signs of toxicity (tip toe gait, hyperactivity, piloerection, and vocalization) and decreased body weight gain of F_1 generation during days 28-64 (8%) were also observed in the mid dose group. Reproductive performance of F_1 generation was not adversely affected at doses up to high dose (40/30 mg/kg/day).

The mutagenicity studies revealed no evidence of mutagenic potential in all tests with GR 68755 including an Ames test, in vitro chromosome aberration test in human lymphocytes, unscheduled DNA synthesis in rat hepatocytes, mouse lymphoma cell assay, and rat micronucleus test. GR 62202, an intermediate in the synthesis of GR 68755, was positive in Ames test with one strain of S. typhimurium, TA 98 (frame shift) at concentrations of μg/plate in the absence of S-9 and μg/plate in the presence of S-9. However, it was negative with strain TA 1537 (frame shift) as well as strains TA 1535 and TA 100 (base pair substitution). GR 62202 is present in the drug product as an impurity at which is below qualification threshold of 0.1% (Guideline for Industry: Impurities in New Drug Substance, ICH Q3A, January 1996). The recommended human dose is 1 mg b.i.d.

The toxicity profiles of GR 68755 were characterized in rats and dogs. Following target organs of toxicity in both rats and dogs were identified: central nervous system (subdued behavior, bulging eyes/partly closed eyes, "croaking", open month, ataxia, labored respiration/noisy breathing, piloerection, prostration, tremor, and reduction of body temperature), thymus (thymic involution), and liver (increased alkaline phosphatase and alanine amino-transferase activity and histopathological changes including multiple basophilic foci, clear cell foci, and fine, minimal fatty vacuolation of periacinar hepatocytes). Decreased hearing acuity and loss of hearing were seen in rats and dogs following chronic treatment with alosetron.

In the present NDA, sponsor is seeking approval to market alosetron for treatment of irritable bowel syndrome (IBS). Adequate preclinical studies have been conducted and relevant findings of the preclinical studies should be included in the labeling as recommended. Therefore, from a preclinical standpoint, this NDA is approvable. Sponsor should be asked to revise the labeling as recommended.

RECOMMENDATION:

From a preclinical standpoint, this NDA is approvable. Sponsor should be asked to revise the labeling as recommended.

/S/ 10/29/99
Ke Zhang, Ph.D.

ATTACHMENTS:

/S/ 11/4/99

Appendix I
Ex. CAC Report on April 23, 1996
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Appendix III
Tumor Data of the Mouse Carcinogenicity Study
Pages 127 - 152

Appendix IV
Tumor and Non-Tumor Data of the Rat Carcinogenicity Study
Pages 153 - 173

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Zhang
HFD-345/Dr. Viswanathan
HFD-530/Dr. Morse

R/D Init.: J. Choudary 10/20/99

KZ/hw/10/27/99

Appendix I

Ex. CAC Report on April 23, 1996

ATTACH TO THE CAC REPORT

Executive CAC
April 23, 1996

IND
Alosetron hydrochloride Tablets
Glaxo Wellcome Inc.

Committee members:	Joseph DeGeorge, Ph.D., HFD-150, Acting Chair
	Joseph Contrera, Ph.D., HFD-900
	James Farrelly, Ph.D., HFD-530, Rotating member
	Jasti Choudary, Ph.D., HFD-180, Team Leader
	Sharon Olmstead, Executive Secretary

Committee Recommendations:

The rat carcinogenicity study (conducted with Wistar rats) used dietary doses of 1, 6.5, and 40 mg/kg. The committee concurred with the division's evaluation of the rat carcinogenicity study results, finding the study design and dose selection to be acceptable and no biologically significant increases in tumors.

In the mouse carcinogenicity study (conducted with B6C3F1 mice), doses of 1, 5.5, and 30 mg/kg via drinking water were used. The sponsor reported no significant carcinogenic findings within the mouse study. The 30 mg/kg dose was considered by the sponsor to be the maximum feasible dose based on a dose-ranging study in which 40 mg/kg suppressed the water consumption by more than 20% in female mice. The committee expressed some concern with the methods used to establish the maximum feasible dose in the mouse study. However, the committee speculated that the maximum feasible dose may serve to support the administration of the drug in the drinking water provided the sponsor could provide evidence to support the use of a MFD. Dr. Choudary indicated that the 15 mg/kg dose administered by gavage in the females was a lethal dose following a single administration.

The committee concurred with the division's assessment that the toxicities reported in the male mice, increased incidences of angiectasis in the lymph nodes without any hemangiomas and testicular interstitial cell tumors suggested that the MTD had been reached within the males. The committee was not convinced that the HD was within 1/3 of the MTD for the female mouse. The body weight data provided by the sponsor did not include measurements across the entire study period - only days 1, 92, 364, and 729. However, the division believed that the body weight data provided suggested a trend for lower body weights in the 30 mg/kg dose females for days 364 and 729. The committee suggested that the division obtain, from the sponsor, body weight data across multiple time points and plot the curve. If a divergence in body weight can be shown over time, the division may be able to document that the HD was within 1/3 the MTD and the study would be considered acceptable.

The committee indicated that the duration of use for the clinical indication may not require a long-term carcinogenicity study under the ICH guidelines. The committee recommended that the division review the guidelines and discuss this issue with their division director.

Post-meeting recommendations:
The division provided a graph comparing the body weight changes for the control and high dose groups during the 24-month study. The data provided support a divergence in body weight from six months to the end of the study. The difference between control group and HD group is near 10% at the 2-year time point. The committee members agreed that HD, based on body weight changes, reached the MTD and therefore, found the mouse carcinogenicity study acceptable.

/S/ 6/20/96

Joseph DeGeorge, Ph.D.
Acting Chair, Executive CAC

cc: IND file
Division file
HFD-180/JChoudary/TAhmad
CAC files

APPEARS THIS WAY
ON ORIGINAL

Appendix II

Ex. CAC Report on October 12, 1999

Executive CAC
October 12, 1999

Committee:
Joseph DeGeorge, Ph.D., HFD 024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Jasti Choudary, B.V.Sc., Ph.D., HFD-180, Team Leader
Ke Zhang, Ph.D., HFD-180, Presenting Reviewer

Author of Draft: Ke Zhang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 21,107
Drug Name: **Alosetron Hydrochloride / GR 68755**
Sponsor: **Glaxo Wellcome, Inc.**

Background:
The preliminary report of the mouse carcinogenicity study was submitted in the *initial submission of IND* *This study was reviewed on April 16, 1996* (Pharmacology review) and discussed at Executive CAC meeting on April 23, 1996. The dose selection was considered adequate and this study was acceptable. Sponsor submitted the final report of the study in NDA 21,107. GR 68755 was negative in the genotoxicity testing which included Ames test, in vitro chromosome aberration test in human lymphocytes, unscheduled DNA synthesis test in rat hepatocytes, mouse lymphoma cell assay, and rat micronucleus test. GR 62202, an intermediate in the synthesis of GR 68755, was positive in Ames test with one strain of S. typhimurium, TA 98 at concentrations of (g/plate in the absence of S9 and (g/plate in the presence of S9. However, it was negative with strain TA 1537 as well as strains TA 1535 and TA 100. Structurally, this intermediate is not similar to any of the known metabolites of the parent drug.

Mouse Carcinogenicity Study:

In this study, mice (B6C3F1) were treated with GR 68755 via drinking water at 0 (water), 0 (vehicle), 1, 5.5, and 30 mg/kg/day for 94/95 weeks in males and 104/105 weeks in females. There were no treatment related clinical signs of toxicity. Mortality rate was comparable in control and treatment groups. The body weight in high dose females was 91.4% of the control. Historical control data from the testing laboratory are not available.

Higher incidences of Harderian gland adenoma and liver cell tumors were found in the treated males and females, respectively.
The incidence of Harderian gland adenoma in males was 2, 2, 8, 7, and 6 in the control 1 (water), control 2 (vehicle), low, mid, and high dose groups, respectively. The incidence of hepatocellular adenoma in females was 2, 7, 11, 11, and 10 in the control1 (water), control2 (vehicle), low, mid, and high dose groups, respectively. The incidence of hepatocellular carcinoma in females was 1, 1, 6, 5, and 4 in the control 1 (water), control 2 (vehicle), low, mid, and high dose groups, respectively. The mean background incidence of Harderian gland adenoma in males was 7.73 +/- 3.9% (range: . The mean background incidences of hepatocellular adenoma and carcinoma in females were 55.0 +/- 21.2% (range:) and 19.7 +/- 12.8% (range: , respectively. These background incidences were obtained from the NTP database. The increased incidences of Harderian gland adenoma and liver cell tumors are not dose related and within the background incidence. The increased incidences were not statistically significant by the trend test. The increased incidences in each of the treatment groups were not significantly (pairwise test) different from the incidences in the vehicle control group. Therefore, these are not considered biologically significant.

Treatment with GR 68755 produced benign interstitial cell tumor of the testes in a dose dependent manner (0, 0, 1, 1, and 2 for control 1 (water), control 2 (vehicle), low, mid, and high dose groups, respectively). A single incidence of malignant interstitial cell tumor in a mid dose male (none in the controls) was also observed. The combined incidences of benign and malignant tumors are 0, 0, 1, 2, and 2 in the control1 (water), control2 (vehicle), low, mid, and high dose groups, respectively. The increased incidences were not statistically significant by the trend test. The increased incidences in each of the treatment groups were not significantly (pairwise test) different from the incidences in the vehicle control group.

Executive CAC Recommendations and Conclusions:

1. The Committee felt in general that the results were either negative or equivocal. They expressed some concern about the increased incidence of the hepatocellular adenoma and carcinoma in female mice. While there is no increase of such tumors in the rat carcinogenicity study, there is some concern about the mutagenic potential of the intermediate, GR 62202.

2. The Committee recommended that the Division investigate (a) whether any of the metabolites of the parent drug is structurally similar to this intermediate and (b) whether this intermediate is present as an impurity in the drug product.

Further examination of the information in the NDA revealed the following: (a) none of the known metabolites of GR 68755 is structurally similar to GR 62202 and (b) GR 62202 is present in the drug product as an impurity at which is below qualification threshold of 0.1% (Guideline for Industry: Impurities in New Drug Substance, ICH Q3A, January 1996). The recommended human dose is 1 mg b.i.d.

3. The Committee expressed concern regarding the lack of historical control data from the testing laboratory.

4. The study is adequate and acceptable. The Committee concluded that there was no evidence for tumorigenicity relevant to humans.

/S/ 10/19/99

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-180
/HFD-181/CSO
/Dr. Choudary, HFD-180
/Dr. Zhang, HFD-180
/ASeifried, HFD

Appendix III

Tumor Data of the Mouse Carcinogenicity Study

GR68755C: Oral (drinking water) oncogenicity study in B6C3F1 mice

Study No.: M12401

Table 7: Tumour Incidences

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GR68755C: Oral (drinking water) oncogenicity study in B6C3F1 mice
Study number: M12401
INCIDENCE OF TUMOURS IN MALES
SEPARATED AS SURVIVORS AND DECEDENTS

MALES : INCIDENCE OF TUMOURS (NUMERIC)

TUMOURS	GROUP	SURVIVORS					DECEDENTS				
		Tap water	Acid/d water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg	# Tap water	Acid/d water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg
Abdominal cavity:		(4)		(2)	(3)	(7)	# (1)	(2)	(5)	(1)	(3)
sarcoma (M)											1
Adrenals:		(32)	(30)	(31)	(39)	(39)	# (28)	(29)	(29)	(21)	(21)
subcapsular adenoma (B)					1	1	1				
cortical adenoma (B)					1						
Bone marrow:		(32)	(30)	(31)	(39)	(39)	# (28)	(30)	(29)	(21)	(21)
haemangioma (B)		2	1						1		
Head:		(6)	(14)	(6)	(17)	(15)	# (5)	(4)	(1)	(5)	(2)
squamous papilloma (B)					1		#				

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not encountered
(B) = Benign (M) = Malignant

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Table 7: Tumour Incidences

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CR68735C: Oral (drinking water) oncogenicity study in B6C3F1 mice
Study number: M12401
INCIDENCE OF TUMOURS IN MALES
SEPARATED AS SURVIVORS AND DECEDENTS

MALES : INCIDENCE OF TUMOURS (NUMERIC)

TUMOURS	GROUP	SURVIVORS					DECEDENTS				
		Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg	# Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg
Hearts		(32)	(30)	(31)	(39)	(39)	# (28)	(30)	(29)	(21)	(21)
haemangioma [B]		1					#				
Lacrimal glands:		(32)	(30)	(31)	(39)	(39)	# (28)	(30)	(29)	(21)	(21)
adenoma [B]		2	1	5	3	4	#	1	3	4	2
Livers		(32)	(30)	(31)	(39)	(39)	# (28)	(30)	(29)	(21)	(21)
liver cell adenoma [B]		16	17	16	17	16	# 11	12	11	4	6
liver cell adenoma with slight cord atypia [B]		1	1	3		1	# 2	1			4
hepatocellular carcinoma [M]		4		2	7	2	# 13	9	13	8	11

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not encountered
[B] = Benign [M] = Malignant

Table 7: Tumour Incidences

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PLACES V8.400

GR687353C1 Oral (drinking water) oncogenicity study in B6C3F1 mice
Study number: M12401
INCIDENCE OF TUMOURS IN MALES
SEPARATED AS SURVIVORS AND DECEDENTS

MALES : INCIDENCE OF TUMOURS (NUMERIC)

TUMOURS	SURVIVORS				DECEDENTS			
GROUP	Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg	Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg
	(32)	(30)	(31)	(39)	(39)	(28)	(30)	(29)	(21)	(21)
Liver:										
metastasizing hepatocellular carcinoma [M]					1	1	5	6		3
haemangioma [B]	3		2		2		2	1	4	2
	(32)	(30)	(31)	(39)	(39)	(28)	(30)	(29)	(21)	(21)
Lungs:										
alveolar/bronchiolar adenoma [B]	3	4	7	1	1	1	1	1		2
alveolar/bronchiolar carcinoma [M]	2	2	4	3	3	1	2		3	
	(3)	(4)	(3)	(4)	(3)	(2)	(7)	(3)	(6)	
Lymphoreticular tissue:										
lymphoma [M]	1	3	3	4	2	2	5	3	4	
histiocytic sarcoma [M]					1		2	2	2	

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not encountered
[B] = Benign [M] = Malignant

M12401 Final Report

Table 7: Tumour Incidences

GR68755C: Oral (drinking water) oncogenicity study in B6C3F1 mice
Study number: M12401
INCIDENCE OF TUMOURS IN MALES
SEPARATED AS SURVIVORS AND DECEDENTS

TUMOURS	GROUP	MALES : INCIDENCE OF TUMOURS (NUMERIC) SURVIVORS: Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg	#	DECEDENTS: # Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg
Lymphoreticular tissue:		(3)	(4)	(3)	(4)	(3)	#	(2)	(7)	(5)	(6)	
mast-cell tumour [M]		2	1				#			1		
Pancreas:		(32)	(30)	(31)	(39)	(39)	#	(27)	(30)	(29)	(21)	(21)
islet-cell adenoma [B]				2			#					
Seminal vesicles:		(32)	(30)	(31)	(39)	(39)	#	(28)	(30)	(29)	(21)	(21)
haemangioma [B]					1		#					
Skeleton:		(7)	(9)	(3)	(5)	(7)	#	(1)	(2)	(1)	(2)	(1)
osteosarcoma [M]							#				1	
haemangioma [B]			1				#					

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not encountered
[B] = Benign [M] = Malignant

Table 7: Tumour Incidences

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GR607356: Oral (drinking water) oncogenicity study in B6C3F1 mice
Study number: M12401
INCIDENCE OF TUMOURS IN MALES
SEPARATED AS SURVIVORS AND DECEDENTS

MALES : INCIDENCE OF TUMOURS (NUMERIC)

TUMOURS	GROUP	SURVIVORS					DECEDENTS				
		Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg	# Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg
		# (32)	# (30)	# (31)	# (39)	# (39)	# (28)	# (30)	# (27)	# (20)	# (21)
skin:											
squamous papilloma (B)			1		1		1				
fibroma (B)							1	2			
sarcoma (M)									1		
fibrosarcoma (M)								1			
lymphangioma (B)									(1)		
Soft tissue:		(1)					(1)				
lipoma (B)		1					1		1		

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not encountered
(B) = Benign (M) = Malignant

Appendix III

Tumor Data of the Mouse Carcinogenicity Study

Table 7: Tumour Incidences

GR68755C: Oral (drinking water) oncogenicity study in B6C3F1 mice
Study number: M12401
INCIDENCE OF TUMOURS IN MALES
SEPARATED AS SURVIVORS AND DECEDENTS

TUMOURS	GROUP	MALES : INCIDENCE OF TUMOURS (NUMERIC)										
		SURVIVORS					#	DECEDENTS				
		Tap water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg	# Tap #water	Acidfd water	1.0 mg/kg	5.5 mg/kg	30.0 mg/kg	
Lymphoreticular tissue:		(3)	(4)	(3)	(4)	(3)	# (2)	(7)	(5)	(6)		
mast-cell tumour [M]		2	1				#		1			
Pancreas:		(32)	(30)	(31)	(39)	(39)	# (27)	(30)	(29)	(21)	(21)	
islet-cell adenoma [B]				2			#					
Seminal vesicles:		(32)	(30)	(31)	(39)	(39)	# (28)	(30)	(29)	(21)	(21)	
haemangioma [B]					1		#					
Skeleton:		(7)	(9)	(3)	(5)	(7)	# (1)	(2)	(1)	(2)	(1)	
osteosarcoma [M]							#			1		
haemangioma [B]			1				#					

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not encountered
[B] = Benign [M] = Malignant