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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-238

Clinical Pharmacology and Biopharmaceutics Review

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-238	Code: 3S		
Submission(s):	Type: NDA	Suppl.:	Letter Date: 8/30/2000	Date Received: 8/31/2000
Reviewer:	Sandip K. Roy, Ph.D.			
Team Leader:	Suresh Doddapaneni, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Granisetron hydrochloride			
Other Name(s):				
Trade Name:	Kytril®			
Molecular Weight:	348.9 (312.4 as free base)			
Molecular Formula:	$C_{18}H_{24}N_4O.HCl$			
Relevant IND(s)/NDA(s):	IND [redacted]			
Drug Class:	5-HT_3 receptor antagonist			
Dosage Form:	Oral solution			
Route of Administration:	Oral			
Dosing Regimen:	2 mg once daily or 1 mg twice daily			
Sponsor:	SmithKline Beecham Pharmaceuticals			
Proposed Indication:	Prevention of nausea and vomiting associated with emetogenic cancer therapy and with radiation			

BACKGROUND

Granisetron is currently approved in both tablet and injection formulations for the prevention of nausea and vomiting associated with emetogenic cancer therapy and with radiation. This NDA is for an oral solution that is being proposed as an alternative to the approved Tablet formulation in patients who have difficulty swallowing tablets, and for children who may be receiving emetogenic cancer therapies. The formulation components are shown below (see Appendix I for details).

Oral Solution: Each 10 ml of clear, orange-colored, orange flavored Kytril Oral Solution contains 2.24 mg granisetron hydrochloride equivalent to 2 mg granisetron. Inactive ingredients: citric acid anhydrous, FD&C Yellow No. 6, orange flavor, purified water, sodium benzoate, and sorbitol.

The indication, dosage and administration are the same for both products. A study to determine the bioequivalence of the oral liquid (2 mg) formulation to the oral tablet (2 mg) formulation was the only study submitted in support of the approval this product. The key question addressed for this NDA is as follows:

Are the approved tablet and the proposed oral solution dosage forms bioequivalent?

Yes, the two formulations were deemed to be bioequivalent based on C_{max}, AUC_{0-t} and AUC_{0-inf}.

Study 308 was conducted by the sponsor to determine the bioequivalence of the approved 2 mg dose of the tablet formulation with a 2 mg dose of the oral solution formulation. The details of this study are as follows:

Study Design

- Open, randomized, four-way crossover study of replicate design in 40 healthy male and female volunteers
- Each volunteer received four oral doses of 2 mg of granisetron – two of 1 mg tablet and 10 ml of 1 0.2 mg/ml liquid formulation
- The order of dosing was randomized and the doses were administered at least 7 days apart

Analytical method

-
- Lower Limit of quantitation (LLQ): ng/ml
- Precision: % (Inter-day over all concentrations)
  % (Intra-day for ng/ml)
  % (Intra-day for ng/ml)
- Accuracy: % (average across all conc.)

Pharmacokinetic Assessments

- Blood samples were taken predose and nominally at 15, 30, 45, 60, 80, 100 minutes and 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, and 30 hrs after dosing with granisetron in each part.
- Pharmacokinetic parameters, C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$ were calculated by non-compartmental analysis.
- Bioequivalence was assessed by estimating the ratio of each AUC and C_{max} for the test formulation relative to the reference formulation with 90% confidence intervals.
- Bioequivalence was concluded if the 90% confidence interval was completely contained within the range [0.80, 1.25].

Results

- Pharmacokinetic comparison between the two formulations of granisetron summarized by the sponsor are shown in the table below:

Parameters	N	Liquid	Tablet	Ratio[b]	90% C.I.
AUC(0-inf) (ng.h/mL)	35	21.50 (2.73 – 154.03)	24.21 (2.22-110.90)	0.92	(0.80, 1.06)
AUC(0-t') (ng.h/mL)	38	15.01 (0.80 - 136.78)	15.74 (0.33 – 103.49)	0.96	(0.85, 1.07)
Cmax (ng/mL)	38	4.304 (0.496 – 15.437)	4.680 (0.351-15.597)	0.93	(0.85, 1.01)
Tmax[a] (hours)	38	1.33 (0.63 – 2.34)	1.33 (0.75-3.00)	0.02[c]	(-0.103,0.145)

a = Data presented as median (range)

b = Liquid: Tablet

c = median difference (liquid – tablet)

See Appendix II for individual AUC_{0-t}, AUC_{0-inf}, and C_{max} data.

- For AUC_{0-inf}, the 90% confidence intervals for the ratio of the oral liquid relative to tablet formulation were not contained within the interval (0.80, 1.25). The lower end of the confidence interval was actually 0.7976.
- For AUC_{0-t} and C_{max}, the 90% confidence intervals for the ratio of the oral liquid relative to tablet formulation were within the interval (0.80, 1.25).
- The range of terminal $t_{1/2}$ for oral liquid formulation was 0.91 to 7.47 hrs and for the tablet formulation was 1.05 to 8.09 hrs.

DSI Inspection

- Since this was the pivotal study, the clinical and analytical portions of the this study were audited by DSI (Division of Scientific Investigations). Upon inspection, it was determined that the sponsor accepted and rejected calibration standards inconsistently when running samples from subjects 14, 16, 17, and 28. Data obtained from these subjects were excluded from the study as suggested by DSI and bioequivalence of the test and reference formulations were reanalyzed (by Dr. Mei-Ling Chen). DSI report is attached in Appendix III.

- ***Comparison of FDA & Sponsor analysis***

	Parameters	Ratio	90% C.I.
FDA Analysis	AUC_{0-inf}	89.5	77.7 – 103.2
	AUC_{0-t}	94.3	84.3 – 105.6
	C_{max}	92.5	85.0 – 100.7
FDA Analysis*	AUC_{0-inf}	93.0	79.6 – 108.7
w/o 14, 16, 17, and 28	AUC_{0-t}	96.1	85.1 – 108.6
	C_{max}	93.8	85.4 – 103.1
Sponsor's Analysis	AUC_{0-inf}	92.0	79.8 – 106.0
	AUC_{0-t}	96.0	85.0 – 107.0
	C_{max}	93.0	85.0 – 101.0

*DSI inspection suggested irregularity in analysis of data from subjects 14, 16, 17, and 28

- FDA analysis yielded results that were almost identical to the results obtained by the sponsor for ratios of AUC_{0-t} and C_{max}. For ratio of AUC_{0-inf}, the lower end of the confidence interval was 0.777, which is lower than that reported by the sponsor.
- As suggested by DSI, subjects 14, 16, 17, and 28 were excluded and data were re-analyzed. This time the lower end of the confidence interval for ratio of AUC_{0-inf} improved to 0.796.

Discussion

The formulations were bioequivalent with respect to C_{max} and AUC_{0-t}. For AUC_{0-inf}, the 90% confidence intervals for the ratio of the oral liquid relative to tablet formulation were not contained within the interval (0.80, 1.25). The lower end of the confidence interval was 0.777. This value improved to 0.796 when subjects 14, 16, 17, and 28 were excluded from the analysis as suggested by the DSI. The sponsor argued that this study was under-powered for the determination of AUC_{0-inf} and that AUC_{0-t} is more relevant because it was measurable in all subjects (this is a highly variable drug). Both the values are reasonably close to 0.80 and there is no reason to believe that ignoring this slight difference will have any clinical significance. The adverse effects profiles were similar for both the formulation (per discussion with the medical officer).

Labeling

Kytril tablets were often simply referred to as *Oral Kytril* in the label in describing results obtained from studies conducted only with *Kytril tablets* and not with *Kytril oral solution.* Thus minor editorial changes are recommended in the label to appropriately reflect that the results obtained were from studies conducted by *Kytril tablets*. Thus the phrase *Oral Kytril* should be replaced with *Kytril tablets*, wherever appropriate.

RECOMMENDATION

This NDA is approvable from OCPB perspective.

/S/

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

5/8/2000
Date

FT initiated by Suresh Doddapaneni, Ph.D.

c.c. /NDA 21-097
/HFD-180 (Division files, MMcNeil)
/HFD-870 (SDoddapaneni, HMalinowski, SRoy)
/HFD-48 (SSubramanium)
/CDR (ZZadeng)

Appendix I

2 Drug Product

2.1 Quantitative Composition

One strength of Kytril® Oral Solution is manufactured for commercial marketing. This strength contains granisetron hydrochloride equivalent to 0.200 mg granisetron free base per mL (200 ug/mL). The unit formula for the oral solution is presented in 3.D. Table 1.

3.D. Table 1 Kytril® Oral Solution, 200 ug/mL, Formula No. 11/0.2

Name of Ingredients	Unit Composition (per mL)	Unit Dose (per 10 mL)	Function	Reference to Standard
Active Ingredient:				
Granisetron Hydrochloride equivalent to 0.200 mg granisetron pure free base	0.224 mg	2.24 mg	Active Ingredient	G472
Other Ingredients:				
Sorbitol				
Sodium Benzoate				
Citric Acid Anhydrous				
Juicy Orange Flavoring				
Orange Flavor				
FD&C Yellow No. 6				
Purified Water				

Appendix II

Cmax [ng/mL] for granisetron following single oral doses of tablet and liquid formulations of granisetron (2 mg) administered on separate dosing days

Subject No.	Tablet admin 1	Tablet admin 2	Liquid admin 1	Liquid admin 2	Tablet average	Liquid average	Liquid :Tablet
1	11.732	12.926	8.895	12.534	12.329	10.715	0.87
2	6.799	3.378	2.868	3.475	5.089	3.172	0.62
3	7.103	5.944	6.033	3.991	6.524	5.012	0.77
4	2.453	5.852	1.272	3.322	4.153	2.297	0.55
5	9.384	10.438	11.497	9.739	9.911	10.618	1.07
6	8.421	10.444	8.449	8.440	9.433	8.945	0.95
7	5.908	3.185	6.457	3.881	4.547	5.169	1.14
8	7.616	8.294	5.836	6.726	7.955	6.281	0.79
9	13.087	ND	ND	ND	ND	ND	ND
10	5.485	4.440	2.478	3.036	*4.963	2.758	0.56
11	7.034	6.697	6.919	8.316	6.866	7.618	1.11
12	4.012	1.632	4.073	3.660	2.822	3.867	1.37
13	7.738	5.793	4.208	6.084	6.766	5.146	0.76
14	1.538	0.856	0.984	1.235	1.197	1.110	0.93
15	5.830	5.645	5.848	5.222	5.738	5.535	0.96
16	21.735	9.458	7.946	11.594	15.597	9.770	0.63
17	9.297	9.837	6.862	11.617	9.567	9.240	0.97
18	3.094	5.971	5.975	3.530	4.533	4.753	1.05
19	ND	ND	6.368	ND	ND	ND	ND
20	9.239	2.673	4.167	2.745	5.956	3.456	0.58
21	12.235	8.590	6.231	7.955	10.413	7.093	0.68
22	9.421	9.833	15.956	8.490	9.627	12.223	1.27
23	7.107	8.831	9.180	9.755	7.969	9.468	1.25
24	6.312	6.586	7.089	5.385	6.449	6.237	0.97
25	3.516	3.024	3.002	2.018	3.270	2.510	0.77
26	0.415	0.476	0.877	0.844	0.446	0.711	1.59
27	2.550	2.767	1.936	3.469	2.659	2.703	1.02
28	8.857	8.381	6.546	6.243	8.604	6.395	0.74
29	1.635	4.665	4.547	3.808	3.250	4.178	1.29
30	2.005	2.859	4.133	2.088	2.432	3.511	1.44
31	8.213	3.825	3.270	4.770	6.019	4.024	0.67
32	2.789	1.518	1.100	1.370	2.154	1.239	0.58
33	0.964	0.810	1.559	0.615	0.887	1.087	1.23
34	3.107	2.767	1.033	2.326	2.937	1.680	0.57
35	8.138	7.106	5.833	6.321	7.622	6.077	0.80
36	2.285	3.367	4.279	4.120	2.826	4.200	1.49
37	0.610	0.292	NR	0.496	0.351	0.496*	1.41
38	13.683	12.748	10.814	8.618	13.216	9.716	0.74
39	5.309	5.840	6.631	6.711	5.575	6.671	1.20
40	11.184	12.270	11.115	19.758	11.727	15.437	1.32

* - single value

ND - not determined, subject withdrew from study

NR - no result, only one reported value above LLQ (0.25 ng/mL)

Tmax [hours] for granisetron following single oral doses of tablet and liquid formulations of granisetron (2 mg) administered on separate dosing days

Subject No.	Tablet admin 1	Tablet admin 2	Liquid admin 1	Liquid admin 2	Tablet average	Liquid average	Liquid - Tablet
1	0.75	2.50	2.50	1.33	1.63	1.92	0.29
2	1.00	1.00	1.00	1.33	1.00	1.17	0.17
3	1.33	3.00	2.00	2.50	2.17	2.25	0.09
4	1.33	0.75	1.33	0.75	1.04	1.04	0.00
5	1.67	2.50	1.67	1.67	2.09	1.67	-0.42
6	1.67	0.75	3.00	1.67	1.21	2.34	1.13
7	1.00	0.75	1.33	1.00	0.88	1.17	0.29
8	0.75	1.33	1.33	1.33	1.04	1.33	0.29
9	1.67	ND	ND	ND	ND	ND	ND
10	1.33	2.00	1.33	2.00	1.67	1.67	0.00
11	1.67	1.67	1.33	2.00	1.67	1.67	-0.00
12	0.75	2.00	0.75	0.75	1.38	0.75	-0.63
13	1.33	2.00	1.00	1.67	1.67	1.34	-0.33
14	1.33	0.50	1.00	0.75	0.92	0.88	-0.04
15	2.50	1.67	1.00	1.00	2.09	1.00	-1.09
16	1.33	1.33	1.00	1.33	1.33	1.17	-0.17
17	0.75	1.67	1.67	1.33	1.21	1.50	0.29
18	0.75	1.00	0.75	0.50	0.88	0.63	-0.25
19	ND	ND	1.00	ND	ND	ND	ND
20	1.00	1.00	0.75	1.33	1.00	1.04	0.04
21	1.00	1.00	1.67	1.33	1.00	1.50	0.50
22	1.33	2.00	3.00	0.75	1.67	1.88	0.21
23	1.67	2.00	0.75	1.00	1.84	0.88	-0.96
24	2.00	1.33	1.00	2.00	1.67	1.50	-0.17
25	0.75	1.67	1.67	0.75	1.21	1.21	0.00
26	0.75	0.75	1.33	1.00	0.75	1.17	0.42
27	1.33	1.33	1.33	2.00	1.33	1.67	0.34
28	1.33	1.67	1.33	1.33	1.50	1.33	-0.17
29	0.75	1.33	1.33	2.00	1.04	1.67	0.63
30	1.33	0.75	1.33	0.75	1.04	1.04	0.00
31	1.67	1.67	1.33	0.75	1.67	1.04	-0.63
32	1.00	1.00	1.00	1.00	1.00	1.00	0.00
33	0.75	1.33	1.67	0.75	1.04	1.21	0.17
34	1.00	1.00	1.00	2.00	1.00	1.50	0.50
35	0.75	0.75	0.75	1.33	0.75	1.04	0.29
36	1.33	1.33	1.67	2.00	1.33	1.84	0.51
37	2.00	1.67	NR	1.33	1.84	1.33*	-0.51
38	1.33	1.33	0.75	1.33	1.33	1.04	-0.29
39	1.67	1.00	2.00	1.70	1.34	1.85	0.52
40	3.00	3.00	2.00	1.33	3.00	1.67	-1.34

* - single value

ND - not determined, subject withdrew from study

NR - no result, only one reported value above LLQ (0.25 ng/mL)

AUC(0-t') [ng.h/mL] for granisetron following single oral doses of tablet and liquid formulations of granisetron (2 mg) administered on separate dosing days

Subject No.	t'	Tablet admin 1	Tablet admin 2	Liquid admin 1	Liquid admin 2	Tablet average	Liquid average	Liquid :Tablet
1	24	75.92	118.52	92.31	111.32	97.22	101.82	1.05
2	4	15.82	8.24	6.21	9.02	12.03	7.62	0.63
3	18	43.42	46.71	60.77	26.19	45.07	43.48	0.96
4	4	5.32	5.72	2.29	7.33	5.52	4.81	0.87
5	18	66.18	83.31	75.88	68.13	74.75	72.01	0.96
6	24	57.77	57.55	65.03	57.19	57.66	61.11	1.06
7	8	23.40	12.23	23.76	11.40	17.82	17.58	0.99
8	10	30.73	31.99	18.64	23.37	31.36	21.01	0.67
10	8	21.43	19.75	8.72	12.75	20.59	10.74	0.52
11	24	53.83	52.68	62.04	77.16	53.26	69.60	1.31
12	4	9.18	3.72	8.28	7.39	6.45	7.84	1.21
13	12	37.07	26.87	20.33	34.63	31.97	27.48	0.86
14	2	1.64	0.98	1.36	1.54	1.31	1.45	1.11
15	8	24.96	25.09	8.50	22.93	25.03	15.72	0.63
16	8	90.64	43.36	21.73	46.52	67.00	34.13	0.51
17	10	26.04	30.06	25.13	34.70	28.05	29.92	1.07
18	4	6.55	8.98	11.30	3.91	7.77	7.61	0.98
20	4	19.38	5.78	9.69	6.21	12.58	7.95	0.63
21	12	44.40	34.44	27.91	31.54	39.42	29.73	0.75
22	30	75.99	117.11	108.86	66.23	96.55	87.55	0.91
23	12	44.89	27.81	46.96	47.01	36.35	46.99	1.29
24	8	21.94	20.86	24.61	22.35	21.40	23.48	1.10
25	6	9.91	7.79	7.81	6.18	8.85	7.00	0.79
26	2	0.53	0.57	1.14	0.69	0.55	0.92	1.66
27	6	7.40	9.23	5.90	12.98	8.32	9.44	1.14
28	12	38.21	46.07	25.26	34.30	42.14	29.78	0.71
29	4	2.86	12.41	13.05	11.14	7.64	12.10	1.58
30	4	4.13	7.68	9.93	7.13	5.81	8.53	1.47
31	8	39.79	21.88	10.95	15.75	30.84	13.35	0.43
32	4	5.91	3.12	2.32	2.69	4.52	2.51	0.55
33	3	1.68	1.46	3.70	0.95	1.57	2.33	1.48
34	4	6.94	7.57	2.46	6.25	7.26	4.36	0.60
35	12	30.31	21.45	23.95	27.75	25.88	25.85	1.00
36	6	7.51	10.40	17.14	15.42	8.96	16.28	1.82
37	2.5	0.36	0.27	NR	0.80	0.33	0.80*	2.42
38	12	69.93	66.52	40.42	39.09	68.23	39.76	0.58
39	8	20.11	13.61	25.87	24.83	16.86	25.35	1.50
40	24	116.45	90.53	96.54	177.02	103.49	136.78	1.32

* - single value

NR - no result, only one reported value above LLQ (0.25 ng/mL)

AUC(0-inf)[ng.h/mL] for granisetron following single oral doses of tablet and liquid formulations of granisetron (2 mg) administered on separate dosing days

Subject No.	Tablet admin 1	Tablet admin 2	Liquid admin 1	Liquid admin 2	Tablet average	Liquid average	Liquid :Tablet
1	78.13	127.78	98.70	120.77	102.96	109.74	1.07
2	25.50	10.15	7.61	13.17	17.83	10.39	0.58
3	47.62	51.58	70.41	28.09	49.60	49.25	0.99
4	ND	ND	ND	ND	ND	ND	ND
5	70.13	91.58	78.27	73.11	80.86	75.69	0.94
6	58.70	58.78	69.61	61.21	58.74	65.41	1.11
7	27.09	14.32	26.44	11.96	20.71	19.20	0.93
8	32.37	33.97	19.57	ND	33.17	19.57*	0.59
10	25.55	23.90	9.43	14.74	24.73	12.09	0.49
11	56.81	54.80	66.73	82.28	55.81	74.51	1.34
12	11.53	4.36	10.19	9.53	7.95	9.86	1.24
13	40.45	31.33	21.63	39.94	35.89	30.79	0.86
14	3.64	ND	2.60	2.85	3.64*	2.73	0.75
15	37.12	38.58	10.19	30.62	37.85	20.41	0.54
16	128.82	47.97	23.09	55.21	88.40	39.15	0.44
17	27.61	33.69	27.66	37.73	30.65	32.70	1.07
18	8.08	10.48	ND	4.36	9.28	4.36*	0.47
20	23.58	7.21	11.84	7.26	15.40	9.55	0.62
21	48.95	38.02	31.35	35.66	43.49	33.51	0.77
22	78.45	127.75	113.87	68.73	103.10	91.30	0.89
23	ND	30.69	54.75	51.50	30.69*	53.13	1.73
24	25.46	21.96	27.45	25.88	23.71	26.67	1.12
25	11.25	9.19	8.52	7.09	10.22	7.81	0.76
26	ND	ND	ND	ND	ND	ND	ND
27	8.42	11.31	7.26	16.24	9.87	11.75	1.19
28	42.04	51.45	26.27	39.15	46.75	32.71	0.70
29	3.67	26.00	23.85	19.76	14.84	21.81	1.47
30	5.20	11.80	12.65	11.58	8.10	12.12	1.50
31	45.45	36.41	11.61	16.66	40.93	14.14	0.35
32	7.29	3.68	2.84	3.52	5.49	3.18	0.58
33	2.16	2.27	5.17	ND	2.22	5.17*	2.33
34	9.87	11.68	3.04	8.82	10.78	5.93	0.55
35	31.45	22.16	25.11	29.16	26.81	27.14	1.01
36	9.20	12.21	22.88	20.46	10.71	21.27	1.99
37	ND	ND	ND	ND	ND	ND	ND
38	77.87	72.74	41.83	41.32	75.31	41.58	0.55
39	22.96	14.17	30.73	27.79	18.57	29.26	1.58
40	129.58	82.22	107.03	201.82	110.90	154.03	1.39

* - single value

ND - terminal rate constant could not be adequately defined, greater than acceptable variability about the fitted line

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