CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

16-295/S-036

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

I. Project Identification

NDA number/serial number	16-295/SE2-036
Submission date	February 19, 2003
Drug name	Droxia
Generic name	Hydroxyurea
Dosage form	200 mg, 300 mg, 400 mg capsules
Applicant	Bristol-Myers Squibb Co. Pharmaceutical Research Institute PO Box 4000 Princeton, NJ 08543-4000
Reviewer	Anne Zajicek, M.D., Pharm.D.
Team Leader	N.A.M. Atiqur Rahman, Ph.D.
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.
Submission Type	NDA-Supplement

II. Executive Summary

This study is submitted by the applicant in accord with a Phase 4 commitment to determine hydroxyurea disposition in adult patients with sickle cell disease with various levels of renal function.

A. Overall Recommendations

The FDA concurs with the applicant's labeling suggestion. Based on the information provided in the submitted study, the recommended starting dose for patients with a creatinine clearance less than 60 ml/minute will be half the usual starting dose of 15 mg/kg/d, or 7.5 mg/kg/d.

B. Comments

The submitted study was a single dose study. There is no concentration-effect or concentration-safety data available in the literature to improve the extrapolation of this single-dose data to chronic dosing.

Due to the lack of exposure-response or exposure-safety relationships, it is difficult to judge the degree of dosage adjustment necessary for patients with impaired clearance. It is clear that 60% of the drug is non-renally eliminated, so an empiric dosage reduction of one half in patients with renal dysfunction is reasonable. This dose adjustment is expected to provide similar exposure to the drug for renally impaired patients as for the patients with normal renal function.

Monte Carlo simulations, which take into account the unexplained variability in clearance, also support the proposed dosage adjustment. This is appropriate in view of the fact that patients are being treated for a chronic condition, and that avoidance of neutropenia is desirable.

C. Labeling Comments

1. From applicant:

Metabolism

[

]

FDA change:

Metabolism

Up to 60% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. One pathway is probably saturable hepatic metabolism. Another minor pathway- may be degrad ation by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of three leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

FDA comment: The submitted study showed 60% non-renal elimination.

2. From applicant:

[

]

FDA change:

In adult patients with sickle cell disease, an open-label, non-randomized, single dose, multi-center study was conducted to assess the influence of renal function on the pharmacokinetics of hydroxyurea. Patients in the study with normal renal function (creatinine clearance (CrCl) > 80 mL/min); and mild (CrCl 50-80 mL/min), moderate (CrCl=30-<50 mL/min) or severe (<30 ml/min) renal impairment received hydroxyurea...

FDA comment: clarifies meaning of normal renal function, adds study patient with moderate renal dysfunction

3. From applicant

Renal Insufficiency

[

]

FDA response:

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of DROXIA in patients with renal impairment. The results of a single dose study of the influence of renal function on the pharmacokinetics of hydroxyurea in adults with sickle cell disease suggest that the initial dose of hydroxyurea should be reduced by 50%, to 7.5 mg/kg/d, when used to treat patients with renal impairment. (See **PRECAUTIONS** and **CLINICAL PHARMACOLOGY**). Close monitoring of hematologic parameters is advised in these patients.

Creatinine Clearance (mL/min)	Recommended Droxia® Initial Dose (mg/kg daily)
≥ 60	15
< 60 or ESRD*	7.5

FDA comment: Reprint of Table will re-state the dosage recommendation for patients with renal dysfunction at defined by creatinine clearance < 60 ml/min.

D. Recommendations

Please forward the above comments to the sponsor.

/S/

Anne Zajicek, M.D., Pharm.D.
Medical Officer
OCPB, DPE1
DODP

/S/

N.A.M. Atiqur Rahman, Ph.D.
Team Leader
OCPB, DPE1
DODP

CC:
NDA 16-295
HFD-150 Division File
HFD-150 CCottrell
HFD-150 RDagher, QRyan
HFD-860 MMehta, CSahajwalla, ARahman, AZajicek
CDR Biopharmaceutics

III. Table of Contents

IV. List of Abbreviations

ANC: absolute neutrophil count
AUC: area under the concentration vs. time curve
AUC $_{0-\infty}$: area under the concentration-time curve extrapolated from time 0 to infinity
BSA: body surface area
C_{max} : peak plasma concentration of the drug
CL: clearance
CL/F: apparent oral clearance
CV: coefficient of variation
CYP450: cytochrome P-450
Hr, hrs: hours
Kg, kg: kilograms
L: liter
LOD: limit of detection
LLOQ: lower limit of quantification
M^2, m^2: square meters, meters squared
Min, min: minutes
ml, mL: milliliter
µg/L: micrograms per liter
µM: micromolar, micromoles per liter
NDA: New Drug Application
ng/ml: nanograms per milliliter
PD: pharmacodynamics
PK: pharmacokinetics
PPK: population pharmacokinetics
RBC: red blood cell
SCD: sickle cell disease
sd: standard deviation
sNDA: supplemental NDA
$T_{1/2}$, $t_{1/2}$: half-life V_z/F: apparent volume of distribution
T_{max}: time to reach maximal concentration
V/F: apparent volume of distribution
WBC: white blood cell count

V. Summary of Clinical Pharmacology Findings

The clinical pharmacokinetics of a single 15 mg/kg oral dose of hydroxyurea in adults with sickle cell disease and varying levels of renal function was studied. Renal function was defined as normal (creatinine clearance >80 ml/min), mildly impaired (50-80 ml/min), moderately impaired (30-50 ml/min), severely impaired (<30 ml/min), or end-stage renal disease (on dialysis). Hydroxyurea clearances were 245 ± 70 ml/min (mean ± sd), 115 ± 20 ml/min, 162 ml/min, 142 ± 42 ml/min, and 95 ± 9 ml/min for each of the five groups, respectively. Exposure correlated inversely, and clearance correlated directly, with renal function. In agreement with previous studies, the drug is approximately 40% renally cleared and 60% cleared by non-renal pathways.

VI. Background

Sickle cell disease (SCD) is an autosomal recessive disorder which occurs primarily in people of African and Mediterranean descent. It is hypothesized to provide a survival advantage in those carrying the gene who are infected with malaria. The cause of the disease is a gene mutation in the β-globin gene, producing the defective sickle cell (S) hemoglobin gene. The red blood cells (RBCs) with hemoglobin SS form a sickle shape in the presence of low oxygen tension; these sickle-shaped cells are less distensible than normal RBCs, and are more easily damaged in the small capillaries. The damaged cells are removed by the spleen, or are broken down in the circulation, causing a hemolytic anemia. The sickled cells also clog small capillaries, leading to end-organ damage from lack of blood supply and to painful crises. The result, in addition to end-organ damage such as renal failure, is transfusion dependence and frequent hospital admissions for pain management.

It has been found that RBCs carrying fetal hemoglobin do not sickle in the presence of low oxygen tension. It has also been found that hydroxyurea increases the percent of fetal hemoglobin in RBCs.

Hydroxyurea is a urea derivative (see Figure 1) which demonstrates antineoplastic activity, and is used as an adjunct in various forms of leukemia to produce a reduction in circulating white blood cells. It also stimulates production of fetal hemoglobin (Hgb F), which has been found to be beneficial in patients with sickle cell disease. The exact mechanism of these effects is not clear, and may include increases in RBC hydration, decrease in vascular wall adherence, and suppression of white blood cell (WBC) counts in addition to the increase in fetal hemoglobin.

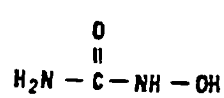

Figure 1. Structure of hydroxyurea

Hydroxyurea is cleared in part by a renal pathway. In view of the renal elimination, and use in sickle cell patients who frequently have renal dysfunction, a Phase 4 commitment to investigate hydroxyurea disposition at various levels of renal function was issued at the time of approval.

VII. Question-Based Review

A. What are the pharmacokinetics of hydroxyurea in patients with normal renal function?

The pharmacokinetics of hydroxyurea have been studied in both the sickle cell population and in patients with cancer. Hydroxyurea is administered as an oral capsule and by intravenous injection. These studies indicate that it has a bioavailability approaching 100%. Following oral administration, hydroxyurea is quickly absorbed, with a t_{max} of 1-4 hours. Its volume of distribution approximates total body water. It is cleared by two processes, a saturable hepatic metabolic process (about 60%), and by a linear renal pathway (about 40 %). The elimination t ½ of hydroxyurea averages 4 hours.

Table 1. Pharmacokinetics of hydroxyurea in patients with normal renal function

Reference	Disease	Dose	Clearance			T1/2
			total	renal	nonrenal	
Villani et al	HIV	500 mg PO BID	12.7 L/h/70kg			2.5 ± 0.5 hr
Smith et al	Cancer	15.2-19.8 gm/m2 over 24 hr	19 L/h/1.73m2	3.64 L/h		4.93 hr
Rodriguez et al	Cancer	2 gm IV or PO	7.6 L/h/1.73m2	37% excreted unchanged		3.32 hr
Newman et al	Cancer	1-3.2 g/m2 over 120 hr	6.3 L/h/m2	2.14 ±0.18 L/hr	3.39±0.28 L/hr	3.25 ± 0.18 hr
Charache et al	Sickle cell	2 gm	7.4 ± 1.8 L/h			
NDA 16,295/s001	Sickle cell	15 mg/kg (700-1400 mg)	14.7 ± 4.2L/h (nl renal fx)	5.2 ± 2 L/h	9.5 ± 4.1 L/hr	3.1 ± 0.84 hr

B. What are the side-effects of hydroxyurea?

The primary side-effect of hydroxyurea is bone marrow suppression, including neutropenia and thrombocytopenia. This effect is not well correlated to hydroxyurea exposure (see Figure 6).

C. What are the pharmacokinetics of hydroxyurea in patients with sickle cell disease and varying levels of renal function?

The pharmacokinetics of hydroxyurea were studied in 17 adults with sickle cell disease. The adults were divided into five levels of renal function, in accordance with FDA guidance. A single dose of hydroxyurea was administered orally, and blood and urine were collected.

Study design: single dose, open label, multi-center
Subjects: Seventeen adult subjects with sickle cell disease and various levels of renal function
Levels of renal dysfunction:
Group 1 (n=7): normal renal function (creatinine clearance >80 ml/min),
Group 2 (n=4): mild renal dysfunction (creatinine clearance 50-80 ml/min),
Group 3 (n=1): moderate renal dysfunction (creatinine clearance 30-49 ml/min),
Group 4 (n=3): severe renal dysfunction (creatinine clearance <30 ml/min),
Group 5 (n=2): end-stage renal disease (creatinine clearance =0) on hemodialysis.

Inclusion-Exclusion Criteria: see Appendix 4

Dosage and administration: Subjects were given a dose of 15 mg/kg Droxia capsules, using the 200mg, 300mg, and 400mg capsule strengths
Pharmacokinetic sampling:

> **Blood:** Samples were collected at 0 hr (pre-dose), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 1, 24, 30 and 36 hours post-dose
> **Urine:** Urine was collected at intervals 0-6, 6-12, 12-24, and 24-36 hours post-dose

Assay method: A validated — method with — was used for blood and urine concentrations of hydroxyurea. The LLOQ was — µg/ml.

Safety measurements:
A complete blood count, serum electrolytes, liver enzymes, bilirubin, albumin, uric acid, amylase, serum creatinine and BUN were drawn at screening, at baseline (pre-dose), at 2 days and at a follow-up appointment 7-12 days after the dose.

Adverse events were recorded as severe and not severe (See Question hydroxyurea).

Table 2. Pharmacokinetics of hydroxyurea in patients with sickle cell disease (Mean ± sd)

Groups by creatinine clearance (crcl)	N	AUC (μg-h/ml)*	Clearance (ml/min) Mean ± sd			T ½
			CL/F	CL renal	CL nonrenal	
Group 1: crcl >80 ml/min	7	73 ± 24	246 ± 70	87 ±33	158 ± 68	3.1 ± 0.8
Group 2: crcl 50-80 ml/min	4	148 ± 26	115 ± 20	29 ± 5	86 ± 16	3.9 ± 0.8
Group 3: crcl 30-50 ml/min	1	103	162	18	144	2.7
Group 4: crcl <30 ml/min	3	127 ± 46	142 ± 42	15 ±13	127 ± 36	5.3 ± 0.8
Group 5: ESRD	2	176 ±16	95 ± 8	0	95 ± 8	4.95 ± 0.6

* AUC normalized to a 1000 mg dose

The AUC for hydroxyurea decreased linearly with increasing creatinine clearance (see Figure 2).

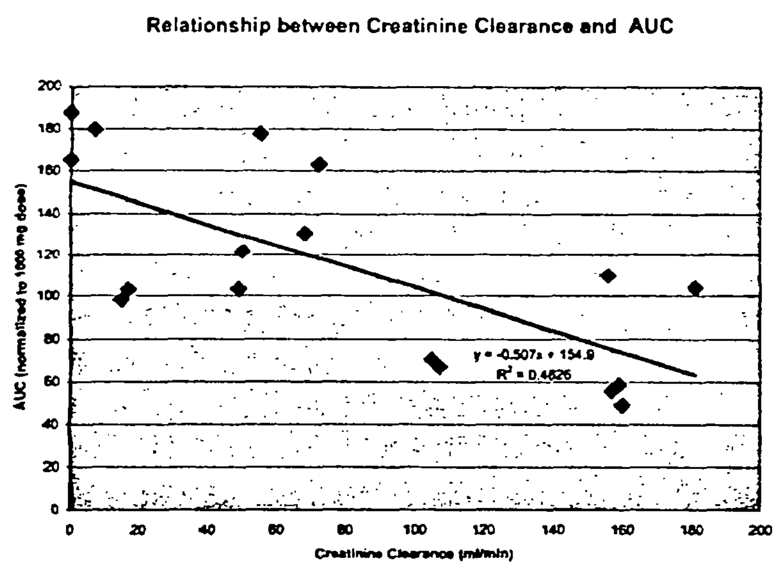

Figure 2.

There was a direct relationship between hydroxyurea clearance and creatinine clearance (see Figure 3). It is apparent that even with no renal function, clearance is approximately 100 ml/min, about a 40% reduction from those with normal renal function.

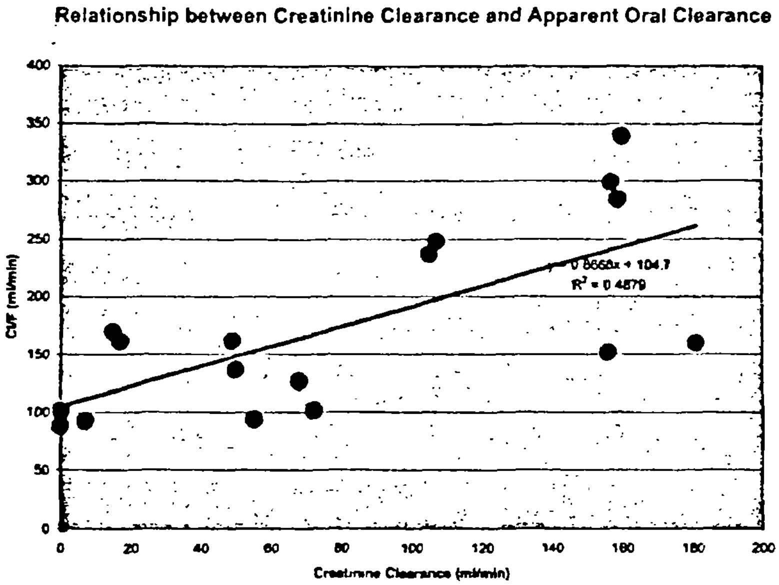

Figure 3.

Renal excretion of hydroxyurea was measured in four timed urine collections over 36 hours: from 0-6, 6-12,12-24, and 24-36 hours after the oral dose (see Figure 4). A mean of 26 % of the administered dose was excreted during the collection time. Renal clearance accounted for 32%, and nonrenal clearance accounted for an average of 62%, of total clearance in patients with normal renal function.

APPEARS THIS WAY ON ORIGINAL

Renal Excretion of Hydroxyurea

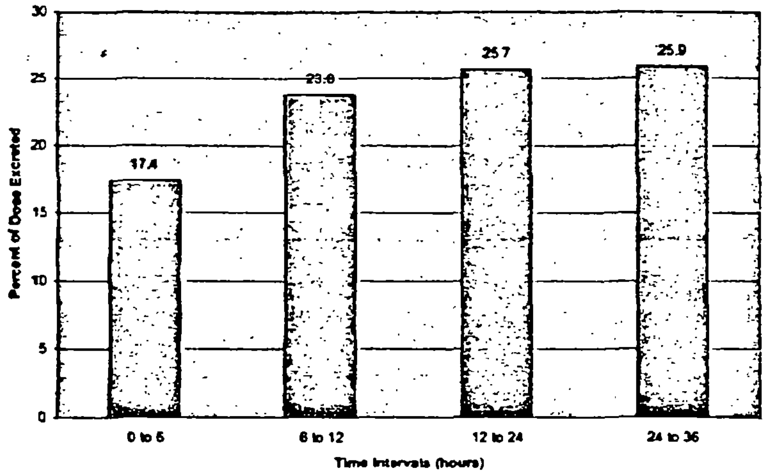

Figure 4.

D. What was the effect of hemodialysis on hydroxyurea clearance?

Two patients were maintained on hemodialysis, and received hydroxyurea both before and after hemodialysis on different days to determine the hemodialysis clearance of hydroxyurea . Results show that 4 hours of hemodialysis decreased AUC by 37 % and 28 % for each of the two patients, and increased clearance by 59% and 39% respectively.

E. Is there a relationship between pharmacokinetic parameters, such as AUC, and effect (white blood cell count on day 9)?

WBC count was determined at baseline, and at days 2 and 9 following the single dose of H. There was a weak relationship between hydroxyurea AUC and decline in WBC and neutrophil count (see Figure 5).

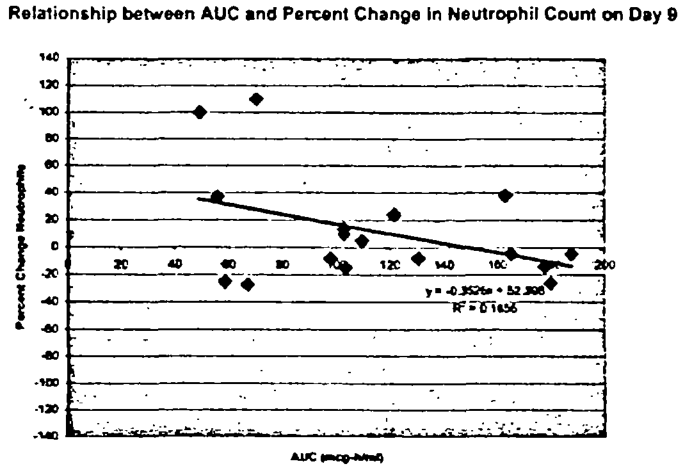

Figure 5.

F. If there is a relationship between AUC and decrease in neutrophil count, can it be extrapolated from a single dose to daily dosing?

It is known that hydroxyurea decreases WBC count in a dose-dependent manner. The figure below shows the decrease in neutrophil count as a function of AUC in oncology patients who received 2 grams of hydroxyurea every three days (Figure 6). [Note that the AUC units are in μM-h; 80 μg-h/ml corresponds to approximately 1000 μM-h.] It is unclear what the exact relationship is: patients with similar AUCs had a range of 0-90% decrease in ANC. Therefore, it is not clear if the AUCs seen in this group of patients with SS disease following a single dose would translate into neutropenia if administered chronically.

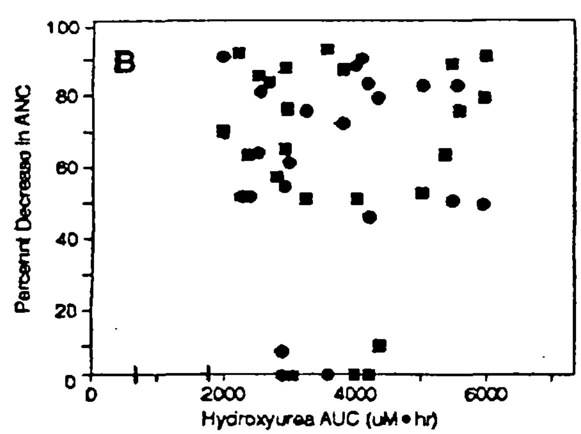

Figure 6. Relationship between AUC and percent decrease in ANC in oncology patients receiving 2 grams hydroxyurea every three days (Rodriguez et al. Blood 1998; 91(5): 1533-1541)

G. **Should the initial dose of hydroxyurea be reduced for patients with renal dysfunction, given that hydroxyurea dosage is titrated to white blood cell count?**

Yes. Hydroxyurea is approximately 40% renally cleared, and 60% nonrenally cleared. In patients with no renal function, total CL was approximately 60% that of patients with normal renal function. Therefore, AUC in patients with ESRD was approximately double. There is no known exposure-response relationship, so it is unclear if the AUC of patients with normal renal function is optimal. However, since sickle cell anemia is a chronic condition, and since the consequence of overdose could be profound neutropenia, it is reasonable to decrease the initial starting dose by 50% as suggested by the applicant. Figure 7 illustrates the relationship between creatinine clearance and AUC if dose was reduced to 7.5 mg/kg in these study patients with a creatinine clearance less than 60 ml/min.

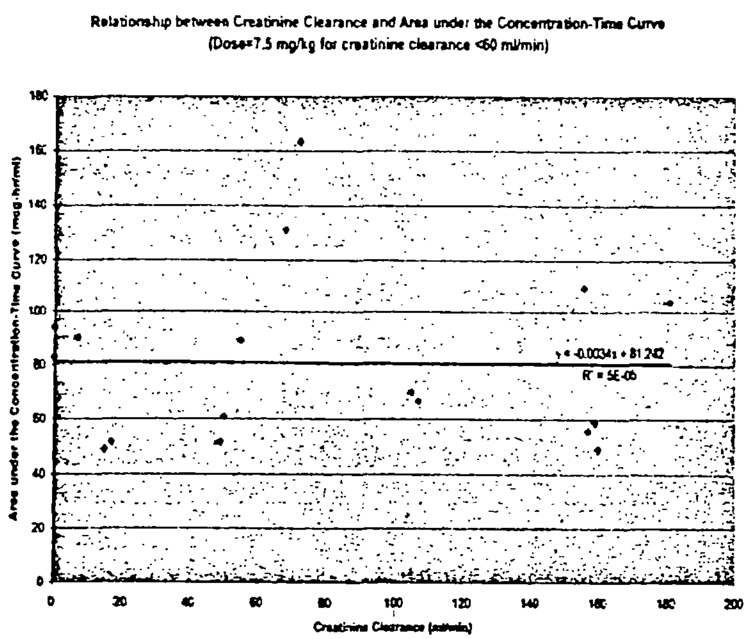

Figure 7. Relationship between creatinine clearance and AUC with a 50% dosage reduction for patients with creatinine clearance < 60 ml/min

Computer Simulations

In order to appreciate the influence of variability of CL in the choice of the dose adjustment and creatinine clearance cut-off (below which the dose needs to be adjusted), a series of computer simulations using S+ were performed.

Objectives: To understand the influence of different dose adjustment schemes on the probability of patient exposures meeting a specific criterion. Specifically, the percentage of patients whose AUCs fall within the target AUC range, for different dosing adjustments (e.g., ½, 2/3 etc of normals) and different creatinine cut-off values (e.g., 60, 30 etc ml/min) were evaluated. The target AUC range was arbitrarily specified as the 66^{th} and 33^{rd} percentiles of the AUCs in normals.

Methods:

CL-Creatinine clearance relationship:

From NONMEM output:

typical log clearance =4.68 L/hr

slope of plot of creatinine clearance vs clearance = 0.00484

standard deviation of clearance = 0.3

Assumptions included:

N=10,000 patients

Range of creatinine clearance: 0-120 ml/min

Range of ages: 18-60 years

Range of serum creatinine: 0.5-2 mg/dl

Mean serum creatinine: 1.5 mg/dl (SD=1 mg/dl)

Weight ranges:

Male 60-100 kg

Female 50-90 kg

Simulations with S+:

Simulations were performed (see Appendix 6 for S+ code) using a sample size of 10,000, with assumptions as listed above. There is no exposure-safety or exposure-response relationship defined in the literature, so the target AUC (66^{th} and 33^{rd} percentiles) was calculated from the AUCs of the seven patients with normal renal function.

Median AUC 100.8 mg-h/L, with upper confidence interval (UCI) 118.12, lower confidence interval (LCI) 86.53

Reference LCI =AUC less than the lower 33.3 % of 1 SD below median value

TSTlo.fail = percent of simulated patients with AUC less than 33.4% of 1 SD below the median AUC

Reference UCI =AUC greater than the 66.6 % of 1 SD above median value

TSThi.fail= percent of simulated patients with AUC greater than 66.6% of 1 SD above median AUC

Results

Histogram of S+ -simulated AUC and creatinine clearances is shown in Figures 7 and 8.

The simulated AUCs resulting from changes in either dose or creatinine clearance, are shown in the Table 3 below. Focusing on the last two columns of TSThi.fail and TSTlo.fail, it is clear that, for a given dose, as the creatinine clearance cut-off approaches 30 ml/min, the percent of patients whose AUCs are higher than the upper limit of the target AUC range increases, and the percent of patients whose AUCs are lower than the lower limit of the target AUC range decreases.

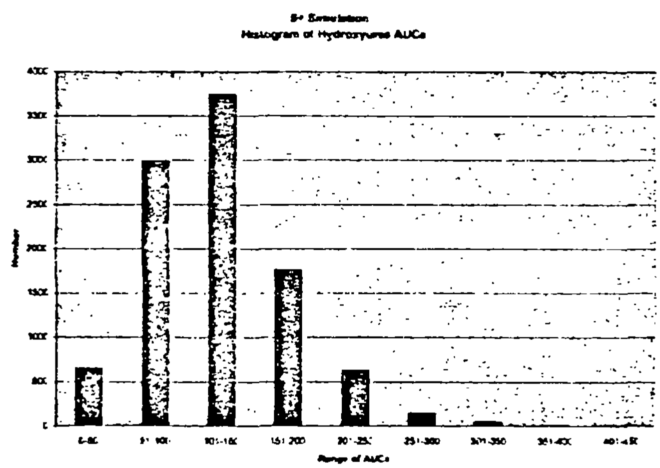

Figure 8. Histogram of AUCs from S+ simulations

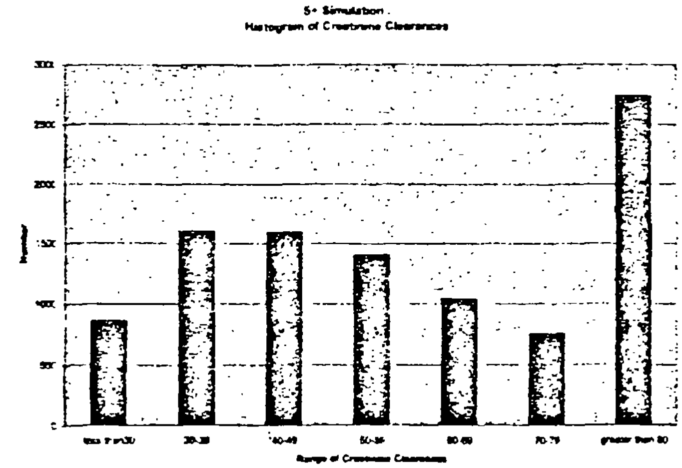

Figure 9. Histogram of creatinine clearances from S+ simulations

Table 3.

Table of S+ Simulation Results

Cut-off	Adj Dose	LCI	MED	UCI	TSThifail	TSTlofail
80	15	86.53	100.8	118.12	56.06	16.36
80	12				38.17	28.44
70	12				39.25	26.06
60	12				41.57	25.12
50	12				45.26	23.54
40	12				49.15	20.95
30	12				51.96	19.28
80	9				18.79	51.54
70	9				21.69	48.9
60	9				27.23	42.46
50	9				34.12	35.42
40	9				42.34	27.62
30	9				50.87	21.26
80	7.5				11.92	66.48
70	7.5				16.92	60.4
60	7.5				23.22	51.69
50	7.5				30.39	43.82
40	7.5				39.92	32.41
30	7.5				49.71	22.1
80	5				9.38	79.43
70	5				13.71	73.27
60	5				19.65	64.43

50	5	27.96	52.18
40	5	39.21	37.83
30	5	50.14	23.91

Discussion
The difficulty in interpreting the results from the pharmacokinetic study in the renally impaired patients is the lack of an exposure-response relationship. In other words, it is unclear what range of exposures is related to effectiveness (increased fetal hemoglobin, decreased number or intensity of pain crises, mortality) or safety (neutropenia). In this analysis, the median AUC ± 1 SD for patients with normal renal function that was used as the target AUC is arbitrary. The applicant also suggested the use of such a target window. The selected target window is conservative, in that it ensures deviations from the mean by ± 33%. Of course, a steep exposure-toxicity relationship might make this target anti-conservative. The safety data included a complete blood count 2 and 9 days after a single dose, clearly not the real clinic setting in which patients take drug every day for months or years and where neutropenia may evolve over a period of time.

The simulations suggest that for the proposed dosing scheme (reduction in dose by 50% for a creatinine clearance <60 ml/min), 23% of the patients in the general population might have AUCs above the target (requiring downward dose titration), and 52% below the target (requiring upward dose titration).

H. **Were there any adverse events?**

A complete blood count, serum electrolytes, liver enzymes, bilirubin, albumin, uric acid, amylase, serum creatinine and BUN were drawn at screening, at baseline (pre-dose), at 2 days and at a follow-up appointment 7-12 days after the dose.

Adverse events were recorded as severe and not severe.

Serious adverse events included pain crises, seizure, and worsening renal function. None of these events was temporally related to hydroxyurea.

Non-serious adverse events included sinusitis, urinary tract infection, vomiting, nausea, seasonal allergies, rash, rales, thrombophlebitis, headache, and backache, none of which was felt to be related to hydroxyurea.

There were no changes in laboratory parameters, and no episodes of neutropenia as defined by ANC < 2500/mm^3.

I. **Was the assay properly validated? (See Appendix 5)**

The sponsor submitted assay validation reports for hydroxyurea in plasma, urine and dialysate. No data was submitted for dialysis concentrations, as the volume of dialysate was mistakenly not recorded.

In brief, the assay method involves [ ]

The assays were validated in accord with FDA guidance, and showed adequate accuracy, precision, and stability. The assay was linear over the concentration range of — μg/ml (the lower limit of quantitation) to — μg/ml.

APPEARS THIS WAY
ON ORIGINAL

Appendix 1. References

1. Villani P, Maserati R, Regazzi M et al. Pharmacokinetics of hydroxyurea in patients infected with human immunodeficiency virus Type 1. J Clin Pharmacol 1996; 36:117-121.

2. Smith DC, Vaughan WP, Gwilt PR et al. A Phase 1 trial of high-dose continuous infusion hydroxyurea. Cancer Chemother Pharmacol 1993; 33:139-143.

3. Rodriguez GI, Kuhn JG, Weiss GR et al. A bioavailability and pharmacokinetic study of oral and intravenous hydroxyurea. Blood 1998; 91(5): 1533-41.

4. Newman EM, CarrollM, Akman SA et al. Pharmacokinetics and toxicity of 120-hour continuous infusion hydroxyurea in patients with advanced solid tumors. Cancer Chemother Pharmacol 1997; 39:254-58.

5. Charache S, Dover GJ, Moyer MA. Hydroxyurea-induced augmentation of fetal hemoglobin production in patients with sickle cell anemia. Blood 1987; 69(1): 109-16.

25 pages redacted from this section of the approval package consisted of draft labeling

Appendix 4. Inclusion-Exclusion Criteria

The following criteria must be met for the subject to be considered eligible for the study:

a) Able to provide written informed consent.

b) Male or female, ≥18-years-old.

c) Females of childbearing potential are eligible, unless serum HCG is documented positive within 24 hours before the dose of DROXIA™ on Day 1, and an acceptable method of contraception (approved oral, injectable, or implantable contraceptive drug, IUD, diaphragm, or condom with spermicidal jelly or foam) is not being used. [Note: A urine HCG test can be used in place of the serum HCG test if the urine assay can detect HCG to a concentration of 25 IU/L.]

d) Documented SCD of either the HbSS or $HbS\beta^0$-thalassemia genotypes.

e) Weight ≥50 kg and no more than 15% below or 40% above ideal body weight (see Appendix B). Ideal body weight values in Appendix B will also apply for subjects 18 to 24 years-old and >59 years-old.

f) Measured CL_{cr} in the range of <30, 30-50, 50-89 or >80 mL/min, documented on at least two occasions, a minimum of 5 days apart, within 1 month before enrollment. Each patient's CL_{cr} will be calculated based on total urinary creatinine excretion, collected over 24 hours, and contemporaneous serum creatinine. Subjects will be assigned to the appropriate stratum when the difference between the two clearance values does not exceed 25%; if the difference between the two values exceeds 25%, a third determination of CL_{cr} value will be performed only if an error is suspected in one of the previous measurements. Otherwise patients with greater than a 25% difference in CL_{cr} will not be enrolled in the study. Baseline CL_{cr} will be determined by taking the mean of the patient's two CL_{cr} values that are within 25% of each other and in the same stratum.

g) All subjects should have no other clinically active diseases, as determined by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory tests conducted within a 2-week period prior to study enrollment (aside from clinically stable complications associated with SCA). With the exception of the clinical laboratory values listed in h) below, all clinical laboratory tests should be within normal limits for the testing laboratory.

h) Patients with the following clinical laboratory values are acceptable for inclusion in this study:

<u>Hematology</u>:	
hemoglobin	> 5.3 g/dL (without transfusion within 4 weeks of enrollment)
neutrophils	> 2,500/mm^3
platelets	> 95,000/mm^3
<u>Serum chemistry</u>:	
AST	< 3 x upper limit of normal
ALT	< 3 x upper limit of normal
albumin	>3.0 g/dL
Na^+	within 10% of upper limit of normal
K^+	within 10% of upper limit of normal
CO_2	within 10% of upper limit of normal
Cl^-	within 10% of upper limit of normal
Mg^{++}	within 10% of upper limit of normal
Ca^{++}	within 10% of upper limit of normal
amylase	within normal limits

i) ECG judged by the investigator to be without clinically significant abnormalities.

j) No evidence of gastrointestinal impairment, atypical bowel movements, previous GI surgery.

7.3 Exclusion Criteria

Meeting any of the following criteria excludes participation in the study.

a) Nursing or pregnant females.

b) Surgery within 4 weeks of enrollment (minor procedures requiring only local anesthesia are accepted).

c) Evidence of acute or chronic unstable cardiovascular, pulmonary, hepatic, hematologic, endocrine, neurological, or other illness.

d) Positive test for Hepatitis B surface antigens (HBsAg) or urine screen for drugs of abuse.

e) Inability to tolerate oral medication.

f) History of allergy or intolerance to HU.

g) Evidence of acute or chronic pancreatitis.

h) Use of an agent known to affect renal tubular function (e.g., probenecid, cimetidine, ß-lactam antibiotic, sulfamethoxazole/trimethoprim) within 2 weeks before enrollment.

i) Use of an agent known to affect hepatic metabolism (e.g., cimetidine, fluconazole, phenytoin, phenobarbital, rifampin, rifabutin) within 1 month before enrollment.

j) Exposure to other investigational agents within 1 month of enrollment.

k) Current or recent gastritis or diarrheal illness (within 1 month of enrollment) or a history of malabsorption or gastrointestinal surgery (except appendectomy), which could alter drug absorption.

l) Evidence of a decrease in renal function within 2 months before enrollment as indicated by a clinically significant increase in serum creatinine (in the opinion of the investigator).

m) Ingestion of alcohol within 48 hours prior to entry into the clinical facility.

n) Donation of blood in any investigation requiring blood samples or to a blood bank, except hematology or serum chemistry tests for this study or routine medical monitoring, within 1 month prior to the initiation of this study.

o) Any clinical condition or prior therapy which, in the opinion of the investigator or as indicated in product labeling, would make the subject unsuitable for the study.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Appendix 6: S+ Programming Code for Hydroxyurea AUC Simulations

```
## CL is in mL/min, so is CLcr
## AUC is in ug.h/mL

## Estimates
cutoff<-30
adjdose<-5

typlgCL<-4.68
slpCLcr<-0.00484
sdCL<-0.3

## Simulation Conditions
Nsubj<-10000
minCLcr<-0
maxCLcr<-120
minAge<-18
maxAge<-60
##minScr<-0.5
##maxScr<-2
meanScr<-1.5
sdScr<-1
minWTmale<-60
maxWTmale<-100
minWTfeml<-50
maxWTfeml<-90

## Initialization
CLcr<-c(rep(0,Nsubj))
CL<-CLcr
dose<-CLcr
age<-CLcr
scr<-CLcr
female<-CLcr
wt<-CLcr
AUC<-wt
grp<-wt

for (i in(1:Nsubj)) {

## Clearance simulation

   age[i]    <- runif(1,minAge,maxAge)
   female[i] <- round(runif(1,0,1))
   wt[i]     <- runif(1,minWTmale,maxWTmale)*(1-female[i]) +
                  runif(1,minWTfeml,maxWTfeml)*female[i]
   ##scr[i]  <- runif(1,minScr,maxScr)

   scr[i]<--1
   while (scr[i]<0.5 ) scr[i]   <- meanScr + sdScr*rnorm(1)

   CLcr[i]  <- (140-age[i])*wt[i]/(72*scr[i])

         if (female[i]==0) {
                  CLcr[i] <- CLcr[i]*0.85
```

```
        }

  CL[i]    <- exp(typlgCL + slpCLcr*CLcr[i] + sdCL*rnorm(1))

## Dosing
  dose[i]  <- 15*wt[i]
  grp[i]   <- 0
  AUC[i]   <- dose[i]*1000/(60*CL[i])
          ## multiply by 1000: mg/kg to ug/kg
                  ## divide by 60: min to hr

  if (CLcr[i] <= cutoff) {
        dose[i] <- adjdose*wt[i]
        grp[i]  <- 1
     AUC[i]  <- dose[i]*1000/(60*CL[i])
          ## multiply by 1000: mg/kg to ug/kg
                  ## divide by 60: min to hr
  }


}

## The following creates the dataset for normal CLcrs
REF.AUC <- AUC[CLcr>80]

Nref<-length(REF.AUC)

REF.LCI <- sort(REF.AUC)[33.4*Nref/100]
REF.MED <- sort(REF.AUC)[50*Nref/100]
REF.UCI <- sort(REF.AUC)[66.6*Nref/100]

##TST1.LCI <- sort(TST1.AUC)[2.5*Ntst1/100]
##TST1.MED <- sort(TST1.AUC)[50*Ntst1/100]
##TST1.UCI <- sort(TST1.AUC)[97.5*Ntst1/100]

TSThi.fail <- length(AUC[AUC>REF.UCI])*100/Nsubj

TSTlo.fail <- length(AUC[AUC<REF.LCI])*100/Nsubj

print (c(REF.LCI, REF.MED, REF.UCI))
TSThi.fail
TSTlo.fail
```

/s/

Anne Zajicek
6/24/03 05:31:17 PM
UNKNOWN

Atiqur Rahman
6/25/03 02:01:08 PM
BIOPHARMACEUTICS