 70	700	3	IV
50 - 60	600	3	IV
40 - 50	500	3	IV
30 - 40	400	3	IV
20 - 30	300	3	IV
15 - 20	200	3	IV
10 - 15	150	3	IV
5 - 10	100	3	IV
2 - 5	50	6	IV
1 - 2	25	6	PO or IV
0.5 - 1	15	6	PO or IV
0.1 - 0.5	15	12	PO or IV
0.05 - 0.1	5	12	PO or IV
< 0.05	Discontinue leucovorin administration		

^aThe l-leucovorin dose was one half the appropriate d,l-leucovorin dose. Frequency and route of administration were the same for d,l-leucovorin.

The expected methotrexate concentrations were < 10 uM at 20 hours, 5 uM at 24 hours, and < 1 uM at 44 hours. Depending on the methotrexate concentration, the leucovorin dosage was adjusted to provide equimolar concentrations of leucovorin using the schedule shown in Table 2.

3. Evaluation of safety and efficacy of leucovorin rescue. The schedule of laboratory assessments was the same as for the POG study.

C. Osteosarcoma studies -- evaluable patients and courses. Too few patients were treated on any one protocol to allow meaningful interpretation of trends if protocols

are considered separately. Although methotrexate doses and leucovorin dose and rescue schedules differed slightly among the protocols, they were sufficiently similar so that pooling results among them is probably justified.

Although data submitted in the NDA includes all patients and every course of treatment where methotrexate and l-leucovorin were given, many of the treatment courses are inevaluable because follow-up was incomplete. These deficiencies in the data are detailed in the "Conclusions" section of this report. Despite these deficiencies, review of all data submitted revealed no unexpected severe side effects from or lack of efficacy of l-leucovorin when used for methotrexate rescue. The results included below are those compiled by reviewing in detail each individual case report submitted. Results for severity of leukopenia and thrombocytopenia, liver function abnormalities, and for severity of mucositis, were considered evaluable only if the patient was assessed at least once 5-15 days after his/her dose of methotrexate.

Since there is evidence that leucovorin will rescue a patient from the toxicities of leukopenia, thrombocytopenia, mucositis and liver function abnormalities caused by folic acid antagonists, the number of evaluable patients and courses measuring these parameters are included below. Comparisons of toxicities between these patients and the historical controls discussed in section 7D are provided in graph form in section 7E.

	Leukopenia	Thrombocytopenia	Mucositis
	-----	-----	-----
# Evaluable Pts	12	12	11
# Total Pts	16	16	16
# Evaluable Courses	27	27	27
# Total Courses	58	58	58

	Bilirubin	Alk Phos	SGOT	SGPT
	-----	-----	-----	-----
# Evaluable Pts	10	9	9	10
# Total Pts	16	16	16	16
# Evaluable Courses	21	20	22	23
# Total Courses	58	58	58	58

D. Osteosarcoma studies -- historical controls.
Data for control patients, treated with d,l-leucovorin were obtained retrospectively as follows. The investigator identified patients who were treated at his/her institution on the same protocol (but with d,l-leucovorin) prior to the institution of the protocol specifying l-leucovorin. The control patients had met the eligibility criteria of the protocol that was subsequently used for selection of the

patients who were treated with l-leucovorin. Data were to be obtained from 2 patients treated with d,l-leucovorin for every patient treated with l-leucovorin. The control patients' courses were to occupy the same relative position in the treatment sequence as were occupied by the l-leucovorin courses. The number of evaluable patients and courses (using the same criteria as used for the l-leucovorin studies) measuring leukopenia, thrombocytopenia, mucositis and liver function abnormalities are listed below.

	Leukopenia	Thrombocytopenia	Mucositis
	-----	-----	-----
# Evaluable Pts	25	25	26
# Total Pts	32	32	32
# Evaluable Courses	108	104	109
# Total Courses	208	208	208

	Bilirubin	Alk Phos	SGOT	SGPT
	-----	-----	-----	-----
# Evaluable Pts	22	21	23	22
# Total Pts	32	32	32	32
# Evaluable Courses	96	77	95	86
# Total Courses	208	208	208	208

E. Osteosarcoma studies -- comparison of toxicities seen after methotrexate with l- or d,l-leucovorin rescue. The graphs in the appendix on pages A-1 to A-14 compare the percentage of patients or courses in which a given degree of toxicity is seen (the most severe toxicity during a course) for l- and d,l-leucovorin. Only evaluable patients or courses, as determined above, are included. As noted, large numbers of patients and courses are inevaluable because data was not collected 5-15 days after methotrexate administration as specified by the protocol.

Other protocol violations occurred routinely as well, including: patients were not followed until resolution of toxicity; leucovorin doses and duration of treatment were often in excess of those specified by the protocol; baseline laboratory studies were often abnormal and should have made the patient ineligible for treatment. In addition, it is often not clear whether a given adverse effect was looked for and not observed, or never assessed; this was obviously the case for mucositis.

In the graphs on pages A-1 to A-14, the number of patients or courses evaluable is written in parentheses above each bar.

8. CONCLUSIONS

Preclinical *in vitro* and *in vivo* studies seem to indicate that the l-isomer of leucovorin is the active isomer, and that the d-isomer is relatively inactive.

Interpretation of the submitted clinical studies is more difficult, for the following reasons:

(1) Data are submitted for only 16 patients treated with l-leucovorin, only 9 of whom are fully evaluable for the toxicities of leukopenia, thrombocytopenia, mucositis and liver function abnormalities. Only 20 courses were evaluable for all of these toxicities.

(2) The data are marred by multiple flaws, including:

(a) the toxicities recorded were not necessarily the most severe grade experienced during a treatment course, since there is no indication that side effects were followed to their resolution;

(b) several times patients inexplicably received longer courses of leucovorin than were specified by protocol criteria;

(c) it is often unclear from reading the abstracted patient chart whether a patient was evaluated for a given side effect and deemed to be free of this effect (e.g., for mucositis), or whether the patient was never evaluated at all (when no toxicity was recorded);

(d) evaluation of a toxic effect at one point in time during a treatment course (which was often done) may well have missed severe toxicity (e.g., evaluating liver function tests on day 7 only may miss earlier enzyme elevations).

(e) some of the regimens may have over-estimated toxicity (e.g. neutropenia could have become increasingly severe in regimens where methotrexate was given weekly).

Because of these deficiencies, no quantitative comparison can be made between the relative efficacies of l- and d,l-leucovorin. To make such a comparison, a fairly large prospectively randomized trial with a homogeneous population receiving a homogeneous high-dose methotrexate regimen, followed intensively and carefully for toxicity, would need to be performed.

On the other hand, data is available on some 20 treatment courses using high-dose methotrexate and l-leucovorin rescue. The doses of methotrexate used in

these protocols would certainly have caused extremely severe toxicity to and probably death of many of the patients treated if no leucovorin were used. The data do support the claim that l-leucovorin is in general able to ameliorate the expected severe toxicity of high-dose methotrexate. From visual inspection of the charts provided in appendix B, it efficacy appears roughly comparable to that of d,l-leucovorin, but whether it is somewhat less or somewhat more efficacious cannot be determined.

Because of the strong preclinical evidence that l-leucovorin is the active isomer of leucovorin, and that the d-leucovorin present in d,l-leucovorin is not likely to add efficacy to the drug, there is compelling rationale to accept l-leucovorin (at one-half the dose of d,l-leucovorin) as a substitute for d,l-leucovorin for methotrexate rescue. The submitted clinical studies, although flawed and incomplete as noted, do provide sufficient ancillary evidence in support of this proposed indication.

9. RECOMMENDED REGULATORY ACTION

The submitted NDAs should be approved, since l-leucovorin has been shown to prevent the expected severe toxicity of high-dose methotrexate. Recommendation for approval is conditional upon FDA Biopharmaceutical review and analysis of new data submitted by the company as part of the 4-month safety update. Since the submitted clinical data are inadequate to demonstrate comparative safety and efficacy, nothing in the labeling l-leucovorin should imply that the drug has been shown to be superior or even equivalent to d,l-leucovorin.

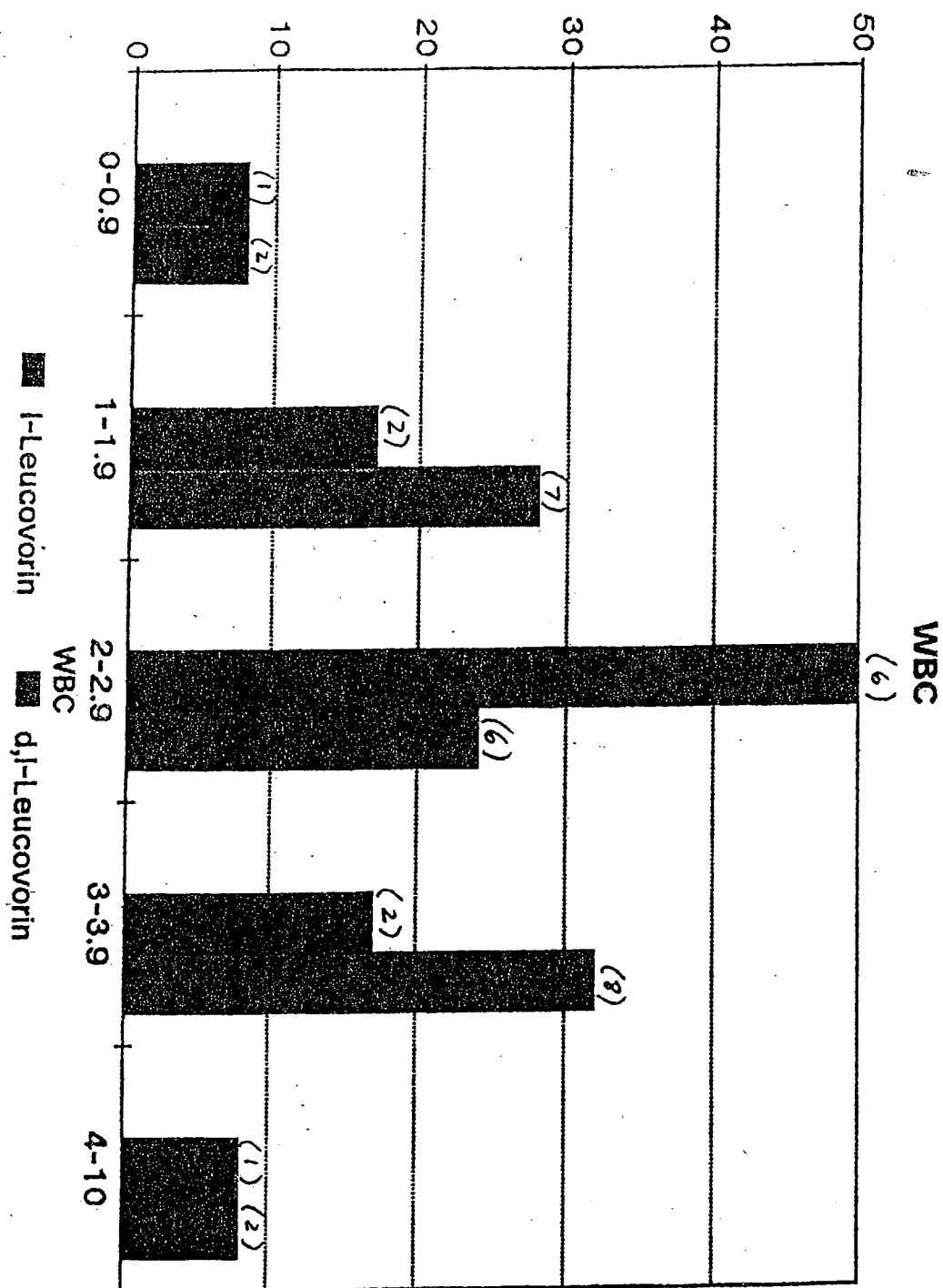
Peter B. Brett, MD
 Peter B. Brett, M.D.
 FDA/NCI Fellow
 May 30, 1991

Robert L. Justice, M.D.
 Robert L. Justice, M.D.
 Medical Officer

John R. Johnson MD
 6-4-91

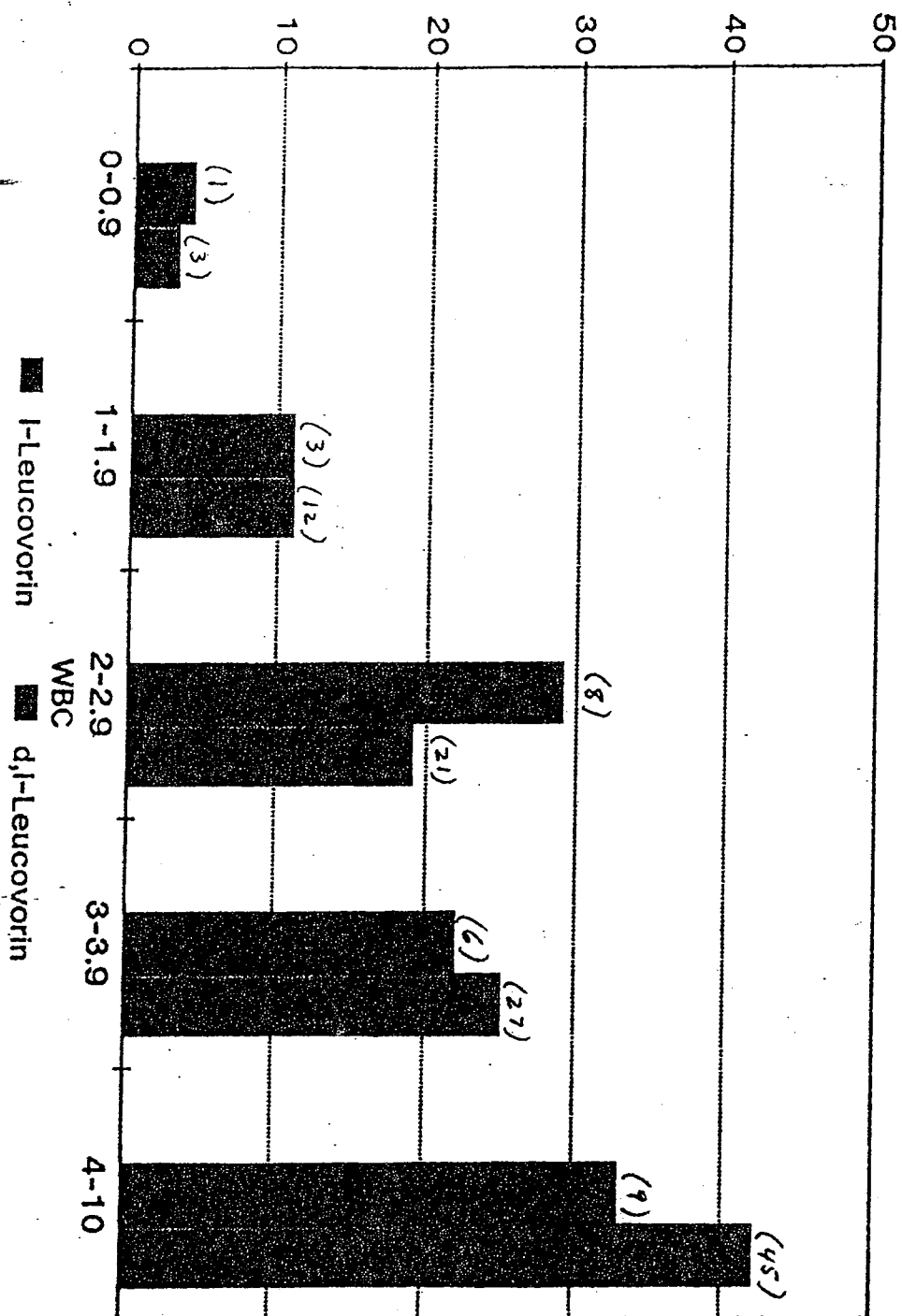
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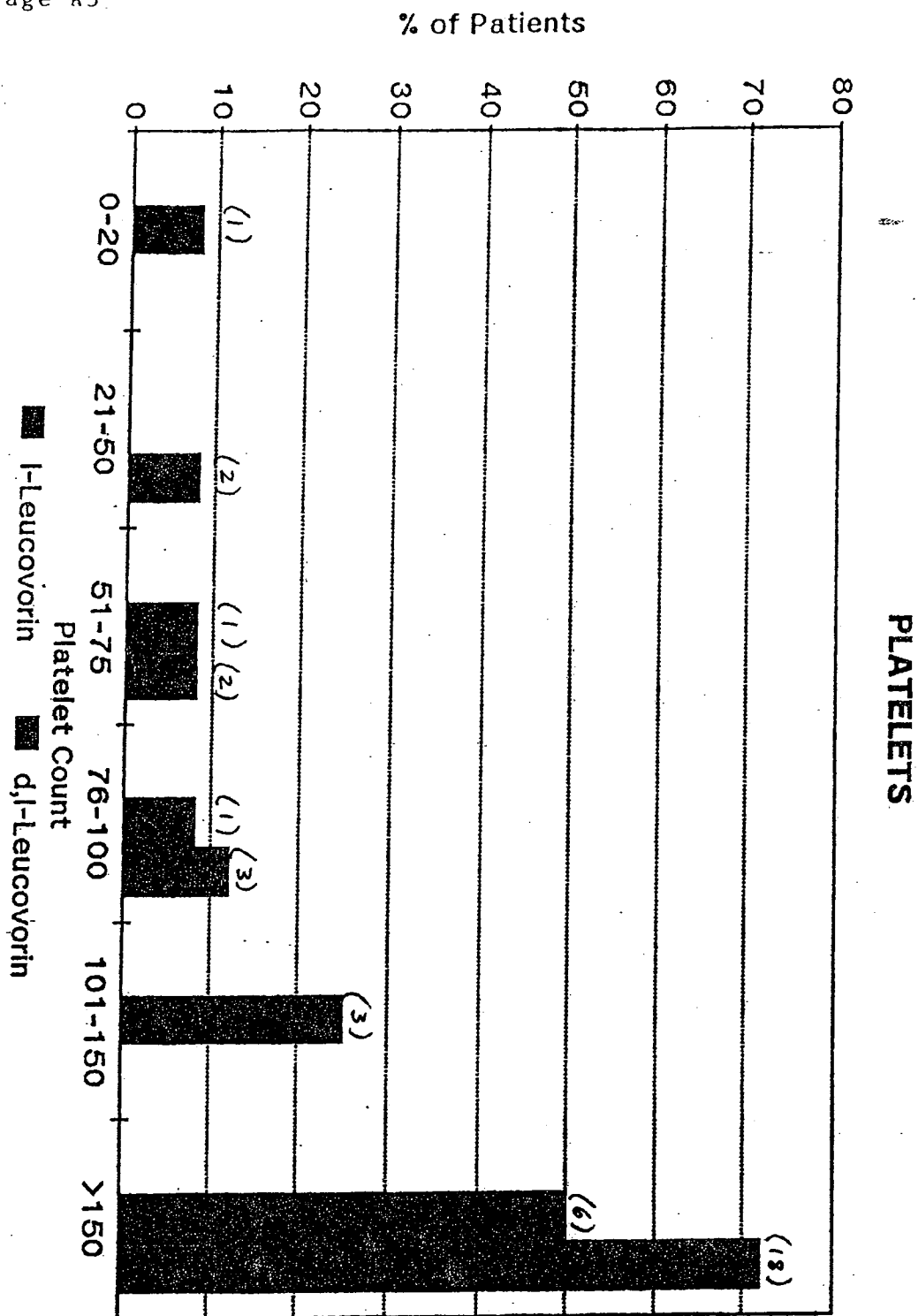
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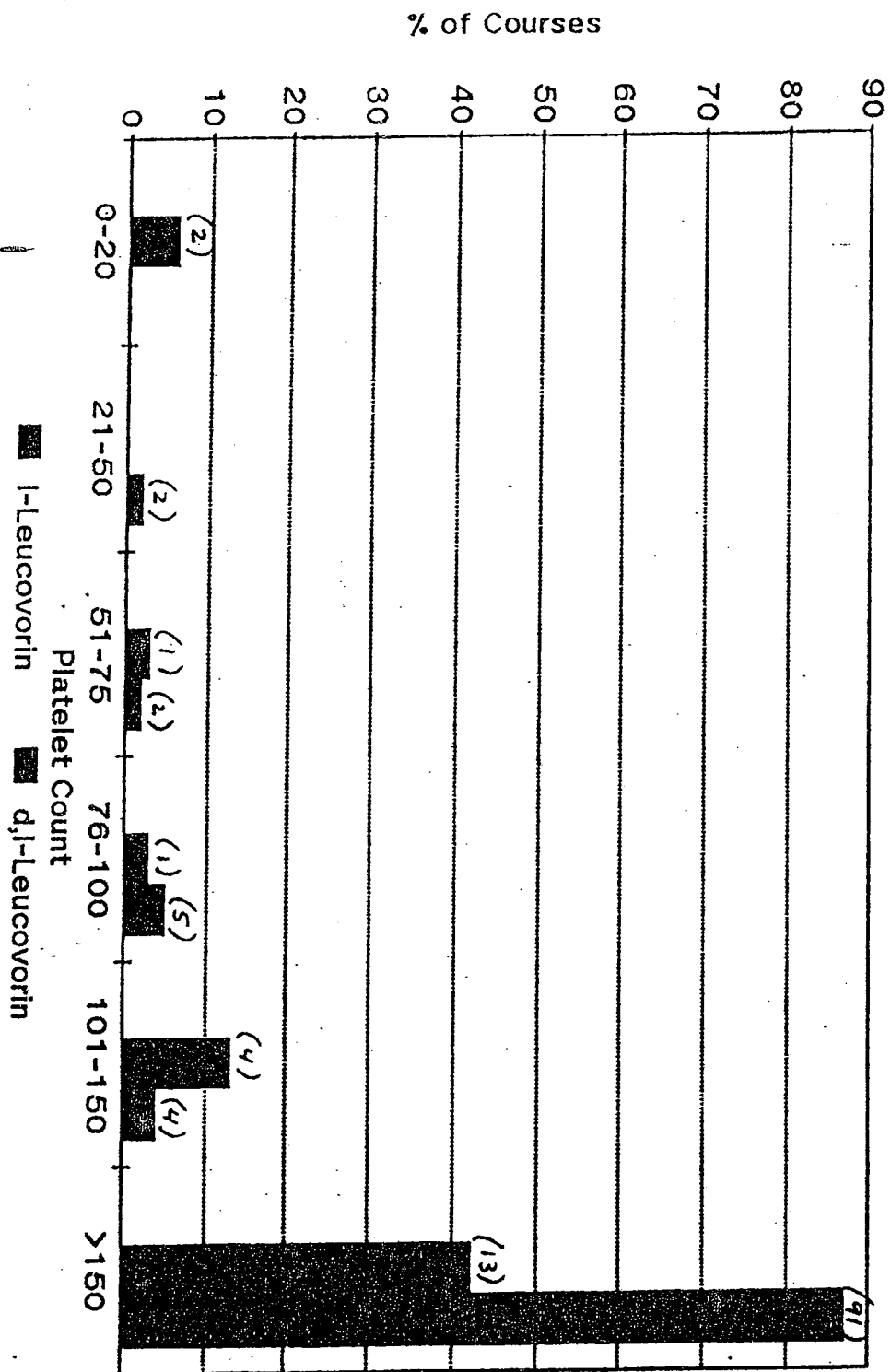
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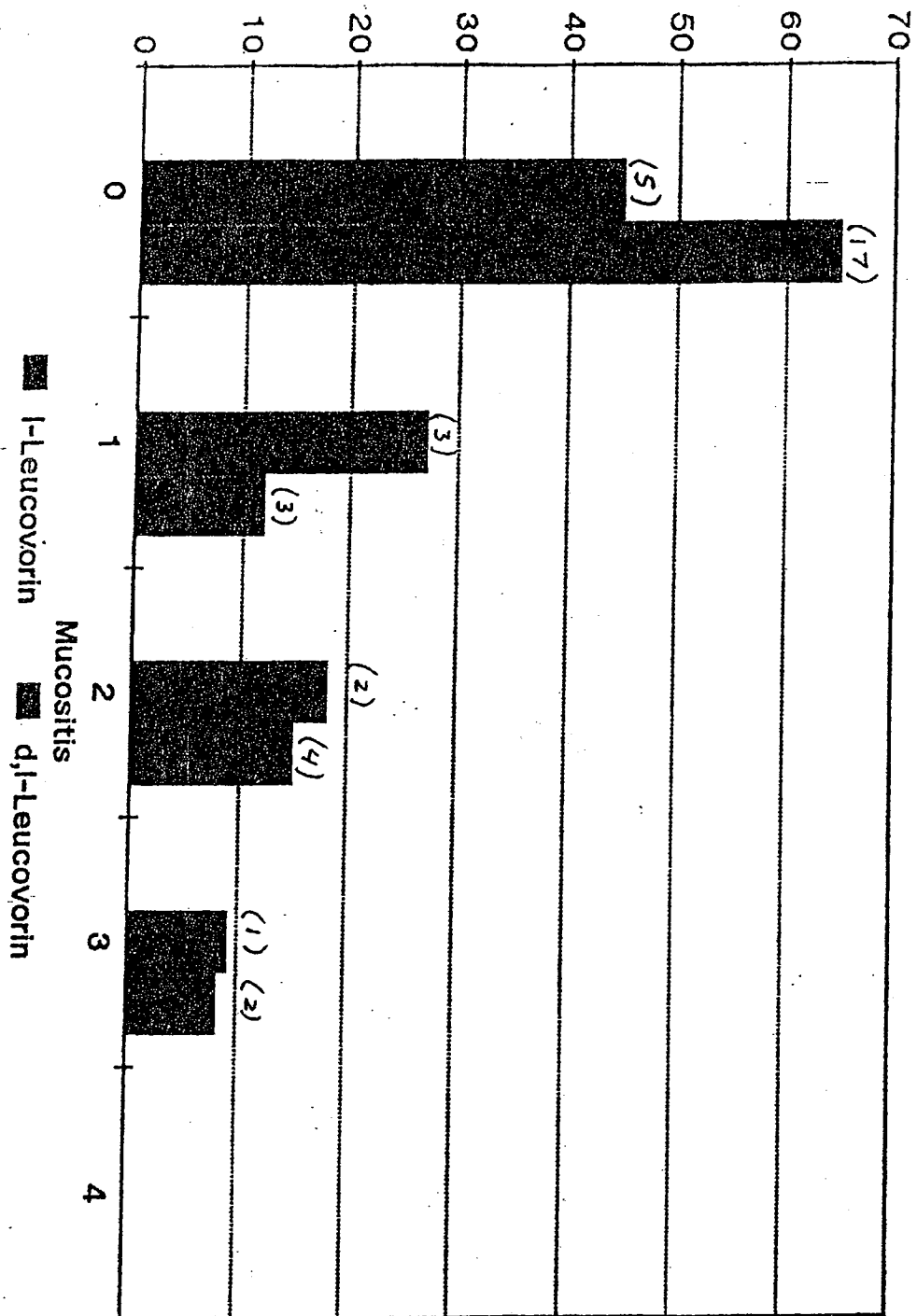


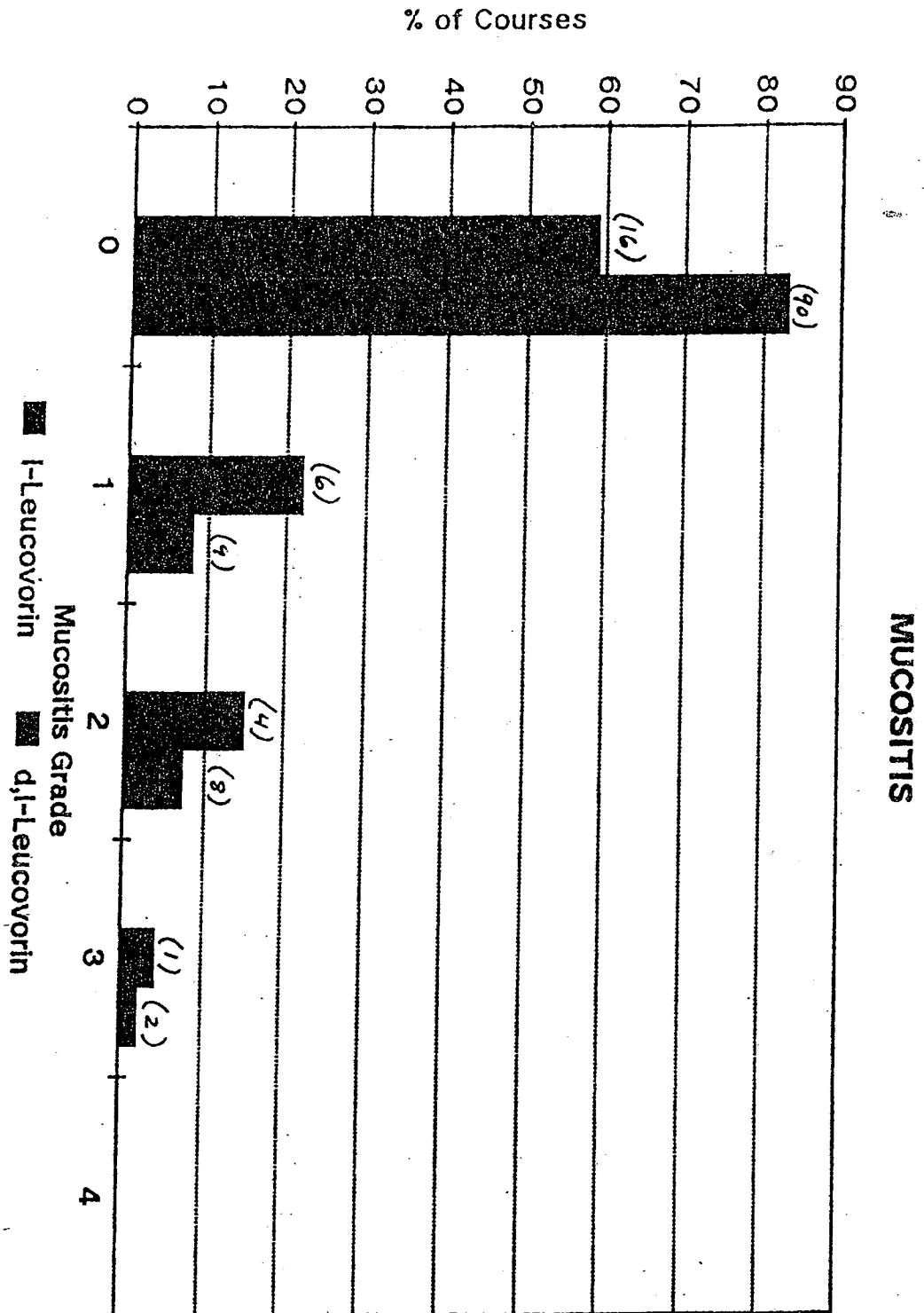
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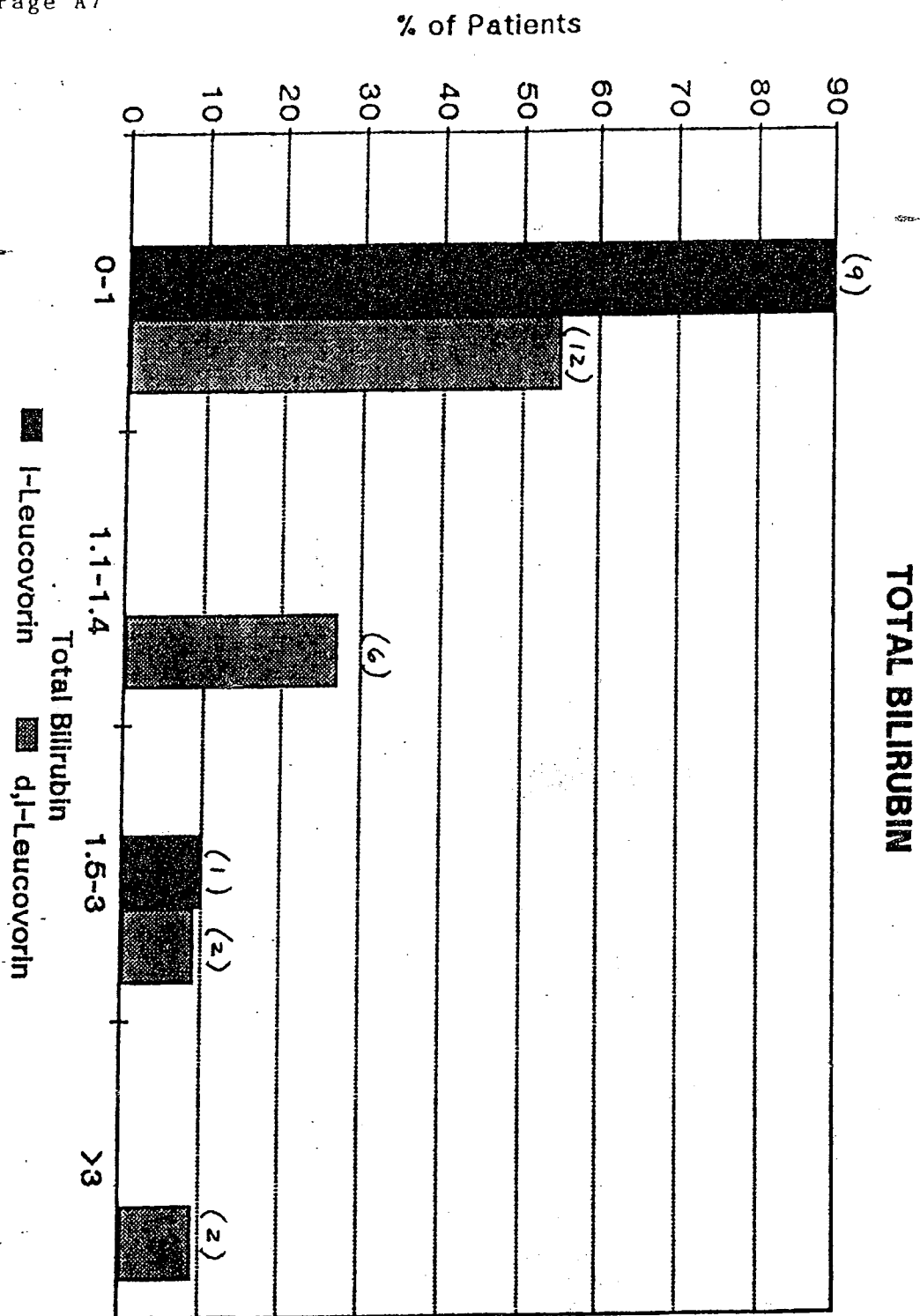


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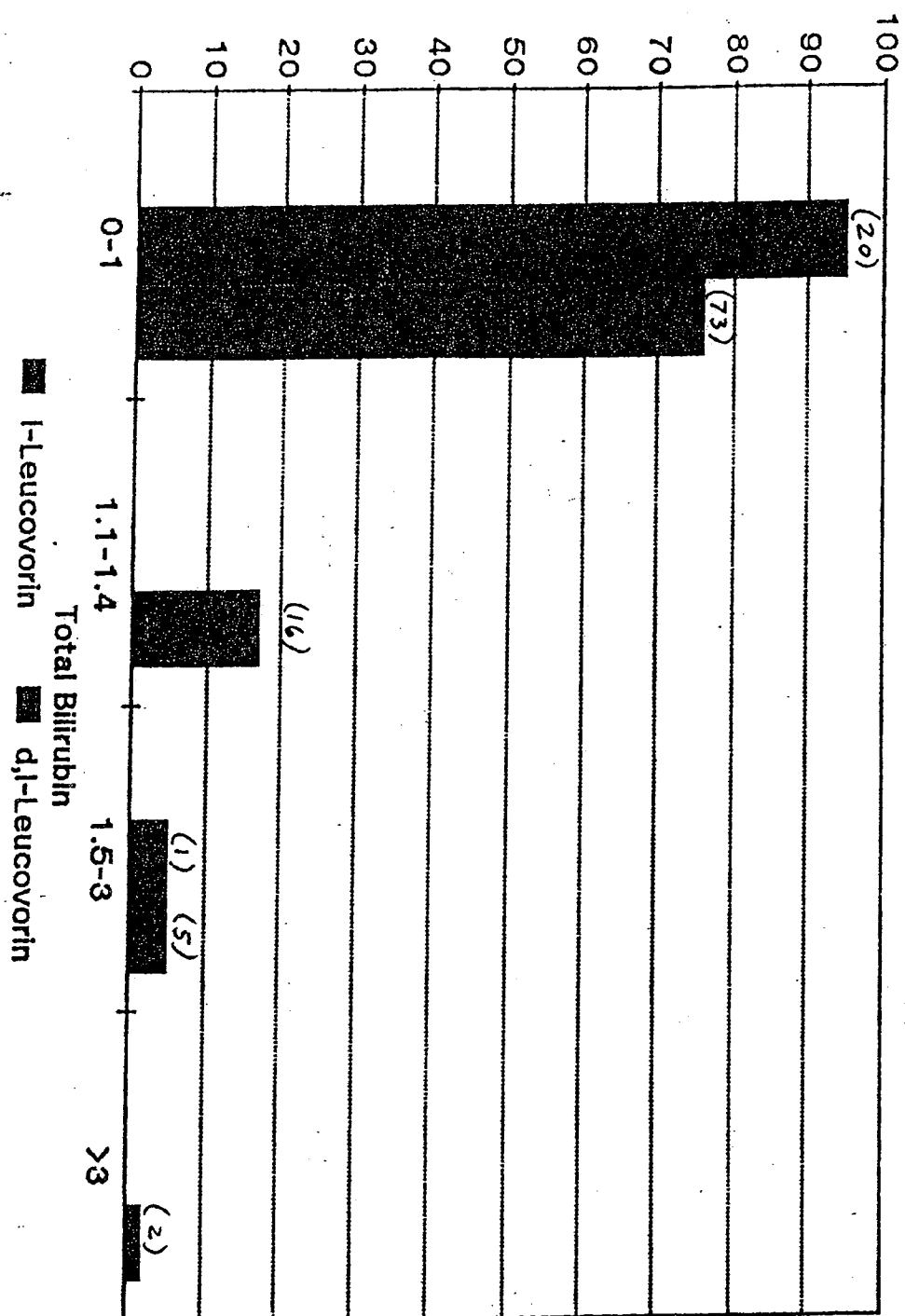


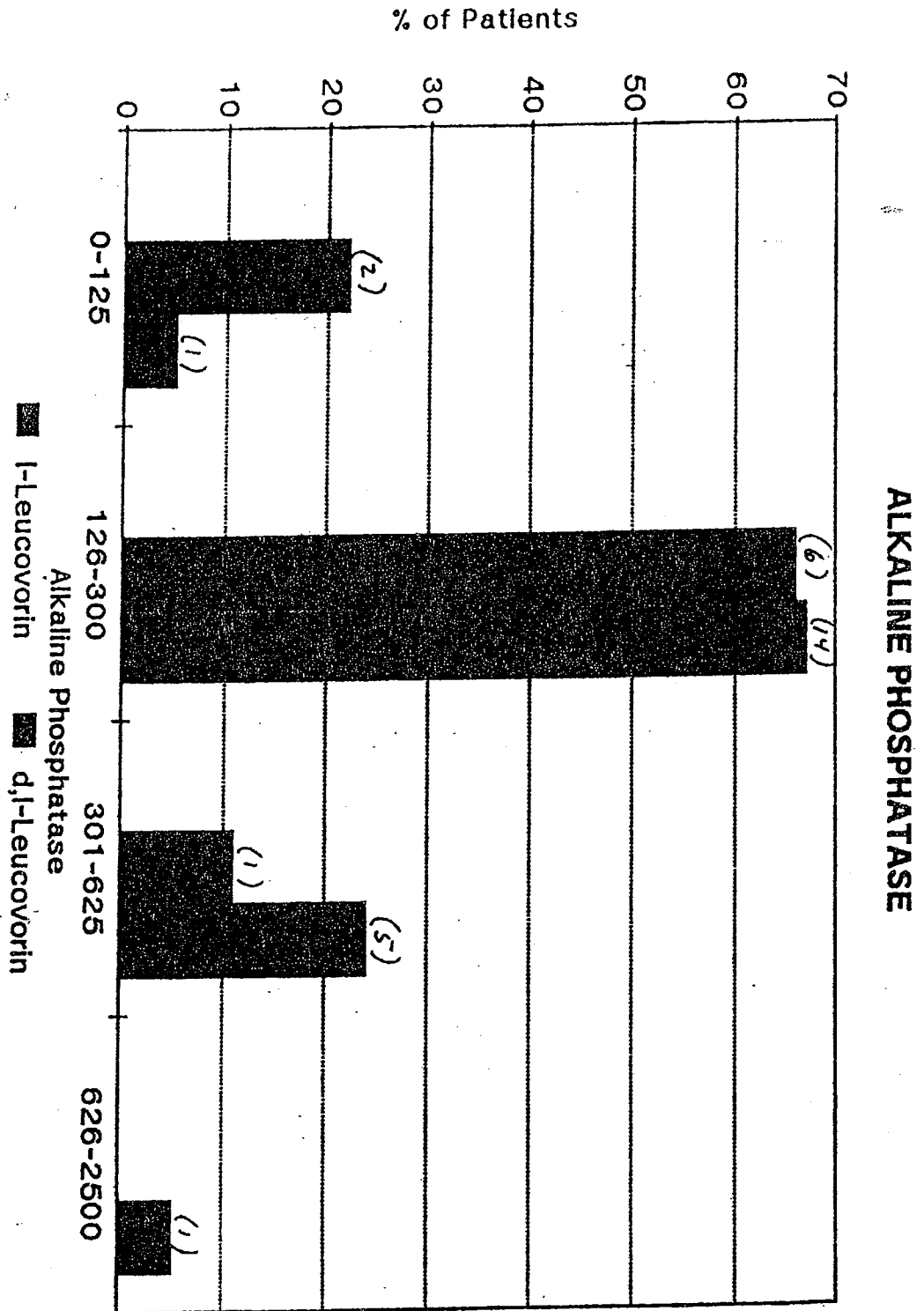


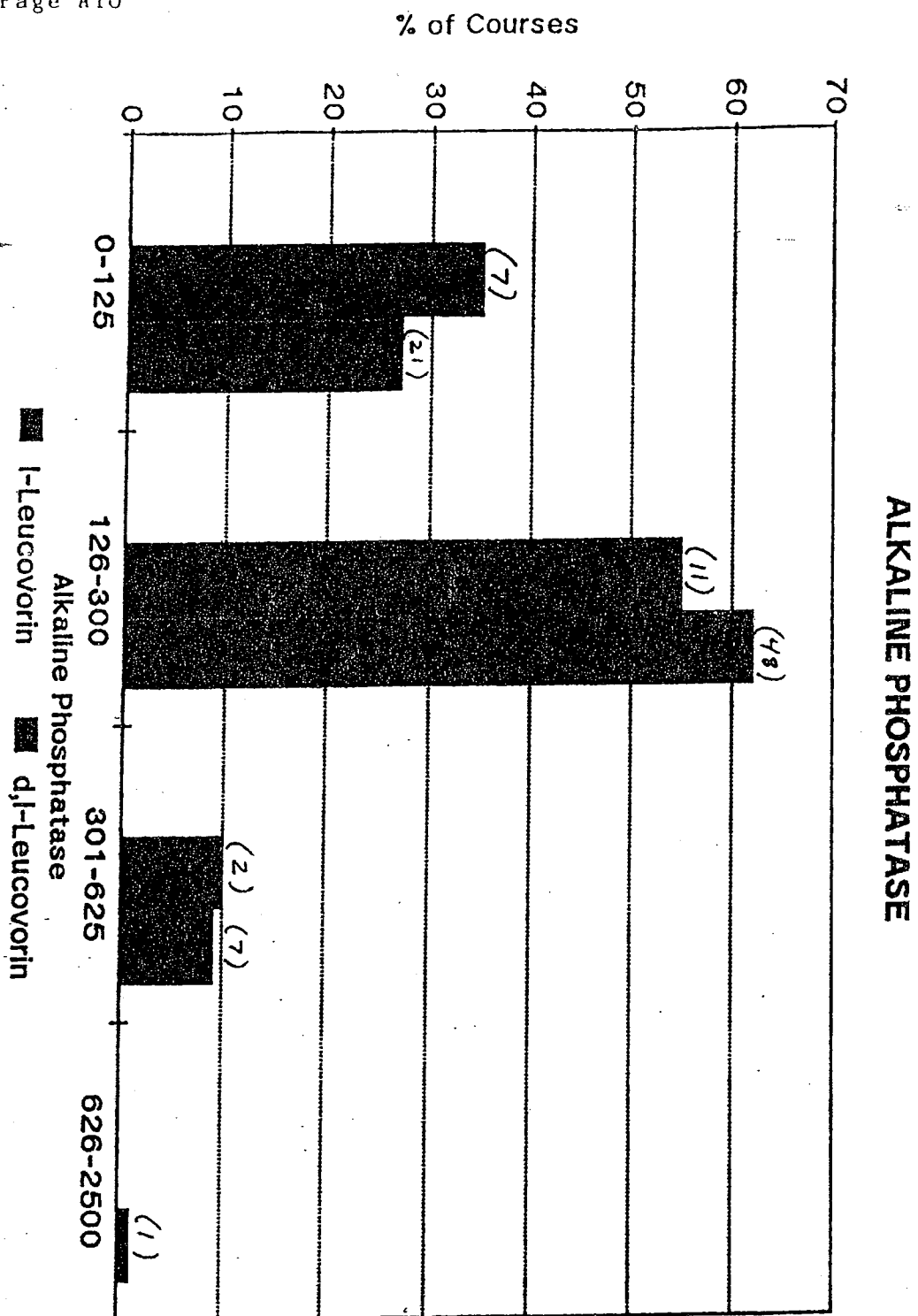


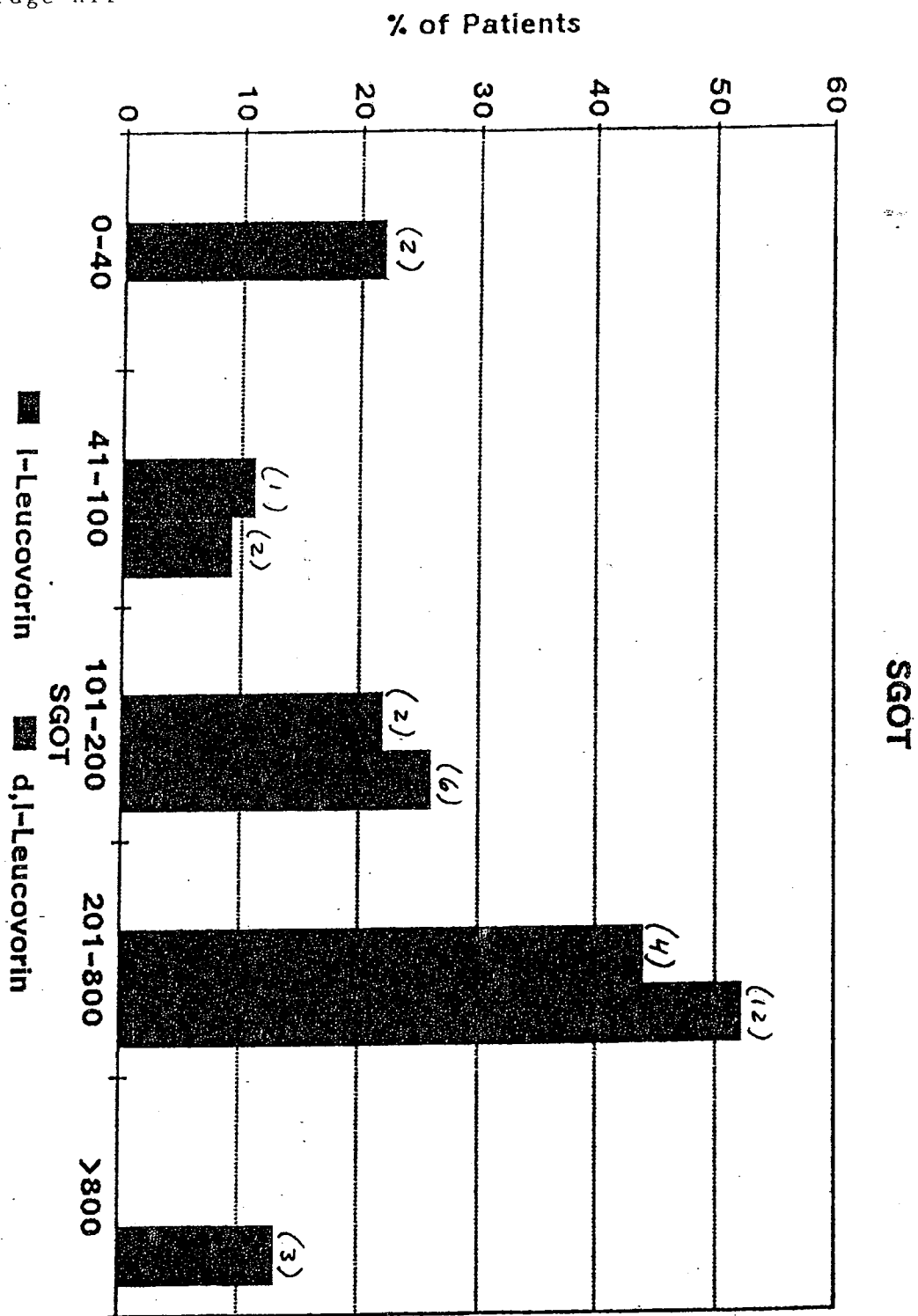
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