

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019651/S005

PHARMACOLOGY REVIEW(S)

Pages: 126 through 150

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PLACES V8.200

Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Mismorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)												
		MALES					FEMALES							
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#			
RESPIRATORY SYSTEM:-														
LUNG:														
Focal/multifocal/MOS pleural/lobar/alveolar hemorrhage		(50)	2	8	(50)	(50)	3	6	3	(50)	(50)	1	1	
Focal/multifocal pleural/MOS fibrosis			1	3	1	2	2	3	2	(49)	(50)	2	2	
Multifocal fibrinous pleural exudate			1	1										
Multifocal hyaline droplet(s)														
Multifocal submucosal glandular dilatation			8	3	3	7				6	3	2	4	
Multifocal proteinaceous deposition														
Focal cyst(s)														
Multifocal/diffuse/MOS congestion				4	3	4				3	1		2	
Autolysis			1									1	3	
Focal/multifocal amyloidosis					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 identified

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)										
		MALES			FEMALES							
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg			
RESPIRATORY SYSTEM:-												
LUNG:												
Focal/multifocal/NOS bronchiolar-alveolar ADENOMA (B)		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Primary site: Focal/multiple/NOS bronchiolar-alveolar ADENOCARCINOMA (M)		5	3	3	4	3	1	2	1	1	1	1
Metastatic site: ADENOCARCINOMA (M)						1	1	1				
MASAL CAVITY/TURBINATE(S):		(49)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
No abnormality detected		3	6	4	1	9	7	4	6			
Metastatic site: HISTIOCYTIC SARCOMA (M)			2			1						
Metastatic site: GRANULOCYTTIC LEUKEMIA (M)			1									
Focal/multifocal acute/NOS rhinitis		1		1	2	1	1					
Focal/multifocal luminal fluid/mucus		6	4	2	2	5	10	13	5			

Figures in brackets represent the number of animals from which this tissue was examined microscopically
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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	INCIDENCE OF OBSERVATION (NUMERIC)												
	TREATMENT	MALES					FEMALES						
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#		
RESPIRATORY SYSTEM:-													
NASAL CAVITY/TURBINATE(S):		(49)	(50)	(50)	(50)								
Multifocal squamous metaplasia													
LYMPHOMA (N)													
Focal/multifocal/NOS chronic-active/NOS inflammation		2	1	1	2								
Multifocal epithelial hyperplasia		9	9	13	9								
Focal/multifocal luminal/NOS hemorrhage					1								
Focal/multifocal submucosal fibrosis		1	3	4	1								
Focal/multifocal glandular dilation		3	3	1	1								
Diffuse congestion													
Autolysis			2	1	1								
Multifocal submucosal amyloidosis		45	40	43	47								

Figures in brackets represent the number of animals from which this tissue was examined microscopically
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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 662.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)											
		MALES				FEMALES							
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg				
RESPIRATORY SYSTEM:-													
TRACHEA:													
No abnormality detected	(49)	(49)	(49)	(50)									
Metastatic site: HISTIOCYTIC SARCOMA (H)													
focal/multifocal submucosal subacute inflammation	39	42	41	45									
LYMPHOMA (H)													
Focal/NOS submucosal/luminal hemorrhage	1	1	1	1									
Multifocal hyaline droplet(s)													
focal/multifocal submucosal/NOS glandular dilation	6	3	4	3									
Autolysis		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 identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 662.09.00-CD
Pathology Table 7

Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES			FEMALES						
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	1000 mg/kg	2000 mg/kg				
SPECIAL SENSE ORGANS AND ADHENA:											
EAR(S):											
Focal/multifocal/diffuse/NOS otitis media/externa	(2)		(1)			(1)			(1)		(3)
EYE(S):											
No abnormality detected	(50)	(50)	(50)	(50)	(50)	(50)					
Metastatic site: MISTIOCYTIC SARCOMA (M)											
Focal/multifocal/diffuse/NOS corneal/NOS acute/subacute/chronic inflammation	10	16	15	13					7		16
Lenticular reduction in size	3	4	2	1					6		2
Focal vasculitis			1								1
One examined	2	1	1						3		2
Focal/multifocal/NOS mineralization	7	4	13	9					20		15

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 identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
SPECIAL SENSE ORGANS AND ADHENA:-											
EYE(S):		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LYMPHOMA (M)		2	1	1	2	3	1	2	2	2	3
Focal/multifocal/diffuse retinal degeneration/dysplasia		2			1	4	2	4			
Cataract(s)		29	20	20	19	17	20	27	15	15	12
Autolysis		6	13	9	13	12	12	8			
Focal amyloidosis						1					
Anterior chamber proteinaceous material		1						1			
HARDERIAN GLAND(S):		(49)	(50)	(49)	(50)	(48)	(50)	(50)	(50)	(50)	(50)
No abnormality detected		2	6	1	3		1	4			
Metastatic site: HISTIOCYTIC SARCOMA (M)			1		1	2		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 identified

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 662.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
SPECIAL SENSE ORGANS AND ADnexa:-											
HARDERIAN GLAND(S):											
Metastatic site: GRANULOCYTTIC LEUKEMIA (M)	(49)	(50)	1	(49)	(50)						
Focal/multifocal/diffuse acute/subacute/chronic inflammation	26	16	31	25	27	30	32	32	32		
One examined	7	8		5	9	1	6	5	6		
Multifocal pigmentation						1					
Focal/multifocal acinar necrosis		1				1					
LYMPHOMA (M)											
Focal/multifocal acinar hyperplasia	2	1	1	1	1	3	3	2	2		
Focal/multifocal hemorrhage	4	2	3	2	1	2	4	4	4		
Focal/multifocal acinar/NOS dilation	45	42	46	46	46	44	41	41	49		

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 identified.

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PLACES V8.200

Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7

Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)							
		MALES				FEMALES			
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
SPECIAL SENSE ORGANS AND ADHESA:-									
HARDERIAN GLAND(S):									
Autolysis	(49)	(50)	(49)	(50)					
Focal acinar atrophy		2					1	1	1
Focal/MOS ADENOMA (B)	4	4		3					2
ADENOCARCINOMA (H)									1
LACRIMAL GLAND(S):									
No abnormality detected	(46)	(49)	(48)	(48)	(42)	(38)	(39)	(36)	
Metastatic site: HISTIOCYTIC SARCOMA (H)	4	3	4	2	3	5	2	7	
Metastatic site: GRANULOCYTIC LEUKEMIA (H)		3		1	1		2		
Focal/multifocal acute/subacute/chronic inflammation	38	37	42	40	30	30	30	26	

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 identified

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 062.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)					
		MALES			FEMALES		
		0 mg/kg	200 mg/kg	1000 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
SPECIAL SENSE ORGANS AND ADHESA:-							
LACRIMAL GLAND(S):							
Multifocal acinar cell necrosis		(46)	(49)	(48)	(48)	(36)	
Multifocal mineralization							
LYMPHOMA (M)							
Multifocal acinar hyperplasia							
Multifocal interstitial fibrosis		3	1	1	1	4	3
Focal/multifocal ductular/acinar dilation		1				1	
Multifocal acinar degeneration							
Multifocal cytomegaly							
Autolysis			1			1	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 identified.

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)											
		MALES				FEMALES							
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg				
SPECIAL SENSE ORGANS AND ADNEXA:-													
LACRIMAL GLAND(S):													
Focal/multifocal/diffuse acinar/lobular atrophy		(46)	(49)	(48)	(48)	(42)	(38)	(39)	(36)				
Multifocal amyloidosis		8	6	3	5	7	5	5	4				
URINARY SYSTEM:-													
KIDNEY(S):													
Metastatic site: HISTIOCYTIC SARCOMA (M)		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)				
Metastatic site: GRANULOCYTTIC LEUKEMIA (M)			3		1	3	3	4	3				
Focal/multifocal Tubular Basophilia		13	7	5	9		1	2	4				
Chronic Progressive Glomerulonephropathy		5	6	8	5	9	10	6	9				

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 identified

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)																		
		MALES					FEMALES													
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#									
URINARY SYSTEM:-																				
KIDNEY(S):		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Focal/multifocal/diffuse capsular/perirenal/NOS acute/chronic inflammation		40	37	39	42	34	31	35	38											
Focal/multifocal vasculitis		3	2	3	2		1													
Multifocal interstitial nephritis		1																		
One examined		1			1															
Multifocal tubular epithelial vacuolation																				
Focal/multifocal glomerular capillary thrombosis		1					1													
Focal glomerular sclerosis																				
Multifocal/diffuse tubular/NOS pigmentation		6	9	5	1		10	9	10											

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 identified

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. B62.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)										
		MALES			FEMALES							
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg			
URINARY SYSTEM:-												
KIDNEY(S):		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Focal/multifocal/diffuse papillary edema			2	2	3							
Diffuse tubular nephrosis												
Multifocal/diffuse/NOS glomerular nephropathy		16	15	17	20							
Focal/multifocal proximal/NOS tubular necrosis		1	2		1							
Focal/multifocal/diffuse papillary necrosis		4	5	7								
Focal/multifocal mineralization		27	17	11	15							
Metastatic site: MESOTHELIOMA (M)		1										
Perirenal/NOS LYMPHOMA (M)		4	2	1	3							

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 identified.

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)										
		MALES			FEMALES							
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg			
URINARY SYSTEM:												
KIDNEY(S):												
Focal/multifocal infarction												
Focal/multifocal urothelial hyperplasia												
Focal tubular epithelial hyperplasia												
Focal/multifocal subcapsular/MOS hemorrhage												
Multifocal acute glomerulonephritis												
Focal/multifocal/diffuse interstitial/papillary fibrosis												
Multifocal/diffuse hyaline droplet(s)												
Multifocal/MOS pelvic dilation												
Focal/multifocal/diffuse tubular/glomerular capsular dilation												

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 identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)												
		MALES				FEMALES								
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg					
URINARY SYSTEM:-														
KIDNEY(S):														
Focal/multifocal cortical/NOS cyst(s)		(50)	16	7	(50)	15	10	(50)	4	6	(50)	1	(50)	1
Multifocal eosinophilic/NOS tubular cast(s)		1	3		1				1		1			
Autolysis			3	2	4				5	3	3	2		
Multifocal/diffuse tubular/medullary/cortical atrophy		1			1				1			1		
Multifocal/diffuse glomerular/NOS amyloidosis		13	17	9	10				17	13	9	13		
Metastatic site: ADENOCARCINOMA (M)		(48)	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(48)	(47)	(45)		
URINARY BLADDER:														
No abnormality detected		9	9	4	6				8	10	3	7		
TRANSITIONAL CELL CARCINOMA (M)														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 identified

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Oncogenicity Study (26-Months) of 5-ASA in the Diet of Swiss Mice
Project No. 862.09.00-CD
Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	INCIDENCE OF OBSERVATION (NUMERIC)												
	TREATMENT	MALES						FEMALES					
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	(N)	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	(N)
URINARY SYSTEM:-													
URINARY BLADDER:													
Metastatic site: HISTIOCYTIC SARCOMA (N)		(48)	(50)	(50)	(50)					(48)	(47)	(45)	
Metastatic site: GRANULOCYTIC LEUKEMIA (N)			1		1					2	2	2	
Focal/multifocal/diffuse submucosal/mural/ROS acute/subacute/chronic inflammation		25	23	33	33					27	37	32	
Multifocal urothelial vacuolation		1	3	2	1					1			
Diffuse mucosal ulceration(s)			1								1		
Multifocal submucosal edema		1											
Focal mucosal necrosis		1											
LYMPHOMA (N)		4	1	1	1					4	3	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 identified.

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)												
		MALES				FEMALES								
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg					
URINARY SYSTEM:														
URINARY BLADDER:														
Multifocal/diffuse urothelial hyperplasia		(48)	(50)	(50)	(50)					(49)	(48)	(47)	(45)	
Luminal/multifocal submucosal hemorrhage		1		2	1									
Multifocal/diffuse submucosal fibrosis				2	2									
Dilation		12	15	19	14					1	1	1	1	
Multifocal/diffuse/MOS acute/chronic-active/MOS cystitis		2	2	1	2									
Diffuse congestion					1									
Multiple luminal calculus(1)		2	3	5	6					5	6	4	4	
Autolysis														

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 identified.

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Oncogenicity Study (24-Months) of S-ASA in the Diet of Swiss Mice
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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)																		
		MALES					FEMALES													
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#									
ORGANS NOT INCLUDED WITHIN BODY SYSTEMS:-																				
ABDOMINAL CAVITY:																				
Metastatic site: HISTIOCYTIC SARCOMA (M)		(2)	(1)	(1)	(1)	(2)	(3)	(2)	(2)											
Multifocal/diffuse peritoneal/MOS acute/chronic inflammation		2	1	1	2	2	1	1	1											
Multifocal vasculitis					1															
ADIPOSE TISSUE/BODY FAT:																				
Multifocal chronic inflammation										(1)										
Focal vasculitis										1										
TAIL:																				
No abnormality detected		(1)		(1)			(1)													
Multifocal hyperostosis																				
Chronic/MOS vertebral dislocation		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 les on specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice
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Pathology Table 7
Summary of all Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)									
		MALES					FEMALES				
		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#	0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg	#
ORGANS NOT INCLUDED WITHIN BODY SYSTEMS:-											
THORACIC CAVITY:											
Metastatic site: HISTIOCYTIC SARCOMA (M)	(2)	(1)	(2)	(3)	(5)	(3)	(2)	(3)			
Multifocal mediastinal/WOS subacute/chronic inflammation	2	1	1	2	2	1	1	2			
Focal mediastinal vasculitis					1						
Metastatic site: MESOTHELIOMA (M)			1								
LYMPHOMA (M)											
Multifocal mediastinal lymphoid hyperplasia								1			
Metastatic site: bronchiolar-alveolar ADENOCARCINOMA (M)				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 identified

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Appendix II.

Incidence of Neoplastic and Non-neoplastic
Histopathological Findings (from sponsor's pathology
tables 4 and 9 on pages 166-169 and 273-287 of volume 29)

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Pathology Table 4:

Summary of Drug-Related Histomorphologic Findings

(3 pages)

Diagnoses may have been merged or simplified for clarity of reporting. Merged diagnoses can be identified by punctuation (e.g. focal/multifocal). Comments concerning tissues which are not diagnostic (e.g. no microscopic correlate to macroscopic observation) are excluded from the table. The table shows the number of animals with each finding. The complete data are presented in Pathology Exhibit 4.

**APPEARS THIS WAY
ON ORIGINAL**

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PLACES VB.200

Summary of Drug-Related Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)											
		MALES						FEMALES					
		0	60	120	360	480	#	0	60	120	360	480	#
		MG/KG	MG/KG	MG/KG	MG/KG	MG/KG		MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	
KIDNEY(S):		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
No abnormality detected		3	3	3	2	3	6	6	4	8	3	3	3
Focal/multifocal/diffuse urothelial hyperplasia		9	10	14	17	25	10	8	11	16	25	25	25
focal/multifocal/diffuse papillary inflammation		4	8	8	11	19		2	4	2	4	4	4
Papillary necrosis					1	4							
focal/multifocal/diffuse papillary edema		1		1	1	3					1	7	7
STOMACH:		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
focal/multifocal ulcerations		1	5	1		6	1	1	2	6	4	4	4
focal/multifocal erosions		4	6	6	6	12	2	2	2	2	5	5	5
focal/multifocal/diffuse epithelial hyperplasia			2	3	5	10	1	5	3	5	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 identified.

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Summary of Drug-Related Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)											
		MALES						FEMALES					
		0	60	120	360	480	#	0	60	120	360	480	#
MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG
STOMACH:		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
focal/multifocal/diffuse inflammation		2	2	4	8	15	3	4	4	1	7		
DUODENUM:		(59)	(60)	(60)	(60)	(59)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
Inflammation		(60)	(59)	(60)	(59)	(59)	(60)	(60)	(60)	(59)	(60)	(58)	(60)
JEJUNUM:		(60)	(60)	(60)	(60)	(59)	(60)	(60)	(60)	(60)	(59)	(57)	(60)
Inflammation		(60)	(60)	(60)	(60)	(59)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
ILEUM:		(59)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Inflammation		1				4							1
CECUM:		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
focal/multifocal ulcerations		1				5							4
focal/multifocal/diffuse inflammation		1	2			5						2	4
focal/diffuse edema		2	1	3		5							3

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 identified.

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Summary of Drug-Related Histomorphologic Findings

OBSERVATIONS	TREATMENT	INCIDENCE OF OBSERVATION (NUMERIC)											
		MALES						FEMALES					
		0	60	120	360	480	#	0	60	120	360	480	#
MG/KG	MG/KG	MG/KG	MG/KG	MG/KG		MG/KG	MG/KG	MG/KG	MG/KG	MG/KG		MG/KG	
COLON:		(59)	(59)	(59)	(60)	(59)	(60)	(60)	(59)	(60)	(60)	(60)	(60)
Ulcerations		1											
focal/multifocal inflammation				2								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 identified

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*NDA 19,651**Page 149***Pathology Table 9:****Summary of Neoplastic Histomorphologic Findings for
All Animals with Similar Tumor Types Combined****(14 pages)**

Diagnoses have been merged or simplified for clarity of reporting. Merged diagnoses can be identified by punctuation (e.g. focal/multifocal). These combinations of tumor types were used for statistical calculations. The table shows the number of animals with each finding. Metastases are not shown on this table. The complete data are presented in Pathology Exhibit 4.

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Summary of Neoplastic Histomorphologic Findings for All Animals
with Similar Tumor Types Combined

TUMORS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)											
		MALES						FEMALES					
		0	60	120	360	480	#	0	60	120	360	480	#
ADRENAL GLAND(S):		MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	#	MG/KG	MG/KG	MG/KG	MG/KG	MG/KG	#
CORTICAL CELL CARCINOMA OR ADENOMA		(60)	(60)	(60)	(60)	(59)	0	(60)	(60)	(60)	(60)	(60)	0
PHEOCHROMOCYTOMA, BENIGN OR MALIGNANT		9	8	16	5	9	5	3	5	3	3	3	3
LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA (M)		1	1	1	1		0						0
AORTA:		(60)	(60)	(60)	(60)	(60)	0	(60)	(59)	(60)	(60)	(60)	0
LARGE GRANULAR-CELL LYMPHOMA (M)		1					0						0
UNDIFFERENTIATED SARCOMA (M)							0						0
BONE MARROW:		(60)	(60)	(60)	(60)	(60)	0	(60)	(60)	(60)	(60)	(60)	0
LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA (M)		4	1	1	1	1	0						0
GRANULOCYTTIC LEUKEMIA (M)					1		0						0

Figures in brackets represent the number of animals from which this tissue was examined microscopically in this table, a benign tumor is ignored if a malignant tumor of the same histogenetic origin is also present in the same tissue the absence of a numeral indicates that the lesion specified was not identified

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