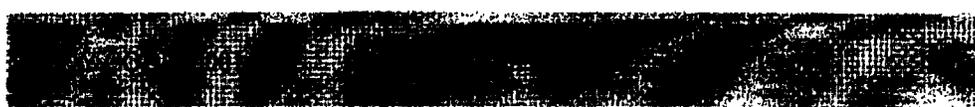


**SUBACUTE ORAL TOXICITY STUDY OF AVMAR WITH 28-DAY
TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RAT
GROSS- AND HISTOPATHOLOGICAL REPORT AND EXPERT OPINION**

STUDY CODE: 0001

**BUDAPEST
September, 2000.**

This report contains 6 pages including cover page and 18 pages appendices



Preparation of tissues and organs for histopathological examination:

Tissues listed above were trimmed to a thickness of 4 to 5 mm, dehydrated and infiltrated in a tissue processor and embedded in paraffin. Paraffin blocks were cut at a nominal thickness of 5 microns and stained with hematoxilin and eosin. Liver, heart, and kidney sections were also stained using periodic acid-Schiff (PAS) method. Sections of liver, and kidney previously fixed, were cut on a freezing microtome at 10 to 15 micrometers, and stained for fat with Fat Red.

Gross and histopathological examination was carried out according to the QGYI (National Institute of Pharmacy, NIP) order No.: P-44-1990 and the guidelines of Good Laboratory Practice for Testing of Chemicals (OECD, 1982).

RESULTS AND CONCLUSIONS

The results of the gross pathological examination are recorded on the individual data sheets entitled "Gross pathological findings", and of the histopathological examination on the data sheets entitled „Histopathological sampling". We presented the gross pathological lesions individually in Appendices 1-8, and the histopathological lesions in Appendices 9-16, and summarised the frequency of changes by group and sex in the attached Tables 1. and 2.

DEAD ANIMALS (GROSS- AND HISTOPATHOLOGY)

Three animals (40, 62, 72 AVEMAR, treatment period) died during the study.

At the necropsy haemorrhages in the cervical zone (40 AVEMAR, treatment period) were detectable in the connective tissue around the oesophagus and trachea, and serous-fibrinous pleuritis and pericarditis (62,72, AVEMAR, treatment period) was observed. Based on the histopathological results /acute serous-purulent



inflammation in the connective tissue around the oesophagus (40,62,72) serous-fibrinous infiltration in the pleura and epicardium (62,72) oedema in the lung (40,62,72)/ it can be concluded that the death of these animals is in connection with the mechanical injury of the wall of oesophagus in the course of daily application pocedure with the orogastric tube. No any degenerative or other lesion of toxic origin was observed in the organs of the three dead animals.

GROSS PATHOLOGY (TERMINAL SACRIFICE, TREATMENT AND POST-TREATMENT PERIOD)

At the gross pathological examination of the animals exsanguinated at the sheduled time, the state of development and condition of animals were of medium degree in the experimental and control groups.

Skin, hairs, and also mucous membrane on the body's orifices were free of any alterations.

According to internal examination the subcutaneous tissue, regional lymph nodes, fatty tissue, sceletal muscles, joints and bone system in all animals were normal.

There was no pathological liquid content in the thoracic and abdominal cavity.

In some cases focal emphysema (CONTROL: 46, AVEMAR: 27,34) was observed in the lung, and focal haemorrhage (CONTROL: 49) was detected in the thymus, and in the stomach (AVEMAR: 24).

The emphysema in the lung and the haemorrhage in the thymus could be related to the hypoxia during the exsanquination.

The haemorrhage in the mucous membrane of the stomach in one animal is an individual lesion, and could be in connection with the application procedure.

At some female animals the dilatation of the uterine horns and accumulation of clean fluid (hydrometra) was detectable (CONTROL: 42,45,48,51,52, AVEMAR:

67,80). The hydrometra is in connection with the individual sexual hormonal activity. The atrophy of testis (one side) can be regarded as a slight individual disorder (AVEMAR: 26).

No treatment related or uncertainly treatment related lesions were detectable at the gross pathological examinations of the experimental animals.

HISTOPATHOLOGY (TERMINAL SACRIFICE, TREATMENT AND POST-TREATMENT PERIOD)

At the histopathological examination of the animals exsanguinated at the scheduled time alveolar emphysema (CONTROL: 4,6,19,46,53,54,58, AVEMAR: 21,22,24,27,33,34,38,65,66,75,80) was observed in the lung. Acute haemorrhage (CONTROL: 4,49) was detectable in the thymus. Focal fibrosis (CONTROL: 4) was seen in the wall of oesophagus. Dilatation of the uterine horns (without inflammation) was established (CONTROL: 42,45,48,51,52, AVEMAR: 67,80).

Atrophy of germinal cell layers (AVEMAR: 26) was seen in the seminiferous tubules of the testis (one side).

The alveolar emphysema in the lung, and the focal acute haemorrhage (without haemosiderocytes) in the thymus could be related - as at the discussion of gross pathological lesions were explained - to the hypoxia and dyspnoea during the exsanguination. The focal fibrosis in the wall of oesophagus could be in connection with the mechanical injury of this organ. The dilatation of the uterine horns signs the presence of the sexual hormonal activity of these animals and can be regarded as a physiological phenomena. The atrophy of germinal cell layers in the seminiferous tubules of the testis (one side) is an individual lesion.

No histological evidence of acute, or subacute injury of toxic or other origin was detectable in the sections of investigated organs of AVEMAR treated animals

listed in the protocol. The structure and the cell morphology of all organs belonging to the immune system, the endocrine glands or nervous and other systems was the same at the control and treated animals, in the treatment and post-treatment period as well.

SUMMARY

In summary it can be stated that the test item marked AVEMAR administered orally to rats in dose of 2000 mg/kg body weight over a 28-day treatment period caused no lesions detectable by gross pathological and histopathological examination.

Budapest, 30 September, 2000.


Robert Glavits
pathologist
D.V.M., Ph.D.

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

GROSS PATHOLOGICAL LESIONS (MALES)

TREATMENT PERIOD

GROUP	CONTROL (D ₀)									
NUMBER	1	2	3	4	5	6	7	8	9	10

GROSS PATHOLOGICAL LESIONS

LUNG: emphysema	-	-	-	-	-	-	-	-	-	-
THYMUS: haemorrhage	-	-	-	-	-	-	-	-	-	-
STOMACH: haemorrhage	-	-	-	-	-	-	-	-	-	-
TESTIS (one side): atrophy	-	-	-	-	-	-	-	-	-	-
haemorrhages in the cervical zone	-	-	-	-	-	-	-	-	-	-
serous-fibrinous pleuritis and pericarditis	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS
GROSS PATHOLOGICAL LESIONS (FEMALES)
TREATMENT PERIOD**

GROUP	CONTROL (D ₀)									
NUMBER	41	42	43	44	45	46	47	48	49	50

GROSS PATHOLOGICAL LESIONS

LUNG:	emphysema	-	-	-	-	-	1	-	-	-	-
THYMUS:	haemorrhage	-	-	-	-	-	-	-	-	1	-
STOMACH:	haemorrhage	-	-	-	-	-	-	-	-	-	-
UTERUS:	hydrometra	-	2	-	-	2	-	-	2	-	-
haemorrhages in the cervical zone		-	-	-	-	-	-	-	-	-	-
serous-fibrinous pleuritis and pericarditis		-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
2 = moderate / m. number / m. size
3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

GROSS PATHOLOGICAL LESIONS (MALES)

TREATMENT PERIOD

GROUP	AVEMAR (D ₁)									
	21	22	23	24	25	26	27	28	29	30

GROSS PATHOLOGICAL LESIONS

LUNG:	emphysema	-	-	-	-	-	-	1	-	-	-
THYMUS:	haemorrhage	-	-	-	-	-	-	-	-	-	-
STOMACH:	haemorrhage	-	-	-	1	-	-	-	-	-	-
TESTIS (one side):	atrophy	-	-	-	-	-	3	-	-	-	-
	haemorrhages in the cervical zone	-	-	-	-	-	-	-	-	-	-
	serous-fibrinous pleuritis and pericarditis	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

GROSS PATHOLOGICAL LESIONS (FEMALES)

TREATMENT PERIOD

GROUP	AVEMAR (D ₁)									
	61	62*	63	64	65	66	67	68	69	70

GROSS PATHOLOGICAL LESIONS

LUNG:	emphysema	-	-	-	-	-	-	-	-	-	-
THYMUS:	haemorrhage	-	-	-	-	-	-	-	-	-	-
STOMACH:	haemorrhage	-	-	-	-	-	-	-	-	-	-
UTERUS:	hydrometra	-	-	-	-	-	2	-	-	-	-
	haemorrhages in the cervical zone	-	-	-	-	-	-	-	-	-	-
	serous-fibrinous pleuritis and pericarditis	-	2	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large
 * = died during the study

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

GROSS PATHOLOGICAL LESIONS (MALES)

POST-TREATMENT OBSERVATION PERIOD

GROUP	CONTROL (D ₀)									
NUMBER	11	12	13	14	15	16	17	18	19	20

GROSS PATHOLOGICAL LESIONS

LUNG:	emphysema	-	-	-	-	-	-	-	-	-	-
THYMUS:	haemorrhage	-	-	-	-	-	-	-	-	-	-
STOMACH:	haemorrhage	-	-	-	-	-	-	-	-	-	-
TESTIS (one side):	atrophy	-	-	-	-	-	-	-	-	-	-
	haemorrhages in the cervical zone	-	-	-	-	-	-	-	-	-	-
	serous-fibrinous pleuritis and pericarditis	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

GROSS PATHOLOGICAL LESIONS (FEMALES)

POST-TREATMENT OBSERVATION PERIOD

GROUP	CONTROL (D ₀)									
NUMBER	51	52	53	54	55	56	57	58	59	60

GROSS PATHOLOGICAL LESIONS

LUNG:	emphysema	-	-	-	-	-	-	-	-	-	-
THYMUS:	haemorrhage	-	-	-	-	-	-	-	-	-	-
STOMACH:	haemorrhage	-	-	-	-	-	-	-	-	-	-
UTERUS:	hydrometra	2	2	-	-	-	-	-	-	-	-
	haemorrhages in the cervical zone	-	-	-	-	-	-	-	-	-	-
	serous-fibrinous pleuritis and pericarditis	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

GROSS PATHOLOGICAL LESIONS (MALES)

POST-TREATMENT OBSERVATION PERIOD

GROUP	AVEMAR (D ₁)									
	31	32	33	34	35	36	37	38	39	40*

GROSS PATHOLOGICAL LESIONS

LUNG:	emphysema	-	-	-	1	-	-	-	-	-	-
THYMUS:	haemorrhage	-	-	-	-	-	-	-	-	-	-
STOMACH:	haemorrhage	-	-	-	-	-	-	-	-	-	-
TESTIS (one side):	atrophy	-	-	-	-	-	-	-	-	-	-
	haemorrhages in the cervical zone	-	-	-	-	-	-	-	-	-	2
	serous-fibrinous pleuritis and pericarditis	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large
 * = died during the study

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS
GROSS PATHOLOGICAL LESIONS (FEMALES)
POST-TREATMENT OBSERVATION PERIOD**

GROUP	AVEMAR (D ₁)									
	71	72*	73	74	75	76	77	78	79	80

GROSS PATHOLOGICAL LESIONS

LUNG:	emphysema	-	-	-	-	-	-	-	-	-	-
THYMUS:	haemorrhage	-	-	-	-	-	-	-	-	-	-
STOMACH:	haemorrhage	-	-	-	-	-	-	-	-	-	-
UTERUS:	hydrometra	-	-	-	-	-	-	-	-	-	2
haemorrhages in the cervical zone		-	-	-	-	-	-	-	-	-	-
serous-fibrinous pleuritis and pericarditis		-	2	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large
 * = died during the study

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

HISTOPATHOLOGICAL LESIONS (MALES)

TREATMENT PERIOD

GROUP	CONTROL (D ₀)									
NUMBER	1	2	3	4	5	6	7	8	9	10

HISTOPATHOLOGICAL LESIONS

LUNG:	alveolar emphysema	-	-	1	-	-	1	-	-	-	-
	oedema	-	-	-	-	-	-	-	-	-	-
	pleuritis	-	-	-	-	-	-	-	-	-	-
OESOPHAGUS:	haemorrhages in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	serous-purulent inflammation in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	focal fibrosis	-	-	-	1	-	-	-	-	-	-
HEART:	epicarditis	-	-	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	1	-	-	-	-	-	-
TESTIS (one side):	atrophy of germinal cell layers	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

HISTOPATHOLOGICAL LESIONS (FEMALES)

TREATMENT PERIOD

GROUP	CONTROL (D ₀)									
NUMBER	41	42	43	44	45	46	47	48	49	50

HISTOPATHOLOGICAL LESIONS

LUNG:	alveolar emphysema	-	-	-	-	-	1	-	-	-	-
	oedema	-	-	-	-	-	-	-	-	-	-
	pleuritis	-	-	-	-	-	-	-	-	-	-
OESOPHAGUS:	haemorrhages in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	serous-purulent inflammation in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	focal fibrosis	-	-	-	-	-	-	-	-	-	-
HEART:	epicarditis	-	-	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	-	-	-	-	-	1	-
UTERUS:	hydrometra	-	2	-	-	2	-	-	2	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

HISTOPATHOLOGICAL LESIONS (MALES)

TREATMENT PERIOD

GROUP	AVEMAR (D ₁)									
	21	22	23	24	25	26	27	28	29	30

HISTOPATHOLOGICAL LESIONS

LUNG:	alveolar emphysema	1	1	-	1	-	-	1	-	-	-
	oedema	-	-	-	-	-	-	-	-	-	-
	pleuritis	-	-	-	-	-	-	-	-	-	-
OESOPHAGUS:	haemorrhages in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	serous-purulent inflammation in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	focal fibrosis	-	-	-	-	-	-	-	-	-	-
HEART:	epicarditis	-	-	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	-	-	-	-	-	-	-
TESTIS (one side):	atrophy of germinal cell layers	-	-	-	-	-	2	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS
HISTOPATHOLOGICAL LESIONS (FEMALES)
TREATMENT PERIOD**

GROUP	AVEMAR (D ₁)									
	61	62*	63	64	65	66	67	68	69	70

HISTOPATHOLOGICAL LESIONS

LUNG:	alveolar emphysema	-	-	-	-	1	1	-	-	-	-
	oedema	-	1	-	-	-	-	-	-	-	-
	pleuritis	-	2	-	-	-	-	-	-	-	-
OESOPHAGUS:	haemorrhages in the perioesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	serous-purulent inflammation in the perioesophageal connective tissue	-	2	-	-	-	-	-	-	-	-
	focal fibrosis	-	-	-	-	-	-	-	-	-	-
HEART:	epicarditis	-	2	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	-	-	-	-	-	-	-
UTERUS:	hydrometra	-	-	-	-	-	-	2	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large
 * = died during the study

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS
HISTOPATHOLOGICAL LESIONS (MALES)
POST-TREATMENT OBSERVATION PERIOD**

GROUP		CONTROL (D ₀)										
		11	12	13	14	15	16	17	18	19	20	
HISTOPATHOLOGICAL LESIONS												
LUNG:	alveolar emphysema	-	-	-	-	-	-	-	-	-	1	-
	oedema	-	-	-	-	-	-	-	-	-	-	-
	pleuritis	-	-	-	-	-	-	-	-	-	-	-
OESOPHAGUS:	haemorrhages in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-	-
	serous-purulent inflammation in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-	-
	focal fibrosis	-	-	-	-	-	-	-	-	-	-	-
HEART:	epicarditis	-	-	-	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	-	-	-	-	-	-	-	-
TESTIS (one side):	atrophy of germinal cell layers	-	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
2 = moderate / m. number / m. size
3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

HISTOPATHOLOGICAL LESIONS (FEMALES)

POST-TREATMENT OBSERVATION PERIOD

GROUP	CONTROL (D ₀)									
	51	52	53	54	55	56	57	58	59	60

HISTOPATHOLOGICAL LESIONS

LUNG:	alveolar emphysema	-	-	1	1	-	-	-	1	-	-
	oedema	-	-	-	-	-	-	-	-	-	-
	pleuritis	-	-	-	-	-	-	-	-	-	-
OESOPHAGUS:	haemorrhages in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	serous-purulent inflammation in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	-
	focal fibrosis	-	-	-	-	-	-	-	-	-	-
HEART:	epicarditis	-	-	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	-	-	-	-	-	-	-
UTERUS:	hydrometra	2	2	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
2 = moderate / m. number / m. size
3 = marked / many / large

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

HISTOPATHOLOGICAL LESIONS (MALES)

POST-TREATMENT OBSERVATION PERIOD

GROUP	AVEMAR (D ₁)									
	31	32	33	34	35	36	37	38	39	40*

HISTOPATHOLOGICAL LESIONS

LUNG:	alveolar emphysema	-	-	1	1	-	-	-	1	-	-
	oedema	-	-	-	-	-	-	-	-	-	3
	pleuritis	-	-	-	-	-	-	-	-	-	2
OESOPHAGUS:	haemorrhages in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	2
	serous-purulent inflammation in the periesophageal connective tissue	-	-	-	-	-	-	-	-	-	3
	focal fibrosis	-	-	-	-	-	-	-	-	-	-
	HEART: epicarditis	-	-	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	-	-	-	-	-	-	-
TESTIS (one side):	atrophy of germinal cell layers	-	-	-	-	-	-	-	-	-	-

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large
 * = died during the study

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS**

HISTOPATHOLOGICAL LESIONS (FEMALES)

POST-TREATMENT OBSERVATION PERIOD

GROUP	CONTROL (D ₀)									
NUMBER	71	72*	73	74	75	76	77	78	79	80

HISTOPATHOLOGICAL LESIONS

LUNG:	alveolar emphysema	-	-	-	-	1	-	-	-	-	1
	oedema	-	2	-	-	-	-	-	-	-	-
	pleuritis	-	2	-	-	-	-	-	-	-	-
OESOPHAGUS:	haemorrhages in the periesophageal connective tissue	-	1	-	-	-	-	-	-	-	-
	serous-purulent inflammation in the periesophageal connective tissue	-	3	-	-	-	-	-	-	-	-
	focal fibrosis	-	2	-	-	-	-	-	-	-	-
HEART:	epicarditis	-	-	-	-	-	-	-	-	-	-
THYMUS:	acute haemorrhage	-	-	-	-	-	-	-	-	-	-
UTERUS:	hydrometra	-	-	-	-	-	-	-	-	-	2

REMARKS: 1 = slight / small / few
 2 = moderate / m. number / m. size
 3 = marked / many / large
 * = died during the study

TABLE 1.

0001

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS
SUMMARY OF GROSS PATHOLOGICAL LESIONS
(TERMINAL SACRIFICE)**

SEX	MALES		FEMALES		MALES		FEMALES	
GROUP	D ₀	D ₁						
OBSERVATION PERIOD	TREATMENT				POST-TREATMENT			

OBSERVED ALTERATIONS / NUMBER OF INVESTIGATED ANIMALS

LUNG:	Emphysema	0/10	1/10	1/10	0/9	0/10	1/9	0/10	0/9
THYMUS:	haemorrhage	0/10	0/10	1/10	0/9	0/10	0/9	0/10	0/9
STOMACH:	haemorrhage	0/10	1/10	0/10	0/9	0/10	0/9	0/10	0/9
UTERUS:	Hydrometra			3/10	1/9			2/10	1/9
TESTIS (one side)	Atrophy	0/10	1/10			0/10	0/9		

TABLE 2.

0001

**SUBACUTE ORAL TOXICITY STUDY OF AVEMAR
WITH 28-DAY TREATMENT AND 14-DAY POST-TREATMENT PERIOD IN RATS
SUMMARY OF HISTOPATHOLOGICAL LESIONS
(TERMINAL SACRIFICE)**

SEX	MALES		FEMALES		MALES		FEMALES	
	D ₀	D ₁						
GROUP								
OBSERVATION PERIOD	TREATMENT				POST-TREATMENT			

OBSERVED ALTERATIONS / NUMBER OF INVESTIGATED ANIMALS

LUNG:	alveolar emphysema	2/10	4/10	1/10	2/9	1/10	3/9	3/10	2/9
THYMUS:	acute haemorrhage	1/10	0/10	1/10	0/9	0/10	0/9	0/10	0/9
UTERUS:	hydrometra			3/10	1/9			2/10	1/9
TESTIS (one side)	atrophy of germinal cell layers	0/10	1/10			0/10	0/9		
OESOPHAGUS:	focal fibrosis	1/10	0/10	0/10	0/9	0/10	0/9	0/10	0/9