CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-105

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 9 2000

NDA 21-105
ZOTRIM UTI therapy

SUBMISSION DATE:
Feb. 18, 1999

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

SPONSOR: DynaGen, Inc
840 Memorial Drive
Cambridge, MA 02139

REVIEWER: HE SUN, Ph.D.

I. BACKGROUND

The sponsor submitted this "Paper NDA" to include publications related to the proposed blister card of Trimethoprim-Sulfamethoxazole DS and Phenazopyridine HCL for the treatment of urinary tract infection and its symptoms.

Phenazopyridine HCL is a pre-1938 drug with no existing NDA. The safety and efficacy of the drug are supported by literature articles.

The effectiveness for Trimethoprim-Sulfamethoxazole DS has been demonstrated in FDA-approved drugs for 10 and 14 days treatment.

FDA has approved an NDA for a similar combination product for treatment of urinary tract infection, namely [redacted] which contains phenazopyridine HCL and sulfamethoxazol, as approved drug.

FDA advised the sponsor to conduct a pharmacokinetics drug-drug interaction and bioavailability study. The study report is included in this submission.

II. RECOMMENDATION:

The current submission is not acceptable to conclude that a drug–drug interaction is not present. Please forward Specific Comments section.

/S/

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. /S/ 5/9/00

cc: NDA 21-105, HFD-520 (Clinical, CSO), HFD-340 (Viswanathan), HFD-880 (Pelsor, Sun), HFD-880 Div. File NDA. CDR

III. STUDY SUMMARY

Title: Study title: coadministration of Trimethoprim-Sulfamethoxazole DS USP tablet and Phenazopyridine HCL 200 mg USP tablet.

Investigators: Angel O. Pietri, M.D.
ClinSites/LeeCoast Research Center, Inc.
3949 Evans Ave., Suite 300
Fort Myers, FL 33901

Study description:

This is an open label, randomized, multiple-dose, two-period, two-treatment drug interaction study in female subjects. (Protocol Number 19050-97-01) to evaluate the effect of coadministration of Trimethoprim-Sulfamethoxazole DS USP tablet and Phenazopyridine HCL 200 mg USP tablet.

The objective of the study is to demonstrate that the combination of both drugs at daily doses required in Zotrim UTI therapy will not cause any significant untoward effects; and to determine whether either drug affected the plasma concentrations of the other.

Twelve healthy female subjects received the drug alone or in combination in crossover fashion. Each study period consisted of six days separated by a nine-day washout period. Three-days of dosing with either Phenazopyridine HCL 200-mg USP tablet or the combination of Trimethoprim-Sulfamethoxazole DS USP tablet was followed by three days of dosing with both drugs. The subjects were sequenced during both study periods.

Blood samples were obtained on Day 1, Days 3 and Days 6 of each period. Urine samples, collected on Day 1 prior to drug administration, and pooled urine collection on Days 2, 3, 5, and 6. Details are shown in Table 1 and 2.

Assay: lowest detection limit for trimethoprim was 10 ng/ml, 250 ng/ml for sulfamethoxazole in plasma, and 1 ug/ml and 5 ug/ml in urine, respectively.

Lowest detection limit for phenazopyridine HCL was 5 ng/ml in plasma and 25 ng/ml in urine.

Results:

1. Hematology and Urinalysis parameter comparison were not reviewed.

2. Plasma concentrations of Trimethoprim-Sulfamethoxazole with and without coadministration of Phenazopyridine HCL, and plasma concentration of Phenazopyridine HCL with and without Trimethoprim-Sulfamethoxazole are listed in the table below.

	Day 3	Day 6 combine	T-test
Trimethoprim	3241.82 ±912.89	4129.13 ±1062.46	P=0.001
Sulfamethoxazole	79.36 ±20.29	98.65 ±31.46	P=0.003
Phenazopyridine	28.14 ±38.41	51.47 ±68.74	P=0.049

[redacted] plots of the individual trimethoprim, sulfamethoxazole, and phenazopyridine concentrations. The plots clearly show that concentrations of trimethoprim and sulfamethoxazole, or phenazopyridine were increased when the multidose regimen of trimethoprim-sulfamethoxazole (160 mg:800 mg) bid or phenazopyridine 200 mg tid was perturbed by addition of the alternate drug regimen at 72 hours after start of the initial regimen.

3. Urine concentrations of Trimethoprim-Sulfamethoxazole with and without coadministration of Phenazopyridine HCL, and urine concentrations of Phenazopyridine HCL with and without Trimethoprim-Sulfamethoxazole are listed in Tables below:

	Day 3	Day 6 combine	T-test
Trimethoprim	72.35 ±32.47	73.16 ±30.9	P=0.925
Sulfamethoxazole	71.41 ±52.57	79.36 ±39.67	P=0.877
Phenazopyridine	133.16 ±61.41	204.09 ±146.64	P=0.032

IV. CONCLUSION

1. Combination therapy causes the plasma concentrations of all three drugs to significantly increase. (As described by the sponsor, the rate of side effects was also increased when drugs are given in combination vs. given alone. Pending Medical Officer's review).

2. Urine samples show concentration over 24 hour period are comparable for Trimethoprim-Sulfamethoxazole but significantly higher for Phenazopyridine (p=0.032) when compared to drug given alone.

V. SPECIFIC COMMENTS

1. Urine volumes were not reported. Therefore, the urine data contains no information about the amount of drugs excreted.

2. Study results indicate that combination therapy causes the plasma concentrations of all three drugs to significantly increase at one hour after combination dose compared to drugs used alone. This information should be incorporated in the drug label.

3. (Need not convey to sponsor) Phenazopyridine HCL is a pre-1938 drug and Federal Register (48:34518, July 29, 1983) states that in vivo demonstration of bioavailability is not required for future applications.

4. (Need not convey to sponsor) The Medical Reviewer will evaluate sponsor's statement: "coadministration of Trimethoprim-Sulfamethoxazole DS and Phenazopyridine HCl does not cause significant untoward reaction compared to when either drug is administered alone".

APPEARS THIS WAY
ON ORIGINAL