CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75020

APPROVAL LETTER

ANDA 75-020

JUL 30 1998

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213

Dear Sir:

This is in reference to your abbreviated new drug application dated December 10, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydroxyurea Capsules USP, 500 mg.

Reference is also made to your amendments dated November 6, 1997; and February 18 and May 22, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Hydroxyurea Capsules USP, 500 mg, are bioequivalent and, therefore, therapeutically equivalent to the listed drug (Hydrea® Capsules, 500 mg, of E.R. Squibb and Sons, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and

Promotional Labeling for Drugs for Human Use) for this initialsubmission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7-30-98

cc: ANDA 75-020
Division File
Field Copy
HFD-92
HFD-210/B.Poole
HFD-610/J.Phillips
HFD-330
HFD-205/F.O.I.

Endorsements:

HFD-625/SBrown/6-10-98
HFD-625/MSmela/6-10-98
HFD-617/DHuie, PM/6-10-98
HFD-613/CHolquist
HFD-613/JGrace

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F/T by: bc/6-16-98 Revised:RLWest:7/29/98

APPROVAL LETTER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75020

DRAFT FINAL PRINTED LABELING

DURAMED PHARMACEUTICALS, INC.

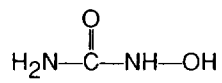
℞ only

HYDROXYUREA CAPSULES, USP

DESCRIPTION

Hydroxyurea Capsules, USP is an antineoplastic agent. Each capsule, for oral administration, contains 500 mg hydroxyurea. Inactive Ingredients: D&C Yellow #10, FD&C Green #3, FD&C Yellow #6, gelatin, lactose monohydrate, magnesium stearate, monobasic sodium phosphate, silicon dioxide, sodium lauryl sulfate, and titanium dioxide.

Hydroxyurea occurs as an essentially tasteless, white crystalline powder. Its molecular weight is 76.06. Its molecular formula is $CH_4N_2O_2$. Its structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action—The precise mechanism by which hydroxyurea produces its cytotoxic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and man lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells, and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation. The third mechanism of action has been theorized on the basis of *in vitro* studies of HeLa cells: it appears that hydroxyurea, by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein syntheses have shown no alteration.

Absorption, Metabolism, Fate and Excretion—After oral administration in man, hydroxyurea is readily absorbed from the gastrointestinal tract. The drug reaches peak serum concentrations within 2 hours; by 24 hours the concentration in the serum is essentially zero. Approximately 80 percent of an oral or intravenous dose of 7 to 30 mg/kg may be recovered in the urine within 12 hours.

Animal Pharmacology and Toxicology—The oral LD_{50} of hydroxyurea is 7330 mg/kg in mice and 5780 mg/kg in rats, given as a single dose.

In subacute and chronic toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1260 mg/kg/day for 37 days then 2520 mg/kg/day for 40 days), testicular atrophy with absence of spermatogenesis occurred; in several animals, hepatic cell damage with fatty metamorphosis was noted. In the dog, mild to marked bone marrow depression was a consistent finding except at the lower dosage levels. Additionally, at the higher dose levels (140 to 420 mg or 140 to 1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and hemosiderosis of the liver or spleen were found; reversible spermatogenic arrest was noted. In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion were found in the lungs, brain and urinary tract. Cardiovascular effects (changes in heart rate, blood pressure, orthostatic hypotension, EKG changes) and hematological changes (slight hemolysis, slight methemoglobinemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

INDICATIONS AND USAGE

Significant tumor response to Hydroxyurea Capsules, USP has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Hydroxyurea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

CONTRAINDICATIONS

Hydroxyurea is contraindicated in patients with marked bone marrow depression, i.e., leukopenia (<2500 WBC) or thrombocytopenia (<100,000), or severe anemia.

WARNINGS

Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed (see **CONTRAINDICATIONS**).

Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often, and are seldom seen without a preceding leukopenia. However, the recovery from myelosuppression is rapid when therapy is interrupted. It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; hydroxyurea should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema.

Severe anemia must be corrected with whole blood replacement before initiating therapy with hydroxyurea.

Erythrocytic abnormalities: megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The morphologic change resembles pernicious anemia, but is not related to vitamin B_{12} or folic acid deficiency. Hydroxyurea may also delay plasma iron clearance and reduce the rate of iron utilization by erythrocytes, but it does not appear to alter the red blood cell survival time.

Hydroxyurea should be used with caution in patients with marked renal dysfunction.

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

Usage in Pregnancy—Drugs which affect DNA synthesis, such as hydroxyurea, may be potential mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception.

Hydroxyurea is a known teratogenic agent in animals. Therefore, hydroxyurea should not be used in women who are or may become pregnant unless in the judgment of the physician the potential benefits outweigh the possible hazards.

PRECAUTIONS

Therapy with hydroxyurea requires close supervision. The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during, treatment. The determination of the hemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxyurea therapy. If the white blood cell count decreases to less than 2500/mm³, or the platelet count to less than 100,000/mm³, therapy should be interrupted until the values rise significantly toward normal levels. Anemia, if it occurs, should be managed with whole blood replacement, without interrupting hydroxyurea therapy.

Information for Patients—Patients who take the drug by emptying the contents of the capsule into water (see **DOSAGE AND ADMINISTRATION**) should be reminded that this is a potent medication that must be handled with care. Patients must be cautioned not to allow the powder to come in contact with the skin or mucous membranes, and must be told not to inhale the powder when opening the capsules. If the powder is spilled, it should be immediately wiped up with a damp towel and disposed of, as should the empty capsules. The medication, particularly open capsules, should be kept away from children and pets.

ADVERSE REACTIONS

Adverse reactions have been primarily bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia), and less frequently gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash and facial erythema. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. Hydroxyurea Capsules, USP occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, and elevation of hepatic enzymes have also been reported.

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea alone. These effects primarily include bone marrow depression (anemia and leukopenia), and gastric irritation. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (<100,000 cells/mm³) has occurred rarely and only in the presence of marked leukopenia. Gastric distress has also been reported with irradiation alone and in combination with hydroxyurea therapy.

It should be borne in mind that therapeutic doses of irradiation alone produce the same adverse reactions as hydroxyurea; combined therapy may cause an increase in the incidence and severity of these side effects.

Although inflammation of the mucous membranes at the irradiated site (mucositis) is attributed to irradiation alone, some investigators believe that the more severe cases are due to combination therapy.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnea has been rarely reported.

DOSAGE AND ADMINISTRATION

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Several guidelines on this subject have been published.[1] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Because of the rarity of melanoma, resistant chronic myelocytic leukemia, carcinoma of the ovary, and carcinomas of the head and neck in children, dosage regimens have not been established.

All dosages should be based on the patient's actual or ideal weight, whichever is less.

NOTE: If the patient prefers, or is unable to swallow capsules, the contents of the capsules may be emptied into a glass of water and taken immediately. (See **PRECAUTIONS: Information for Patients**). Some inert

material used as a vehicle in the capsule may not dissolve, and may float on the surface.

SOLID TUMORS

Intermittent Therapy—80 mg/kg administered orally as a *single* dose every *third* day.

Continuous Therapy—20 to 30 mg/kg administered orally as a *single* dose *daily*.

The intermittent dosage schedule offers the advantage of reduced toxicity since patients on this dosage regimen have rarely required complete discontinuance of therapy because of toxicity.

Concomitant Therapy with Irradiation *Carcinoma of the head and neck*—80 mg/kg administered orally as a single dose every *third* day.

Administration of Hydroxyurea should be begun at least seven days before initiation of irradiation and continued during radiotherapy as well as indefinitely afterwards provided that the patient may be kept under adequate observation and evidences no unusual or severe reactions.

Irradiation should be given at the maximum dose considered appropriate for the particular therapeutic situation; adjustment of irradiation dosage is not usually necessary when hydroxyurea is used concomitantly.

RESISTANT CHRONIC MYELOCYTIC LEUKEMIA

Until the intermittent therapy regimen has been evaluated, CONTINUOUS therapy (20 to 30 mg/kg administered orally as a *single* dose *daily*) is recommended.

An adequate trial period for determining the antineoplastic effectiveness of hydroxyurea is six weeks of therapy. When there is regression in tumor size or arrest in tumor growth, therapy should be continued indefinitely. Therapy should be interrupted if the white blood cell count drops below 2500/mm^3, or the platelet count below 100,000/mm^3. In these cases the counts should be rechecked after three days, and therapy resumed when the counts rise significantly toward normal values. Since the hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combined Hydroxyurea Capsules, USP and irradiation therapy, irradiation may also be interrupted. However, the need for postponement of irradiation has been rare; radiotherapy has usually been continued using the recommended dosage and technique. Anemia, if it occurs, should be corrected with whole blood replacement, without interrupting hydroxyurea therapy. Because hematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that hydroxyurea be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anesthetics and orally administered analgesics. If the reaction is severe, hydroxyurea therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed. However, it has rarely been necessary to terminate these therapies.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by temporary interruption of hydroxyurea administration; rarely has the additional interruption of irradiation been necessary.

HOW SUPPLIED

Hydroxyurea capsules, USP are available in 500 mg capsules.

500 mg capsules are tan and green colored, imprinted "$" and "548", bottles of 100 (NDC 51285-548-02).

Storage - Store at controlled room temperature 15°-30°C (59°-86°F); avoid excessive heat. Keep tightly closed.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publications No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA. 1985; 253(11): 1590-1592.
3. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med. J. Australia. 1983; 1: 426-428.
5. Jones, RB, *et al*: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.
7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm 1986; 43: 1193-1204.

Mfd. for: DURAMED PHARMACEUTICALS, INC.
Cincinnati, OH 45213 USA

by: KIEL LABORATORIES
Gainesville, GA 30504

I00310A Rev. 05/98

HYDROXYUREA CAPSULES, USP

Mary

Each capsule contains:
Hydroxyurea ..... 500 mg

Bulk Container — Not For Household Dispensing

Usual Dosage: Intermittent therapy — single doses of 80 mg per kg every third day. Daily regimen — 20 to 30 mg per kg as a single dose.

See insert.

Lot No.:

Exp. Date:

DURAmed

NDC 52185-548-02

Hydroxyurea

Capsules, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Capsules

Keep tightly closed. Store at room temperature; avoid excessive heat. Dispense in tight containers.

Mfd. for: DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

by: KIEL LABORATORIES, INC.
GAINESVILLE, GA 30504

L00551 ISS. 8/97

0 28176 54802 7

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CINCINNATI, OH 45213 USA

by: KIEL LABORATORIES, INC.
GAINESVILLE, GA 30504

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Exp. Date:

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NDC 52185-548-02

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Mfd. for: DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

by: KIEL LABORATORIES, INC.
GAINESVILLE, GA 30504

L00551 ISS. 8/97

0 28176 54802 7

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75020

CHEMISTRY REVIEW(S)

ANDA NUMBER 75-020

FIRM: Duramed Pharmaceuticals, Inc.

DOSAGE FORM: Capsule

STRENGTH: 500 mg

DRUG: Hydroxyurea

CGMP STATEMENT/EIR UPDATE STATUS: Withhold on 5/28/97 and on 5/8/98.

BIO STUDY: Review stamp dated 9/14/97.

The single dose two-way crossover *in vivo* bioequivalence study is acceptable, and the *in-vitro* dissolution testing is acceptable.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug Product is listed in the USP 23, and the USP verification is satisfactory.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes

150 cc, opaque, white HDPE bottle with a mm white, PPL closure with a polystyrene foam pressure sensitive seal, rayon fiber for dunnage, and desiccant canister with g of silica gel.

Studies: 6 month accelerated (40°C/75% RH with testing at 0, 1, 2, 3 and 6 months) data are provided for test batch GA199, and 12 months room temperature data are submitted. Data support a tentative 24 month expiry date.

LABELING:

Satisfactory. Review dated 5/29/98 per CHolquist.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

GA199 - capsules (theoretical yield)

capsules packaged

Active ingredient by DMF is acceptable.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA SAME PROCESS):

Same as bio batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Yes

Proposed production batch size - capsules.

Review Chemist: Shirley S. Brown/6-10-98 /S/ 6/23/98
Supervisor: Michael Smela/6-10-98
Date: June 10, 1998

/S/
6/23/98

1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA #75-020**

3. **NAME AND ADDRESS OF APPLICANT**

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, OH 45213

4. **LEGAL BASIS FOR SUBMISSION**

Section 505(j)

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Hydroxyurea

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

Duramed

12/10/96	Original Filing
1/24/97	Withdrawal of the 250 mg strength
11/6/97	Response to deficiencies per review #1
2/18/98	Withdrawal of the request for approval of the 250 mg strength and all related documentation
*5/22/98	Response to deficiencies per review #2 (*subject of this review)

FDA

1/17/97	Refuse to File
2/10/97	Acknowledgment
6/10/97	Response to petition to file an ANDA for a 250 mg strength product
7/9/97	Deficiency letter per chemistry review #1
9/29/97	Bio's comments to applicant - re: No Questions at this time
5/1/98	Deficiency letter per chemistry review #2

10. **PHARMACOLOGICAL CATEGORY**

Antineoplastic

11. **Rx or OTC**

Rx

12. **RELATED IND/NDA/DMF(s)**

NDA 16-295 Hydrea© (Bristol-Myers Squibb)
DMF

13. **DOSAGE FORM** 14. **POTENCY**

Capsules 500 mg

15. **CHEMICAL NAME AND STRUCTURE**

Hydroxyurea

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

The applicant noted and acknowledged the following comments as requested:

1. The package insert must be revised to eliminate reference to the mg capsule.

2. A satisfactory compliance evaluation is required for all facilities involved in the manufacture/testing of the subject drug product prior to the approval of the application.

Satisfactory

18. **CONCLUSIONS AND RECOMMENDATIONS**

Chemistry issues are closed.

The application is not approvable. Pending - Acceptable EER. (Not Acceptable for - manufacturer of the drug product.)

19. **REVIEWER:** **DATE COMPLETED:**

/S/ 6/10/98

Shirley S. Brown June 10, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75020

BIOEQUIVALENCY REVIEW(S)

SEP 14 1997

Hydroxyurea Capsules
500 mg
ANDA #75-020
Reviewer: Moheb H. Makary
75020SD.197

Duramed Pharmaceuticals, Inc.
Cincinnati, Ohio
Submission Date:
January 24, 1997

Review of Bioequivalence Study and Dissolution Data

I. Objective:

The objective of this study was to determine the bioequivalence of Hydroxyurea Capsules, USP, 500 mg, manufactured by Duramed Pharmaceuticals, Inc., relative to the listed drug product, Hydroxyurea Capsules, USP, 500 mg, Hydrea^{R}, manufactured by Bristol-Myers Squibb, in healthy, normal males under fasting conditions.

II. Background:

Hydroxyurea is an antineoplastic indicated for melanoma; resistant chronic myelocytic leukemia; recurrent, metastatic, or inoperable carcinoma of the ovary.

It is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are expected within 2 hours following oral administration. Plasma half-life ranges from 2 to 5 hours following a single 1000 mg dose. Approximately 80% of the drug is recovered in the urine within 12 hours of drug administration.

III. Hydroxyurea's Study #9690603B for a single-dose 2-way crossover study under fasting conditions:

Study site:

Sponsor:	Duramed Pharmaceuticals, Inc.
Study design:	Single-dose, randomized, 2-way crossover, open-label, under fasting conditions.
Subjects:	Twenty-six healthy male subjects enrolled in the study. Two subjects did not complete the study. Subject #14 dropped out after period I for personal reasons, subject #15 dropped from the study prior to period II due to a positive drug test urine screen. Per the study protocol, plasma samples were analyzed only for those subjects who completed the crossover.

Inclusion criteria:

* Healthy male
* Age 18-40
* Weight within 15% of ideal body weight
* No clinically significant abnormalities
* Normal clinical laboratory values
* Able to understand and sign informed consent

Exclusion Criteria: Subjects who met any of the following criteria were excluded from the study:

* History of allergy and/or sensitivity to hydroxyurea
* Significant history or current evidence of gastrointestinal, chronic infectious disease, system disorder or organ dysfunction
* History of psychiatric disorders occurring within last 2 years which required hospitalization and/or medication for more than 6 weeks
* Medical condition requiring regular treatment with any prescription drug
* Use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes within 30 days prior to initial study dosing
* Drug or alcohol addiction requiring treatment in the past 12 months
* Positive test results for drugs of abuse
* Within 30 days of the start of the study:
- Participated in a previous clinical trial
- Donated or significant loss of more than 480 mL of whole blood or blood or plasma within 14 days of the start of study.

Dose dates: July 26 and August 2, 1996

Dose and treatment:

A. Test product:
4 x 500 mg Hydroxyurea Capsules manufactured by Duramed Pharmaceuticals, Inc., lot #GA199, lot size capsules (actual yield: capsules), potency %, content uniformity %, following an overnight fast.

B. Reference product:
4 x 500 mg Hydrea® Capsules manufactured by Bristol-Myers Squibb, lot #MA006, Exp. 2/01/01, potency %, content uniformity %, following an overnight fast.

Washout period: One week

Food and fluid intake: Prior to each period there was an overnight fast of at least 10 hours. Water was consumed ad lib except within 1 hour before and after dosing. Water (240 mL at room temperature) was consumed at the time of dosing. Four (4) hours post-dose a standardized meal was served. No other food or beverage was allowed from 12 hours pre-dose until 4 hours post-dose. Meals plans were identical for both periods.

Blood samples: During each period, plasma samples were obtained from blood drawn into heparinized tubes at 0 (pre-dose), 10, 20, 30 and 45 minutes and 1, 1.33, 1.67, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 18 and 24 hours after administration of the dose. The blood samples were centrifuged at -4°C plasma collected and stored at -70°C until assayed.

Safety Monitoring: Blood pressure (sitting), pulse rate, respiratory rate and oral temperature were measured before each dosing. In addition, Blood pressure and pulse rate measurements (sitting) were obtained 2 hours after each dose and prior to release in each study period to monitor the health of the subjects. Measurements were repeated if clinically warranted.

Analytical Methodology

Data Analysis

ANOVA was performed on untransformed AUC(0-t), AUCinf, Cmax, Tmax, kel and t1/2. Additionally, log-transformed data were used for the analysis of AUC(0-t), AUCinf and Cmax. The ANOVA model included sequence, subjects nested within sequence, period and treatment as factors.

Confidence Intervals and Ratio Analysis

Consistent with the two one-sided test for bioequivalence, 90% confidence intervals for the difference between drug formulation least-square means (LSM) were calculated for both the untransformed and log-transformed AUC(0-t), AUCinf and Cmax.

IV. In Vivo Results:

Twenty-six (26) normal, healthy subjects enrolled and twenty-four successfully completed the study. There were three adverse events reported. Subject #9 experienced rhinitis which was related to the study drugs. Subject #24 experienced abdominal cramps and diarrhea. The Investigator judged that two events were possibly related to the study drug (Reference Drug).

The plasma concentrations and pharmacokinetic parameters for hydroxyurea is summarized in Table I.

Table I

Mean Plasma Hydroxyurea Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 2000 mg(4x500 mg Capsules) Hydroxyurea Under Fasting Conditions
(N=24)

Time hr	Treatment A Duramed Lot #GA199 ug/mL (C.V.)	Treatment B Bristol-Myers Lot #MA006 ug/mL (C.V.)
0	0.00 (0.0)	0.00 (0.0)
0.17	9.08 (144.3)	8.51 (119.8)
0.33	30.60 (65.6)	33.89 (54.3)
0.50	42.09 (23.2)	42.38 (43.3)
0.75	43.30 (14.2)	39.15 (27.2)
1.0	39.38 (14.8)	35.70 (24.6)
1.33	34.89 (14.8)	32.97 (24.2)
1.67	32.65 (13.7)	31.00 (23.3)
2	30.14 (14.2)	29.31 (23.6)
3	24.86 (14.9)	23.86 (23.6)
4	20.31 (16.2)	19.73 (20.6)
5	16.64 (18.5)	16.25 (17.7)
6	13.28 (20.9)	13.59 (17.8)
7	10.81 (20.7)	11.01 (18.9)
8	8.79 (22.3)	9.04 (20.6)
9	7.22 (23.5)	7.44 (22.3)
10	5.96 (24.7)	6.12 (24.2)
12	4.01 (27.3)	4.23 (24.7)
15	2.14 (36.8)	2.28 (29.8)
18	0.91 (83.9)	1.03 (71.9)
24	0.0 (0.0)	0.04 (489.9)

			90% CI
AUC(0-t) (ug.hr/mL)	208.04 (16.2)	205.85 (18.7)	
AUCinf (ug.hr/mL)	215.39 (16.1)	212.96 (18.5)	
Cmax(ug/mL)	50.45 (16.1)	48.05 (29.4)	
Tmax(hr)	0.61 (36.1)	0.84 (137.3)	
Kel (1/hr)	0.21	0.20	
T1/2 (hr)	3.38	3.43	
LnAUC(0-t)			99.4-103.5%
LnAUCinf			99.5-103.4%
LnCmax			97.4-121.8%

1. For hydroxyurea, the least squares means for AUC(0-t), AUCinf and Cmax values were 0.9%, 1.0% and 5.1% higher, respectively,

for the test product than for the reference product. The differences were not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

2. The hydroxyurea plasma levels peaked at 0.5 and 0.75 hour for the reference and the test and products, respectively, following their administration under fasting conditions.

3. In the final report of the study, subject #24, period II (reference product) had diarrhea and abdominal cramps for approximately 6 hours after the reference dose. The subject had significantly slower absorption in period II compared to period I. After excluding subject #24 from the statistical analysis of the study for the above reasons, the resulting 90% confidence intervals for hydroxyurea are as following:

LnAUC(0-t)	%
LnAUCinf	%
LnCmax	%

All confidence intervals remain within the acceptable % range.

V. Formulations:

Duramed's formulation for its Hydroxyurea Capsules 500 mg is shown in Table II.

VI. In vitro Dissolution Testing: (USP Method)

The dissolution testing for the test and reference products is summarized below:

Method: USP 23 apparatus II (paddle) at 50 rpm
Medium: 500 mL of water at 37°c
Number of Capsules: 12
Test product: Duramed's Hydroxyurea Capsules, 500 mg, lot #GA199

Reference product: Bristol-Myers Squibb's Hydrea® Capsules, 500 mg, lot #MA006

Specifications: NLT % in 30 minutes.

Dissolution Testing results are shown in Table III.

VII. Comments:

1. The firm's single-dose bioequivalence study #9690603B under fasting conditions, conducted on its 500 mg Hydroxyurea Capsule

Concur: /S/ Date: 9/24/97

for Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence

MMakary/6-17-97 wp 75020SD.197
cc: ANDA #75-020, original, HFD-650 (Director), HFD-658 (Makary), Drug File, Division File.

Table III

Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Hydroxyurea Lot #GA-199 Capsule Strength(mg) 500			Reference Product Hydrea Lot #MA006 Capsule Strength(mg)500		
	Mean %	Range	%CV	Mean %	Range	%CV
10	46.3		16.1	64.1		9.4
20	72.3		12.5	95.6		4.5
30	91.1		5.0	101.9		2.2

is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of % for Hydroxyurea.

2. The in vitro dissolution testing for the test product 500 mg Hydroxyurea Capsules is acceptable. Hydroxyurea Capsules, 500 mg, manufactured by Duramed Pharmaceuticals, Inc., exhibited a slower dissolution rate at 10 and 20 minutes time points when compared with reference product.

VIII. Recommendations:

1. The single-dose bioequivalence study #9690603B, conducted by Duramed Pharmaceuticals, Inc., on its Hydroxyurea 500 mg capsule, lot #GA199, comparing it to Hydrea® 500 mg capsule, manufactured by Bristol-Myers Squibb, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Hydroxyurea Capsule, 500 mg, is bioequivalent to Bristol-Myers Squibb's Hydrea® Capsule, 500 mg.

2. The dissolution testing conducting by Duramed Pharmaceuticals, Inc., on its Hydroxyurea 500 mg Capsules, lot #GA199, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than % of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, PH.D. Date:
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 6/17/97

Table II

Formulation Comparison of Hydroxurea Capsules, USP

Component	250 mg Capsules	500 mg Capsules
Hydroxyurea, USP-Micronized	mg	mg
Lactose Monohydrate NF	mg	mg
Magnesium Stearate, NF	mg	mg
Sodium Phosphate Monobasic Monohydrate, USP	mg	mg
Total Theoretical Weight [1] :	**mg**	**mg**

[1] Weight of blended powder mixture not including capsule shell weight. Approximate mean empty capsule weights are 96±8 mg for 500 mg capsule and 62±5 mg for 250 mg capsule.

The 250 mg batch was initially formulated to be identical to the 500 mg batch with a fill weight, into a smaller capsule, equal to one-half that of the 500 mg capsule (365 mg vs. 730 mg). Due to the bulk density of the formulation, it was not possible to accurately fill 365 mg into any size capsule. The batch (and formulation) was modified, with the addition of % filler (lactose), to achieve a fill weight of mg.

Study Results, Continued

Figure 1
Mean Plasma Hydroxyurea Concentrations
(Semi-Log Plot)

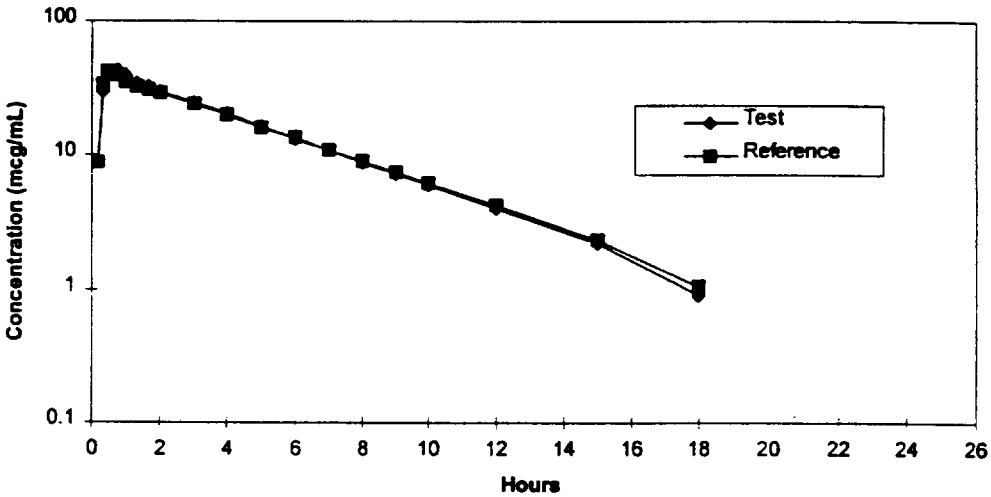
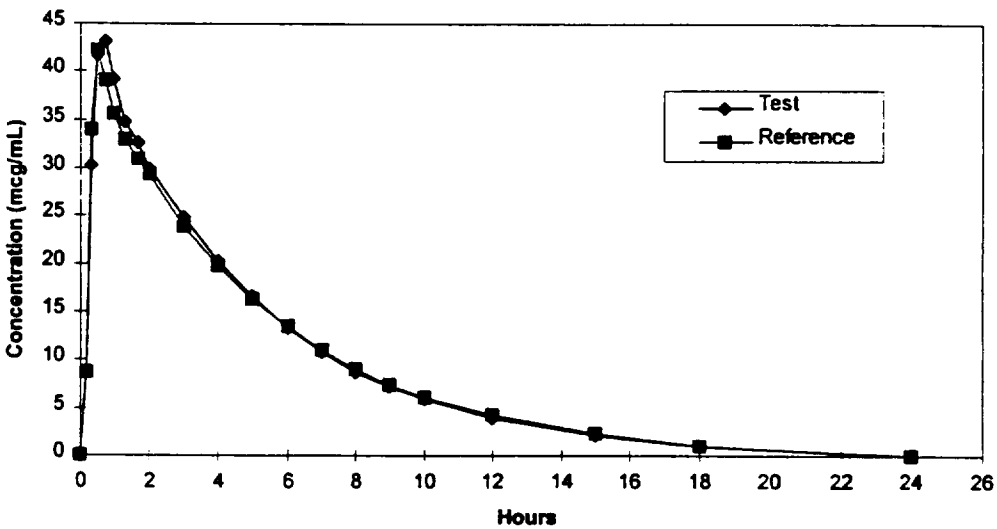


Figure 2
Mean Plasma Hydroxyurea Concentrations
(Linear Plot)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75020

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-020 Date of Submission: January 24, 1997

Applicant's Name: **Duramed Pharmaceuticals, Inc.**

Established Name: **Hydroxyurea Capsules USP, 500 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   We acknowledge your comments regarding the withdrawal of the 250 mg strength from your application. In addition we acknowledge your comment regarding the deletion of all references to the 250 mg capsule from your labeling. We find them acceptable.

2. CONTAINER (100s - 500 mg)

   Delete which appears on the main panel.

3. INSERT

   a. See GENERAL COMMENT

   b. DESCRIPTION

      i. Revise paragraph one to read as follows:

         ...agent. Each capsule, for oral administration, contains 500 mg hydroxyurea.

      ii. Inactive Ingredients - Revise to read "lactose monohydrate".

      iii. Include the molecular weight, molecular formula and chemical name.

   c. ACTIONS

      Revise the section heading to read "CLINICAL PHARMACOLOGY".

d. HOW SUPPLIED

i. See GENERAL COMMENT.

ii. We note you describe the 500 mg capsule as "buff". However, in your finished dosage specifications you describe the capsule as "tan". Please revise and/or comment.

e. REFERENCES

Revise the second reference to read as follows:

...1985; 253(11):1590-1592.

f. Include a revision date of the insert.

Please revise your container labels and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75020

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Duramed Pharmaceuticals, Inc.
Attention: William P. Stoltman, J.D.
5040 Lester Road
Cincinnati, OH 45213

JUN 10 1997

Docket No. 96P-0407/CP1

Dear Sir:

This is in response to your petition filed on October 25, 1996, and your amendment dated December 9, 1996, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug product: Hydroxyurea Capsules, 250 mg. The listed drug product to which you refer in your petition is Hydrea® (Hydroxyurea) Capsules, 500 mg, manufactured by Bristol-Myers Squibb Company.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act) and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced drug product.

Your request involves a change in strength from that of the listed drug product (i.e., from 500 mg to 250 mg). The change you request is the type of change that is authorized under the Act.

Under Section 505(j)(2)(C)(i) of the Act, the Agency must approve a petition seeking a strength which differs from the strength of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing strength.

The Agency finds that the change in strength for the specific proposed drug product does not pose questions of safety or effectiveness because the uses, dose, and route of administration of the proposed drug product are the same as that of the listed drug product. The Agency concludes, therefore, that investigations are not necessary in this instance. In addition, if shown to meet bioavailability requirements, the proposed drug product can be expected to have the same therapeutic effect as the listed reference drug product.

The approval of this petition to allow an ANDA to be submitted for the above-referenced drug product does not mean that the Agency has determined that an ANDA will be approved for the drug product. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

To permit review of your ANDA submission, you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the drug product will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you contact the Director, Division of Bioequivalence, at (301) 827-5847 to determine the specific requirements for this drug product. During the review of your application, the Agency may require the submission of additional information.

The listed drug product to which you refer in your ANDA must be the one upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, HFA-305, Park Building, 12420 Parklawn Drive, Room 1-23, Rockville, MD 20857.

Sincerely yours,

/S/ for

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-020

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza, M.S., R.Ph.
5040 Lester Road
Cincinnati, OH 45213

FEB 10 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated January 17, 1997, and your amendment dated January 24, 1997.

NAME OF DRUG: Hydroxyurea Capsules USP, 500 mg

DATE OF APPLICATION: December 10, 1996

DATE OF RECEIPT: December 11, 1996

DATE ACCEPTABLE FOR FILING: January 24, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 594-0370

Sincerely yours,

/S/

Jerry Phillips for 2/10/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-020

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza, M.S., R.Ph.
5040 Lester Road
Cincinnati, Ohio 45213

JAN 17 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 10, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydroxyurea Capsules USP, 250 mg and 500 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> You may not submit an application for hydroxyurea capsules, 250 mg until your ANDA Suitability Petition is approved. Therefore, please withdraw all references to hydroxyurea capsules 250 mg from this application.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Also, please provide a packaging reconciliation record which explains the amount packaged for your test batch.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions please call:

Anna Marie H. Weikel
Project Manager
(301) 594-0315

Sincerely yours,

/S/

for 1/17/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 29 1997

ANDA 75-020

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydroxyurea Capsules USP, 500 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

November 6, 1997

ORIG AMENDMENT

Mr. Douglas Sporn,
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-020 Hydroxyurea Capsules, USP 500 mg

Subject: Major Amendment

Dear Mr. Sporn:

Reference is made to a letter dated July 9, 1997 concerning major deficiencies in our Abbreviated New Drug Application 75-020 for Hydroxyurea Capsules, USP 500 mg.

In this **major amendment** we now respond to all the deficiencies listed in the referenced letter as well as include an additional new strength 250 mg Hydroxyurea Capsules, USP. The 250 mg strength capsule was originally included in the initial ANDA filing. However, it was later withdrawn in a letter dated January 24, 1997 because our filed suitability petition for that strength had not yet been approved by the Agency. In a letter dated June 10, 1997 from the Office of Generic Drugs we were informed that our petition, Docket No. 96P-0407/CP1 was approved for filing Hydroxyurea Capsules, USP 250 mg strength.

Thus, we now include the 250 mg strength capsule for review in this ANDA and withdraw the January 24, 1997 letter by re-inserting the applicable 250 mg capsule ANDA sections and pages.

In addition and in light of the Division's review of the 500 mg capsule, we have revised and included in this amendment all of the associated documents pertaining to the 250 mg capsule strength; namely, the batch manufacturing record, product specifications, post-approval stability protocol and stability tables. All other sections and pages remain applicable as originally submitted.

As requested, we have included a side-by-side comparison of our final printed labeling for both capsule strengths with the labeling in our original submission.

This **major amendment** is submitted in one (1) volume, an archival copy (blue) and a technical review copy (red).

We certify that a true copy of this amendment has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, GA.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482 or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

May 22, 1998

ORIG AMENDMENT
FA

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-020 Hydroxyurea Capsules, USP 500 mg
Subject: MINOR AMENDMENT

Dear Dr. Patel:

Reference is made to your facsimile amendment dated May 1, 1998 concerning ANDA 75-020 for Hydroxyurea Capsules, USP 500 mg in which you describe minor chemistry and labeling deficiencies.

In this minor amendment we respond by restating the FDA comment/question followed by our response.

This **amendment** is submitted in two (2) volumes, an archival copy and a technical review copy. We certify that a true copy of this amendment has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, GA.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482 or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

enclosure: completed Form FDA 356h

RECEIVED
MAY 26 1998
GENERIC DRUGS

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

February 18, 1998

Mr. Douglas Sporn,
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-020 Hydroxyurea Capsules, USP 500 mg
Subject: Withdrawal of the 250 mg Strength

Dear Mr. Sporn:

Reference is made to our major amendment dated November 6, 1997 in which we included the 250 mg strength capsule for review in our Abbreviated New Drug Application (ANDA) 75-020 for Hydroxyurea Capsules, USP 500 mg.

With this **amendment** we withdraw the 250 mg strength of Hydroxyurea Capsules, USP from our pending ANDA. This withdrawal is based upon the pre-approval inspection which took place at the contract manufacturer of this product. During the inspection, processing issues were noted regarding the 250 mg submission batch. Please consider all sections and pages of the original ANDA and the 11/6/97 major amendment pertaining to the 250 mg strength capsule to be withdrawn. We will resubmit the Hydroxyurea 250 mg strength capsule for review post-approval of this ANDA.

This **amendment** is submitted in two (2) volumes, an archival copy and a technical review copy. We certify that a true copy of this amendment has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, GA.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482 or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

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Refuse to File
Anna Marie H. Weidel
1/8/97

1/13/97

Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

December 10, 1996

Mr. Douglas Sporn,
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA for Hydroxyurea Capsules, USP 250 or 500 mg

Dear Mr. Sporn:

Duramed Pharmaceuticals, Inc. (Duramed) submits today an original abbreviated new drug application (ANDA) seeking approval to market Hydroxyurea Capsules, USP, 250 and 500 mg, that are bioequivalent to the listed drug, Hydrea® (hydroxyurea capsules, USP), manufactured by Bristol-Myers Squibb Co. pursuant to NDA # 16295.

The facility for manufacturing of this dosage form is

A Citizen Petition for the 250 mg capsule strength was filed with the Dockets Management Branch of FDA on Wednesday, October 23, 1996.

In accordance with the study protocol, approved by the Office of Generic Drugs (refer to documents included in Section XX), Duramed conducted one definitive *in vivo* bioequivalence study using 500 mg Hydroxyurea Capsules, USP. Duramed requests a waiver of the *in vivo* bioequivalence study for the 250 mg capsules based on conformance with 21 CFR 320.22(d)(2) of the regulations.

Hydroxyurea Capsules, USP, 250 mg and 500 mg, are stable and a two year expiration dating is requested for all package sizes. The two year expiration dating is supported by accelerated stability testing.

This ANDA is submitted in three (3) volumes. Duramed is filing an archival copy (in blue folders) of the application that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section. A separate copy of the Bioequivalence section is provided (in orange folders) and includes a computer disk, in 3.5" format, containing ASCII files of the measured concentrations of the drug substance and the kinetic parameters for the bioequivalence study.

For more detailed information on the organization of this ANDA, please refer to the "Executive Summary - Organization of the ANDA" which follows this letter.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please feel free to contact Mr. James Mason at (513) 731-9900, extension 7322, or me at (513) 731-9900, extension 7274.

Thank you for your prompt handling of this submission.

Sincerely,

James Mason

for John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs