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TABLE 101 - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

Printed: 12-APR-93
Page: 11

Group Compound 1 Control 2 3 4
Dose (mg/kg/day) 0 1.0 6.3 40.0

Schedule numbers GLX 041
--- NUMBER OF ANIMALS AFFECTED ---

SEX:	MALE				FEMALE				
	GROUP	1	2	3	4	1	2	3	4
ORGAN AND FINDING DESCRIPTION	NUMBERS	120	60	60	60	120	60	60	60
	NUMBER EXAMINED	2	2	0	1	6	3	3	2
ABDOMINAL FAT	NUMBER EXAMINED	1 <td>2<th>0</th><th>0</th><th>3</th><th>3</th><th>3</th><th>2</th></td>	2 <th>0</th> <th>0</th> <th>3</th> <th>3</th> <th>3</th> <th>2</th>	0	0	3	3	3	2
--FOCAL FAT NECROSIS									
AORTA	NUMBER EXAMINED	3 <th>2</th> <th>0</th> <th>1</th> <th>1</th> <th>0</th> <th>0</th> <th>0</th>	2	0	1	1	0	0	0
--MEDIAL MINERALISATION									
CLITORAL GLAND	NUMBER EXAMINED	0 <th>0</th> <th>0</th> <th>0</th> <th>0</th> <th>1</th> <th>0</th> <th>0</th>	0	0	0	0	1	0	0
--CHRONIC INFLAMMATION									
FOOT/FEET	NUMBER EXAMINED	11 <th>3</th> <th>2</th> <th>1</th> <th>5</th> <th>1</th> <th>2</th> <th>0</th>	3	2	1	5	1	2	0
--PODITIS									
--HAEMATOMA									
LEFT MANDIBULAR GLAND	NUMBER EXAMINED	1 <th>2</th> <th>0</th> <th>0</th> <th>2</th> <th>1</th> <th>0</th> <th>1</th>	2	0	0	2	1	0	1
--PORPHYRIN CONCRETIONS									
RIGHT MANDIBULAR GLAND	NUMBER EXAMINED	2 <th>3</th> <th>1</th> <th>0</th> <th>3</th> <th>1</th> <th>0</th> <th>1</th>	3	1	0	3	1	0	1
--CHRONIC ACTIVE INFLAMMATION									
--PORPHYRIN CONCRETIONS									
L N AXILLARY	NUMBER EXAMINED	20	12	11	9	23	11	18	13
--SINUS HISTIOCYTOSIS									
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES									
--PARAFOLLICULAR HYPERPLASIA									
--ANGIECTASIS									
--SITE ONLY									
L N BRONCHIAL	NUMBER EXAMINED	1 <th>0</th> <th>1</th> <th>1</th> <th>0</th> <th>0</th> <th>0</th> <th>0</th>	0	1	1	0	0	0	0
--SINUS HISTIOCYTOSIS									
L N ILLIAC MED.	NUMBER EXAMINED	5	7	3	6	10	3	3	3
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES									
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GGR Report No: WPT/93/134

TABLE 10F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

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Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	1220	1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TABLE 10F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

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Schedule numbers: SLX 041

Group Compound Dosage (mg GR68755X/kg/day):
Control 0 1.0 2 3 4
GR68755C 40.0

NUMBER OF ANIMALS AFFECTED

SEX: MALE FEMALE
GROUP: 1-2-3-4-1-2-3-4

NUMBER: 120 60 60 60 120 60 60 60

ORGAN AND FINDING DESCRIPTION

FROM PREVIOUS PAGE ** NUMBER EXAMINED: 8 10 7 7 8 5 3 4

LYMPHATIC ** PLASMACTOSIS ** NAECOSIDEROSIS

LEFT LACRIMAL GLAND ** PORPHYRIN CONCRETIONS ** CHRONIC INFLAMMATION

NUMBER EXAMINED: 20 5 7 10 2 0 1 1

RIGHT LACRIMAL GLAND ** PORPHYRIN CONCRETIONS ** CHRONIC INFLAMMATION

NUMBER EXAMINED: 19 5 7 10 2 0 1 1

MAMMARY A.C.R.A. ** SECRETORY ACTIVITY ** ACINAR HYPERPLASIA ** GALACTOCOELE(S)

NUMBER EXAMINED: 0 0 0 2 10 5 4 3

MAMMARY, OTHER ** GALACTOCOELE(S) ** SECRETORY ACTIVITY ** ACINAR HYPERPLASIA

NUMBER EXAMINED: 2 1 1 0 47 32 36 19

MESENTERY ** ARTERITIS

NUMBER EXAMINED: 3 2 0 0 1 0 0 0

MUSCULO-SKELETAL ** HAEMORRHAGE INTO MUSCLE ** FOCAL CARTILAGINOUS PROLIFERATION OF STERNUM

NUMBER EXAMINED: 2 1 2 1 2 1 2 3

PREPUTIAL GLAND ** DILATED ** CHRONIC INFLAMMATION

NUMBER EXAMINED: 0 0 0 2 0 0 0 0

Significant when compared with Group 1: b - p<0.01

APPEARS THIS WAY
ON ORIGINAL

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TABLE 10f - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

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Group Compound 1 Control 2 3 4
Dose (mg/kg/day) 0 1.0 6.5 40.0

Schedule number: ALX 041

NUMBER OF ANIMALS AFFECTED

SEX: MALE FEMALE
GROUP: 1- 2- 3- 4- 1- 2- 3- 4-

NUMBER: 120 60 60 60 120 60 60 60

ORGAN AND FINDING DESCRIPTION

RIGHT EYE 16 5 3 7 10 4 2 6

ACUTE IRITIS 1 0 0 0 0 0 0 0

PUS IN ANTERIOR CHAMBER 1 2 0 0 0 0 0 0

CHRONIC KERATITIS 2 1 1 2 0 0 0 0

ACUTE KERATITIS 1 0 0 0 0 0 0 0

RETINAL DEGENERATION 0 0 0 0 1 0 0 1

LENTICULAR DEGENERATION 0 0 0 0 0 1 0 1

SKIN OTHER 59 27 28 25 41 34 36 25

ABSCESSES 3 0 0 0 1 0 0 0

EPIDERMAL INCLUSION CYST 7 3 2 2 2 1 0 0

FOCAL COLLAGEN DEPOSITION 2 1 1 2 0 0 1 0

ULCER(S) 0 0 0 1 0 0 0 0

KERATIN GRANULOMA 3 1 1 0 0 0 0 0

FOLLICULAR HYPERPLASIA 0 0 0 1 0 0 0 0

SCAB(S) 0 0 0 1 0 0 0 0

CHRONIC INFLAMMATION 2 0 0 1 0 0 0 0

SUBCUTANEOUS HISTIOCYTE PROLIFERATION 0 0 0 1 0 0 0 0

INCREASED FAT 0 0 0 0 0 0 1 0

ACANTHOSIS 0 0 0 0 0 0 0 0

TAIL 5 1 2 2 0 0 0 0

EPIDERMAL INCLUSION CYST(S) 3 0 0 0 0 0 0 0

ABSCESSES 0 1 0 1 0 0 0 0

SEBACEOUS GLAND HYPERPLASIA 1 0 0 0 0 0 0 0

ULCER(S) 0 0 1 0 0 0 0 0

URETHRA 0 0 0 0 1 0 0 0

DILATED 0 0 0 0 1 0 0 0

END OF LIST

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TABLE 10C

Histopathology - group distribution of neoplastic findings for all animals

Group Compound 1 Control 2 3 4
Dose (mg GR6755X/kg/day): 0 1.0 4.5 40.0

Schedule number: 01K 041

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND FINDING DESCRIPTION	SEX:		MALE				FEMALE			
	GROUP	1	2	3	4	1	2	3	4	
NUMBER:	120	60	60	60	60	120	60	60	60	60
NUMBER EXAMINED:	120	60	60	60	60	120	60	60	60	60
ADRENAL MED LAR	1	2	1	2	0	0	0	0	0	1
ADRENAL CTX LAR	1	2	1	2	0	0	0	0	0	1
ADRENAL MED LAR	120	60	60	60	60	120	60	60	60	60
ADRENAL CTX LAR	2	0	1	0	0	0	0	0	0	0
BRAIN X 3	20	6	4	9	3	1	0	2		
BRAIN X 3	120	60	60	60	60	120	60	60	60	60
CAECUM	1	0	0	0	0	0	0	0	0	0
CAECUM	120	60	60	60	60	120	60	60	60	60
DUODENUM	119	60	60	60	60	120	60	60	60	60
DUODENUM	0	0	0	0	0	1	1	0	0	0
JEJUNUM	120	59	60	60	60	119	40	60	60	60
JEJUNUM	0	0	0	0	0	1	0	0	0	0
JEJUNUM	1	0	0	0	0	0	0	0	0	0
JEJUNUM	0	0	0	0	0	0	0	0	0	0
JEJUNUM	120	60	60	60	60	120	59	59	59	60
JEJUNUM	2	4	2	0	0	0	0	0	0	0
JEJUNUM	6	4	3	6	2	1	1	1	1	1
JEJUNUM	116	60	59	59	118	59	59	59	59	59
JEJUNUM	0	0	1	0	0	0	0	0	0	0

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Misoparathology - group distribution of neoplastic findings for all animals

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Group	1	2	3	4
Compound	Control	---	CR68755C	----
Dosage (mg CR68755H/kg/day)	0	1.0	6.5	40.0

Schedule number: GLX 041
.....
LS - AFFECTION -

[illegible]

Significant when compared with Group 1: c - $p < 0.001$

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Schedule number: 041

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TABLE 10C - continued.

Histopathology - group distribution of neoplastic findings for all animals

Group Compound 1 Control 2 3 4
Dose (mg GR6755X/kg/day): 0 1.0 6.5 40.0

ORGAN AND FINDING DESCRIPTION	NUMBER OF ANIMALS AFFECTED									
	MALE					FEMALE				
	GROUP: 1	2	3	4		1	2	3	4	
	NUMBER: 120	60	60	60	60	120	60	60	60	60
SPLEEN	NUMBER EXAMINED: 120	60	60	60	60	120	60	60	60	60
--M-HEMANGIOSARCOMA	0	1	0	0	0	0	0	0	0	0
STOMACH X 3	NUMBER EXAMINED: 120	60	60	60	60	120	60	60	60	60
--B-SQUAMOUS CELL PAPILLOMA	0	0	0	0	0	0	0	0	0	0
LEFT SUBMANDIB SL GL	NUMBER EXAMINED: 117	59	59	58	119	59	60	60	60	60
--M-MYOEPITHELIAL TUMOUR	0	0	1	0	0	0	0	0	0	0
TESTES (L&R)	NUMBER EXAMINED: 120	60	60	60	60	60	60	60	60	60
--B-INTERSTITIAL CELL TUMOUR	16	3	8	9	0	0	0	0	0	0
THYMUS	NUMBER EXAMINED: 116	58	60	59	117	60	59	59	59	59
--M-INTRAGLOSSAL DUCT CARCINOMA	1	0	0	0	0	0	0	1	0	0
--B-THYMOMA	1	0	1	1	8	3	3	3	3	5
THYROID (L&R)	NUMBER EXAMINED: 115	60	60	60	120	60	60	60	60	60
--B-FOLLICULAR CELL ADENOMA	2	0	3	0	1	3	0	0	0	0
--M-PARAFOLLICULAR CELL CARCINOMA	2	1	0	1	1	0	0	1	0	1
--B-PARAFOLLICULAR CELL ADENOMA	12	4	6	2	11	3	1	3	1	3
--M-FOLLICULAR CELL CARCINOMA	0	0	1	0	0	0	0	0	0	0
TONGUE	NUMBER EXAMINED: 119	60	60	60	120	60	60	60	60	60
--B-SQUAMOUS CELL PAPILLOMA	0	0	0	1	0	0	0	0	0	0
UTERINE CERVIX	NUMBER EXAMINED: 0	0	0	0	120	60	60	60	60	60
--M-HEMANGIOSARCOMA	0	0	0	0	0	0	0	1	0	0
--M-ENDOMETRIAL SARCOMA	0	0	0	0	4	1	0	2	0	0
--B-STROMAL POLYP	0	0	0	0	1	0	0	0	0	0
UTERUS	NUMBER EXAMINED: 0	0	0	0	120	60	60	60	60	60
--M-ENDOMETRIAL SARCOMA	0	0	0	0	5	0	0	0	0	0

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TABLE 10C - continued.

Mistopathology - group distribution of neoplastic findings for all animals

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Group Compound 1 Control 2 3 4
Dose (mg GR6755X/kg/day): 0 1.0 6.5 40.0

Schedule number: BLX 041
--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND FINDING DESCRIPTION	SEX:				MALE				FEMALE			
	GROUP:				1	2	3	4	1	2	3	4
NUMBER	120	60	60	60	120	60	60	60	60	60	60	60
FROM PREVIOUS PAGE	0	0	0	0	0	0	0	0	0	0	0	0
UTERUS	0	0	0	0	0	0	0	0	0	0	0	0
--M-ADENOCARCINOMA	0	0	0	0	0	0	0	0	0	0	0	0
--B-ADENOMA	0	0	0	0	0	0	0	0	0	0	0	0
--B-STROMAL POLYP	0	0	0	0	0	0	0	0	0	0	0	0
--B-ADENOMATOUS POLYP	0	0	0	0	0	0	0	0	0	0	0	0
--B-WAENANGIOMA	0	0	0	0	0	0	0	0	0	0	0	0
VAGINA	0	0	0	0	0	0	0	0	0	0	0	0
--M-LEIOMYOSARCOMA	0	0	0	0	0	0	0	0	0	0	0	0
--M-SARCOMA	0	0	0	0	0	0	0	0	0	0	0	0
ABDOMEN	2	0	1	1	3	0	0	0	0	0	0	0
--M-SARCOMA	0	0	0	0	0	0	0	0	0	0	0	0
ABDOMINAL FAT	2	2	0	1	6	5	3	2	0	0	0	0
--B-LIPOMA	0	0	0	0	0	0	0	0	0	0	0	0
FOOT/FEET	11	3	2	1	5	1	2	0	0	0	0	0
--B-PAPILLOMA	1	0	0	0	0	0	0	0	0	0	0	0
N/POIETIC TUMOUR	1	2	3	3	4	1	2	1	0	0	0	0
--M-MALIGNANT LYMPHOMA	1	1	3	2	0	1	0	0	0	0	0	0
--M-LYMPHOCTIC LEUKAEMIA	0	1	0	0	1	0	0	0	0	0	0	0
--M-HISTIOCYTIC SARCOMA	0	0	0	0	2	0	0	0	0	0	0	0
--M-LARGE GRANULAR CELL LEUKAEMIA	0	0	0	0	0	0	0	0	0	0	0	0
--M-CRANULOCYTIC LEUKAEMIA	0	0	0	0	0	0	0	0	0	0	0	0
RIGHT MANDIBULAR GLAND	2	3	1	0	3	1	0	1	0	0	0	0
--M-CARCINOMA	0	0	0	0	0	0	0	0	0	0	0	0
L M THYROID	8	10	7	7	8	5	3	4	0	0	0	0
--M-WAENANGIOSARCOMA	1	0	0	0	0	0	0	0	0	0	0	0

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TABLE 10C - continued.

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Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	Printed: 12-APR-95
Compound	Control	---	AR6755C	---	Page: 5
Dose (mg AR6755H/kg/day):	0	1.0	6.5	40.0	Schedule number: BLX 041
					--- NUMBER OF ANIMALS AFFECTED ---
					SEX: --- MALE --- FEMALE ---
					GROUP: -1- -2- -3- -4- -1- -2- -3- -4-
					NUMBER: 120 60 60 60 120 60 60 60
ORGAN AND FINDING DESCRIPTION					
MAMMARY, OTHER	2	1	1	0	47 32 36 19
--M-CARCINOMA	0	0	0	0	3 3 4 3
--B-FIBROADENOMA	2	1	1	0	46 27 33 14
--B-ADENOMA	0	0	0	0	1 0 1 1
MESENTERY	3	2	0	0	1 0 0 0
--M-MESOTHELIOMA	1	0	0	0	0 0 0 0
--M-CARCINOMA	1	0	0	0	0 0 0 0
MISCELLANEOUS	0	0	1	0	0 0 0 0
--M-SCHWANNOMA	0	0	1	0	0 0 0 0
MUSCULO-SKELETAL	2	1	2	1	2 1 2 3
--M-OSTEOSARCOMA	0	0	1	0	0 0 1 1
--M-MYOEPITHELIAL TUMOR	0	0	0	0	0 0 0 1
SKIN OTHER	59	27	28	25	61 34 38 25
--M-SARCOMA	4	1	0	1	1 0 0 0
--M-CARCINOMA	0	0	1	0	0 0 0 0
--M-MISTOCTIC SARCOMA	2	0	1	0	2 0 0 1
--M-MYOEPITHELIAL TUMOR	0	0	0	0	0 0 0 0
--M-MAENANGIOSARCOMA	0	0	0	0	0 0 0 0
--B-FIBROMA	12	3	10	7	6 2 1 1
--B-PAPILLOMA	4	1	2	0	1 0 0 0
--B-KERATOCARCINOMA	14	10	3	4	2 1 1 0
--B-BASAL CELL TUMOR	2	0	0	0	0 0 0 0
--B-LIPOMA	1	2	1	1	2 0 1 0
--B-LEIOMYOMA	1	0	0	0	0 0 0 0
TAIL					
--B-PAPILLOMA	5	1	2	2	0 0 0 0

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TABLE 10C - continued.

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4
Compound	Control	GR68755C	GR68755C	GR68755C
Dose (mg GR68755H/kg/day)	0	1.0	6.5	40.0
Schedule number: 01X 041				
--- NUMBER OF ANIMALS AFFECTED ---				
SEX: ---MALE--- ---FEMALE---				
GROUP: 1	2	3	4	1
2	3	4	1	2
3	4	1	2	3
4	1	2	3	4
NUMBER: 120 60 60 60 120 60 60 60				
ORGAN AND FINDING DESCRIPTION				
THORAX				
---M-SARCOMA				
---M-MESOTHELIOMA				
.. END OF LIST ..				
NUMBER EXAMINED: 0 0 1 1 1 0 1 0 0 0				

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PHARMACOLOGIST'S REVIEW OF MOUSE CARCINOGENICITY
STUDY IN NDA 21,107

Sponsor & Address: GlaxoWellcome Inc.
Research Triangle Park, North Carolina

Reviewer: Ke Zhang, Ph.D.
Pharmacologist

Date of Submission: June 29, 1999

Date of HFD-180 Receipt: July 1, 1999

Date of Review: October 1, 1999

DRUG: Alosetron Hydrochloride / LotronexTM / GR 68755, Tablets

CATEGORY: 5-HT₃ receptor antagonist for treatment of irritable bowel syndrome (IBS).

Submission Contents: Oral (drinking water) oncogenicity study in B6C3F1 mice.

BACKGROUND: Sponsor submitted the preliminary report of the carcinogenicity study in mice and the final report of the carcinogenicity study in rats in the initial submission of IND (August 4, 1995). These studies were reviewed on April 16, 1996 (Pharmacology review) and discussed at the Executive CAC meeting on April 23, 1996. The dose selections of both studies were considered adequate and both studies were acceptable. Alosetron did not have tumorigenic potential in the rat carcinogenicity study. A copy of the Ex. CAC report is attached in Appendix I. It was not conclusive for the mouse study at that time since the final report of this study was not available. Sponsor submitted the final report of the carcinogenicity study in mice in this NDA 21,107 and this study is reviewed below.

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**CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT
AND
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET**

P/T REVIEWER(s): Ke Zhang, Ph.D.
DATE: October 1, 1999

IND/NDA: NDA 21,107
DRUG CODE#:
CAS#:
DIVISION(s): HFD-180
DRUG NAME(s): Alosetron / GR 68755

SPONSOR: GlaxoWellcome Inc.
LABORATORY: GlaxoWellcome, UK
CARCINOGENICITY STUDY REPORT DATE: November 30, 1998

THERAPEUTIC CATEGORY:
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: 5-HT₃ Antagonist
MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay): No

MOUSE CARCINOGENICITY STUDY (multiple studies? Std1; Std2 etc.):

MOUSE STUDY DURATION (weeks): 94/95 weeks (males) and 104/105 weeks (females).
STUDY STARTING DATE: December 21, 1990
STUDY ENDING DATE: November 30, 1998
MOUSE STRAIN: B6C3F1
ROUTE: Drinking water
DOSING COMMENTS: Dose selection was considered adequate and the study was acceptable by Executive CAC on April 23, 1996 (See Appendix I).

NUMBER OF MICE:

- Control-1 (water): 60
- Control-2 (Acidic water, pH = 5.5): 60
- Low Dose (LD): 60
- Middle Dose (MD): 60
- High Dose (HD): 60

MOUSE DOSE LEVELS (mg/kg/day):

- Low Dose: 1
- Middle Dose: 5.5
- High Dose: 30

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible): Maximum feasible (palatable) dose via drinking water.

NDA 21,107

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PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): Dose selection was considered adequate and the study was acceptable by Executive CAC on April 23, 1996.

MOUSE CARCINOGENICITY (conclusion: negative; positive; MF; M;F):

MOUSE TUMOR FINDINGS (details):

The incidence of Harderian gland adenoma was higher in the treated males (8, 7, 6 in low, mid, and high dose groups) than in control (2) but it was not statistically significant and the increased incidence was not dose related (trend test, $p = 0.27$). A single incidence of Harderian gland carcinoma was found in the low and high dose female groups (none in the mid dose female group and in males). The incidence of liver cell tumors was higher in the treated females (13, 15, and 13) than in controls (3, 8) but it was not statistically significant and was not dose related (trend test, $p = 0.28$ for carcinoma, $p = 0.16$ for adenoma). The incidences of both Harderian gland adenoma and liver cell tumors are within the background incidence. Treatment with GR 68755 produced benign interstitial cell tumor of the testes in a dose dependent manner (1, 1, and 2 in the low, mid, and high dose groups, trend test $p = 0.047$) and a single incidence of malignant interstitial cell tumor of the testes in a mid dose male (none in the controls).

MOUSE STUDY COMMENTS:

In the oral carcinogenicity study in mice, mice (60/sex/group) were treated with GR 68755 via drinking water at 0, 0, 1, 5.5, and 30 mg/kg/day for 94/95 weeks in males or 104/105 weeks in females. There were no treatment related clinical signs of toxicity. Mortality rate was comparable in control and treatment groups. The terminal body weight in the high dose female was 91.4% of the control. Higher incidences of Harderian gland adenoma and liver cell tumors were found in the treated males and females, respectively. These increased incidences were not dose related and not statistically significant. They are within the background incidence. Treatment with GR 68755 produced benign interstitial cell tumor of the testes in a dose dependent manner (trend test $p = 0.047$) and a single incidence of malignant interstitial cell tumor of the testes in a mid dose male (none in the controls).

COVERSHEET FOR CARCINOGENICITY STUDY IN MOUSE

1. Study No.: M12401
2. Name of Laboratory: GlaxoWellcome, UK
3. Strain: B6C3F1
4. No./sex/group: 60
5. Dose (O,L,M,H): 0, 1, 5.5, and 30 mg/kg/day
6. Basis for dose selection stated: Yes
7. Interim sacrifice: No
8. Total duration (weeks): 94/95 for males, 104/105 for females.
9. Week/site for first tumor:

	Male	Female
Control (water)	42/M. adenoma in liver	57/M. cystic adenocarcinoma in mammary gland and M. lymphoma in lymphoreticular tissue
Control 2 (acidic water, pH=5.5)	59/M. lymphoma & histiocytic sarcoma in lymphoreticular tissue	57/M. hepatocellular carcinoma
Low dose	63/M. hepatocellular carcinoma in liver	59/M. lymphoma in lymphoreticular tissue
Mid dose	50/M. osteosarcoma in skeleton	65/B. adenoma in liver and M. fibrosarcoma in skin
High dose	57/M. hepatocellular carcinoma & adenoma	65/M. lymphoma in lymphoreticular tissue

B = Benign, M = malignant

10. No. alive at termination:

	Male (%)	Female (%)
Control 1	32/60 (53.3)	34/60 (56.7)
Control 2	25/60 (41.7)	29/60 (48.3)
Low dose	21/60 (35.0)	19/60 (31.7)
Mid dose	29/60 (48.3)	27/60 (45.0)
High dose	29/60 (48.3)	23/60 (38.3)

11. Statistical Methods used: The prevalence method of Peto (Peto, R. et.al., Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiment in Long-term and short term screening assays for carcinogens: a critical appraisal. IARC, pp 311-426, 1980).

12. Attach tumor and non-tumor data for each tissue (i.e. benign, malignant, hyperplastic): See Appendix II.

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Oral (drinking water) Carcinogenicity Study in Mice
(Study # M12401)

Testing Laboratory: Sponsor's Lab, UK

Study Start and Completion Dates: December 21, 1990 and
November 30, 1998.

GLP and QAU Compliance Statement: Statements of compliance with GLP regulations and the quality assurance unit were included.

Animals: Male (20.1-32.2 g, 5-6 weeks old)
Female (15.6-27 g, 5-6 weeks old)
B6C3F1 mice

Drug Batch No.: C1026/120/1

Methods: To determine the carcinogenic potential of GR 68755, mice (60/sex/group) were treated with GR 68755 via drinking water at 0 (tap water), 0 (acidified water, pH=5.5), 1, 5.5, and 30 mg/kg/day for 94/95 weeks in males or 104/105 weeks in females. The dose selected was considered adequate in Executive CAC meeting held on April 23, 1996. The dosages achieved were calculated by multiplying the mean water consumption for each group (g/kg/day, 1 ml solution = 1 g) by the solution concentration in mg/ml. The achieved dosages were summarized in a table on page 219 in Volume 1.10 and this table is attached below.

Achieved dosages

Target dosage (mg/kg)	Sex	Achieved dosage (mg/kg/day)	
		Mean	Range
1.0	M	1.01	
	F	1.01	
5.5	M	5.51	
	F	5.53	
30.0	M	29.86	
	F	29.84	

In the current study, clinical signs of toxicity and mortality were observed daily. Body weights were determined weekly. Food consumption was determined weekly during the first 13 weeks and then at ~3 month interval throughout the study. Water consumption was determined over each 3 or 4 day period throughout the study except for the 1 mg/kg/day group for which it was determined daily