Bayer CropScience

REGULATORY TOXICOLOGY

Subject:

Spirotetramat (syn. BYI 08330)

Request for Historical Control Data

Position Paper

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Table of contents

INTRODUCTION **3**

HISTORICAL CONTROL DATA **3**

Dysplasia of forelimb bones *3*
Alterations at sacral vertebral arches and pelvic shift *3*

CONCLUSION **4**

REFERENCES **5**

ATTACHMENT 1: Historical control data (excerpt from study report AT 01413)

ATTACHMENT 2: Historical control data (supplemental data)

Introduction

The registration process of Spirotetramat is currently ongoing in Europe, USA, and Canada via a Joint Review Process. Due to increased incidences of skeletal malformations and skeletal deviations observed at the limit dose of 1,000 mg/kg bw in the developmental toxicity study in rats, conducted in the year 2002 ([redacted], 2004), Spirotetramat is proposed to be classified to "category 3 of reproductive substances" and labeled with the risk phrase "R 63 – Possible risk of harm to the unborn child". The labeling is proposed because of uncertainties regarding the assessment of a relationship to treatment for the following skeletal endpoints

1. Dysplasia of forelimb bones (scapula, humerus, radius and/or ulna)
2. 1st sacral vertebral arch shaped like lumbar vertebral arch, cartilagineous part not fused with processus transversus of the 2nd sacral vertebral arch, pelvis shifted caudally

since historical control data for these endpoints are lacking. The following paper provides additional information on historical control data from GLP studies conducted at this site for the above mentioned endpoints.

Historical control data

Dysplasia of forelimb bones

Forelimb dysplasia at the dose of 1,000 mg/kg bw/day (4 fetuses out of 4 litters) has been covered by the historical control data provided on page 658 of the study report AT 01413 ([redacted] 2004; see also attachment 1 of this paper). Maximum figures of 10 fetuses out of 4 litters have been determined for this spontaneous finding in the year 2000 (study number T5068551) and 7 fetuses out of 3 litters for the year 1999 (study number T9061318). Further data have been submitted with this paper in attachment 2.

Alterations at sacral vertebral arches and pelvic shift

Historical control data have been attached to this position paper for the second endpoint (attachment 2). Sacral vertebral arch alterations at the dose of 1,000 mg/kg bw in the actual study (3 fetuses out of 3 litters, i.e. 1.1% / 13.6%, respectively) have not been covered by the incidences noted in control groups provided for the years 1999-2006. However, when looking also into low- and mid-dose groups of these historical studies, maximum incidences of 2 fetuses out of 2 litters (0.9% / 10.0 %) were found in the mid dose and 1 fetus in the corresponding control group of a study performed in 2004.

Although the findings of sacral vertebral alterations is not fully covered by previous study data, the attached figures of historical data show that the finding is appearing spontaneously in the rat strain used. Furthermore, an extensive pilot dose range finder study, conducted prior to the Guideline study in 2001, did not show this alteration at doses of 800 and 1,000 mg/kg bw. In this pilot study (summary report can be found on page 542 of report no. AT 01413), 14 pregnant females have been dosed with 1,000 mg/kg bw (58 fetuses for skeletal evaluation) and 4 pregnant dams have been dosed with 800 mg/kg bw (25 fetuses for skeletal examination).

Conclusion

The increased incidences of dysplastic forelimb bones and sacral vertebral alterations in rat fetuses observed at the limit dose of 1,000 mg/kg bw/day in the developmental toxicity study ([redacted] 2004) are considered to be spontaneous findings, since the study incidence is either covered by historical control data (dysplastic forelimb bones) or ranged only slightly above the maximum historical incidence observed in a mid dose group without dose relation (sacral vertebral arch alterations). Furthermore, sacral vertebral arch alterations were not noted at skeletal examinations in the dose range finder study, using a total litter number of 18 for the high dose levels of 800 and 1,000 mg/kg bw/day.

References

1. [redacted] 2004, BYI 08330: Developmental Toxicity Study in Rats after Oral Administration, Report No. AT 01413, study number T9062786

ATTACHMENT 1:

Historical control data
(excerpt from study report AT 01413)

Historical Data of Control Groups (1999-2000)

Spontaneous Malformations

Species: Rat Strain: Hsd Cpb·WU

Year	Study	Number of examined litters	Litters with malformations no.	%	Number of examined fetuses	Fetuses with malformations no.	%	Type of Malformation
1999	T9067880	21	1	4.76	243	1	0.41	1st sacral vertebral arch left has the shape of a lumbar vertebral arch; pelvis shifted caudally
			1	4.76		1	0.41	dysplasia of forelimb bones
			1	4.76		1	0.41	atrial septal defect
1999	T2062311	22	2	9.09	242	3	1.24	dysplasia of forelimb bones
1999	T9061318	21	3	14.29	256	7	2.73	dysplasia of forelimb bones
			2	9.52		2	0.78	microphthalmia
			1	4.76		1	0.39	anophthalmia
			1	4.76		1	0.39	umbilical hernia with eventration of intestines
2000	T5068551	20	4	20.00	232	10	4.31	dysplasia of forelimb bones
			1	5.00		1	0.43	eye rudiment flat
			1	5.00		1	0.43	eyeball reduced in size
			3	15.00		5	2.16	interatrial septal defect

Percentage of fetal skeletal/visceral malformations refers to total number of fetuses.

Strain BOR:WISW (SPF Cpb) is identical with Hsd Cpb·WU

30

ATTACHMENT 2:

Historical control data (supplemental data)

Sacral vertebral arch shaped like lumbar vertebral arch together with pelvic shift

Incidence in Developmental Toxicity Studies in Rats 1999 - 2006

Species: Rat Strain: Hsd Cpb:WU

- Data of Different Study Groups -

Year	Study	Control	Dose 1	Dose 2	Dose 3
1999	T9067880	1	-	-	-
	T2061311	-	-	-	1
	T9061318	-	-	-	-
	T3068630[a]	1	-	-	1
2000	T5068551	-	-	-	-
2001	T5067750	-	-	-	-
	T1067765	-	-	-	-
	T8068563	-	-	-	-
	T6062800	-	-	-	-
	T9062777	-	-	-	-
2002	T3068568	-	1	-	-
	T7062784	-	-	-	-
	T6071558	-	-	-	-
	T9062786	-	-	-	3 (3)
	T3063590	-	-	-	-
	T5063600	-	-	-	-
2003	**T7063008**	-	-	-	-
	T7062955	-	-	-	-
	T0063010	-	-	-	7 (5)*
	T6062954	-	-	-	-
	T7072620[b]	-	-	-	-
	T1062959	-	-	-	4 (1)
2004	T0073280	-	-	-	1
	T4062961	-	-	1	-
	T0073271[a]	1	-	2 (2)	-
	T6062963	-	-	-	-
2005	T1062968	-	-	-	-
2006	T8062974	-	-	-	-
	T1062977[c]	-	-	-	-
	T5062971[c]	-	1	1	-
	T3074525	-	-	-	9 (5)

( ) no. of litters # no further dose group [a] not checked by QAU [b] inhalation [c] not reported yet
* (partly) as part of a multiple malformation

Sacral vertebral arch shaped like lumbar vertebral arch together with pelvic shift

% Incidence in Developmental Toxicity Studies in Rats 1999 - 2006

based on total number of fetuses (litters)

Species: Rat Strain: Hsd Cpb:WU

- Data of Different Study Groups -

Year	Study	Control	Dose 1	Dose 2	Dose 3
1999	T9067880	0.4 (4.8)	-	-	-
	T2061311	-	-	-	0.4 (4.2)
	T9061318	-	-	-	-
	T3068630[a]	0.4 (4.8)	-	-	0.4 (4.5)
2000	T5068551	-	-	-	-
2001	T5067750	-	-	-	-
	T1067765	-	-	-	-
	T8068563	-	-	-	-
	T6062800	-	-	-	-
	T9062777	-	-	-	-
2002	T3068568	-	0.4 (4.2)	-	-
	T7062784	-	-	-	-
	T6071558	-	-	-	-
	T9062786	-	-	-	1.1 (13.6)
	T3063590	-	-	-	-
	T5063600	-	-	-	-
2003	**T7063008**	-	-	-	-
	T7062955	-	-	-	-
	T0063010	-	-	-	3.8 (26.3)*
	T6062954	-	-	-	-
	T7072620[b]	-	-	-	-
	T1062959	-	-	-	1.9 (5.3)
2004	T0073280	-	-	-	1
	T4062961	-	-	0.4 (4.2)	-
	T0073271[a]	0.4 (4.8)	-	0.9 (10.0)	-
	T6062963	-	-	-	-
2005	T1062968	-	-	-	-
2006	T8062974	-	-	-	-
	T1062977[c]	-	-	-	-
	T5062971[c]	-	0.3 (4.5)	0.3 (4.5)	-
	T3074525	-	-	-	3.1 (22.7)

( ) no. of litters # no further dose group [a] not checked by QAU [b] inhalation [c] not reported yet
* (partly) as part of a multiple malformation

Historical Data of Control Groups (2003-2005)

Number of Malformations

Species: Rat Strain: Hsd Cpb:WU

Year	Study	Number of examined litters	Litters with malformations number	Litters with malformations %	Number of examined fetuses	Fetuses with malformations number	Fetuses with malformations %
2003	T7063008	22	5	22.7	266	5	1.9
	T7062955+++	21	6	28.6	264	9	3.4
	T0063010	22	3	13.6	235	3	1.3
	T6062954	19	0		213	0	
	T7072620+++	24	3	12.5	267	3	1.1
	T1062959	18	1	5.6	202	1	0.5
2004	T0073280	19	7	36.8	230	8	3.5
	T4062961	20	3	15.0	219	3	1.4
	T0073271[a]	21	4	19.0	258	4	1.6
	T6062963	19	0		225	0	
2005	T1062968	20	2	10.0	210	4	1.9
2006	T8062974	23	3	13.0	315	4	1.3
	T1062977[1)]	19	5	26.3	268	6	2.2
	T5062971[1)]	24	5	20.8	323	5	1.5
	T3074525	22	5	22.7	311	6	1.9

+++ inhalation
[a] not checked by QAU
[1)] not reported yet

Historical Data of Control Groups (2002-2003)

Spontaneous Malformations

Species: Rat Strain: Hsd Cpb:WU

Year	Study	Number of examined litters	Litters with malformations no.	%	Number of examined fetuses	Fetuses with malformations no.	%	Type of Malformation
2002	T9062786[a] (continued)	20	2	10.00	247	3	1.21	lobe of thyroid gland missing
			1	5.00		1	0.41	interatrial septal defect of the heart
2002	T3063590	19	1	5.26	213	1	0.47	eyeball missing; mandible shortened;domed head
			1			1		thyroid gland missing
2002	T5063600	20	1	5.00	239	1	0.42	dysplasia of forelimb bones (humerus, scapula)
			1	5.00		1	0.42	dysplasia of scapula
			1	5.00		1	0.42	atrial septal defect of the heart
2002	T9063000*							
2003	T7063008	22	2	9.09	266	2	0.75	combined thoracic vertebral malformation
			1	4.55		1	0.38	dysplasia of forelimb bones (humerus, scapula)
			1	4.55		1	0.38	dysplasia of forelimb bones (humerus, radius, scapula)
			1	4.55		1	0.38	atrial septal defect of the heart
2003	T7062955[c]	21	1	4.76	264	1	0.38	multiple malformation of cervical, thoracic and lumbar vertebrae, sternum and ribs
			1	4.76		1	0.38	dysplasia of humerus
			1	4.76		1	0.38	dysplasia of scapula
			1	4.76		1	0.38	dysplasia of forelimb and hind limb bones (humerus, ulna, radius, scapula, clavicle, femur)
			1	4.76		1	0.38	one supernumerary lumbar vertebra
			1	4.76		1	0.38	eyehole reduced in size

Percentage of fetal skeletal/visceral malformations refers to total number of fetuses.

* same control group as study T5063600
a visceral evaluation performed by a contract laboratory
c inhalation

Historical Data of Control Groups (2003-2004)

Spontaneous Malformations

Species: Rat Strain: Hsd Cpb:WU

Year	Study	Number of examined litters	Litters with malformations no.	%	Number of examined fetuses	Fetuses with malformations no.	%	Type of Malformation
2003	T7062955[b] (continued)	21	1	4.76	264	1	0.38	anophthalmia
			1	4.76		1	0.38	retroesophageal aortic arch
			1	4.76		1	0.38	ventricular septal defect of the heart
			1	4.76		1	0.38	atrial septal defect of the heart
2003	T0063010	22	1	4.55	235	1	0.43	head of 1st rib right missing
			1	4.55		1	0.43	eyeball reduced in size
			1	4.55		1	0.43	dilation of brain ventricle(s)
2003	T6062954	19	0		213	0		
2003	T7072620[b]	24	1	4.17	267	1	0.37	combined vertebral malformation
			1	4.17		1	0.37	eyehole reduced in size; hole between frontal bones
2003	T1062959	18	1	5.56	202	1	0.50	lumbar vertebral arch(es) misshapen
2004	T0073280	19	1	5.26	230	1	0.43	right-sided aortic spur
			5	26.32		5	2.17	ventricular septal defect of the heart
			1	5.26		2	0.87	atrial septal and ventricular septal defect
2004	T4062961	20	1	5.00	219	1	0.46	7th cervical vertebral arch left has the shape of a 6th cervical vertebral arch in the osseous and cartilaginous (lamina ventralis) parts, and the cartilaginous parts of 6th and 7th cervical vertebral arches left are fused
			1	5.00		1	0.46	eyeball reduced in size
			1	5.00		1	0.46	ventricular septal defect of the heart

Percentage of fetal skeletal/visceral malformations refers to total number of fetuses.

b inhalation

Historical Data of Control Groups (2004-2005)

Spontaneous Malformations

Species: Rat Strain: Hsd Cpb:WU

Year	Study	Number of examined litters	Litters with malformations no.	%	Number of examined fetuses	Fetuses with malformations no.	%	Type of Malformation
2004	T0073271[1)]	21	1	4.76	258	1	0.39	dysplasia of humerus
			1	4.76		1	0.39	hairline ventricular septal defect of the heart
			1	4.76		1	0.39	ventricular septal defect of the heart
		21	1	4.76		1	0.39	1st sacral vertebral arch has the shape of a lumbar vertebral arch, right or left; pelvis shifted caudally, right or left
2004	T6062963	19	0		225	0		
2005	T1062968	20	1	5.0	210	1	0.5	eye hole reduced in size
			1	5.0		1	0.5	supernumerary ossification center between 5th and 6th sternal segments; 14th rib present bilateral; one supernumerary lumbar vertebra
			1	5.0		1	0.5	generalized edema; scapula dysplastic right (bent); femur dysplastic right (shortened, thickened, and kinked); iliac bone dysplastic bilateral (kinked); maxilla dysplastic bilateral (shortened); 1st rib left shortened; cartilaginous part of 1st rib left is not fused with osseous part of rib; additional cartilage between the dorsal cartilage of 1st and 2nd lumbar vertebral arches left; clefted cartilage in the area of the symphysis
			1	5.0		1	0.5	supernumerary ossification center between 5th and 6th sternal segments; 14th rib present bilateral; one supernumerary lumbar vertebra; pelvis shifted cranially

Percentage of fetal skeletal/visceral malformations refers to total number of fetuses.

1) not checked by QAU

Historical Data of Control Groups (2006)

Spontaneous Malformations

Species: Rat Strain: Hsd Cpb:WU

Year	Study	Number of examined litters	Litters with malformations no.	%	Number of examined fetuses	Fetuses with malformations no.	%	Type of Malformation
2006	T8062974	23	1	4.3	315	1	0.3	cartilaginous part of 6th lumbar vertebral body bipartite; osseous part of 6th lumbar vertebral body is reduced in size and is lying in in the right part of the bipartie cartilage
			1	4.3		1	0.3	vertebral column S-shaped
			1	4.3		1	0.3	eye ball reduced in size
			1	4.3		1	0.3	ventricular septal defect of the heart
	T1062977[1)]	19	1	5.3	268	1	0.4	fusion of ribs (9-10th right)
			1	5.3		1	0.4	eyehole reduced in size and eye ball reduced in size
			1	5.3		1	0.4	atrial septal defect of the heart
			3	15.8		3	1.1	ventricular septal defect of the heart
	T5062971[1)]	24	1	4.2	323	1	0.3	eye rudiment flat (confirmed as malformation), eye ball reduced in size
			1	4.2		1	0.3	thyroid gland missing, unilateral
			1	4.2		1	0.3	ventricular septal defect of the heart
			2	8.3		2	0.6	hairline ventricular septal defect of the heart
	T3074525	22	1	4.5	311	1	0.3	14th rib comma shaped; one supernumerary lumbar vertebra
			1	4.5		1	0.3	eyehole reduced in size
			3	13.6		3	1.0	ventricular septal defect of the heart
			1	4.5		1	0.3	hairline ventricular septal defect of the heart

Percentage of fetal skeletal/visceral malformations refers to total number of fetuses.
[1)] not reported yet

Number of Fetuses (Litters) Used for Evaluation (1999 - 2006)

Species: Rat Strain: Hsd Cpb:WU

- Data of Different Study Groups –

Year	Study	Control	Dose 1	Dose 2	Dose 3
1999	T9067880	243 (21)	247 (22)	248 (22)	230 (22)
	T2061311	242 (22)	254 (23)	219 (20)	256 (24)
	T9061318	256 (21)	261 (22)	253 (22)	253 (21)
	T3068630[a]	239 (21)	226 (19)	234 (21)	231 (22)
2000	T5068551	232 (20)	257 (21)	283 (23)	282 (23)
2001	T5067750	233 (20)	230 (22)	223 (21)	243 (20)
	T1067765	283 (22)	262 (20)	307 (25)	285 (24)
	T8068563	285 (24)	261 (21)	302 (23)	266 (21)
	T6062800	275 (23)	249 (22)	269 (24)	253 (21)
	T9062777	236 (19)	217 (20)	228 (19)	201 (17)
2002	T3068568	269 (24)	279 (24)	309 826)	279 (23)
	T7062784	269 (23)	269 823)	211 (19)	266 (22)
	T6071558	244 (20)	278 (24)	219 (21)	224 (20)
	T9062786	247 (20)	301 (24)	253 (23)	270 (22)
	T3063590	213 (19)	249 (22)	217 (20)	230 (19)
	T5063600	239 (20)	208 (18)	240 (21)	207 (18)
2003	T7063008	280 (23)	279 (23)	275 (22)	265 (23)
	T7062955	264 (21)	317 (26)	224 (20)	248 (23)
	T0063010	235 (22)	235 (21)	216 (20)	186 (19)
	T6062954	213 (19)	220 (18)	205 (20)	100 (12)
	T7072620[b]	267 (24)	258 (23)	294 (24)	300 (26)
	T1062959	202 (18)	205 (17)	191 (17)	210 (19)
2004	T0073280	230 (19)	224 (19)	209 (21)	215 (17)
	T4062961	219 (20)	284 (22)	276 (24)	225 (20)
	T0073271[a]	258 (21)	226 (20)	232 (20)	220 (20)
	T6062963	225 (19)	259 (21)	202 (19)	203 (17)
2005	T1062968	210 (22)	222 (20)	233 (21)	196 (19)
2006	T8062974	315 (25)	271 (21)	311 (23)	293 (23)
	T1062977[c]	268 (19)	254 (19)	295 (22)	170(20)
	T5062971[c]	323 (24)	303(22)	303 (229	314 (23)
	T3074525	311 (22)	300 (22)	256 (19)	290 (22)

( ) no. of litters # no further dose group
[a] not checked by QAU [b] inhalation [c] not reported yet

Historical Data of Control Groups (2001-2003)

Vehicle

Species: Rat Strain: Hsd Cpb:WU

Year	Study	Vehicle
2001	T5067750	corn oil
	T1067765	10% ethanol / 90% lutrol (polyethylene glycol 400)
	T8068563	demineralised water
	T6062800	0.5% aqueous CMC suspension
	T9062777	0.5% aqueous tylose suspension
2002	T3068568	polyethylene glycol 400 (lutrol)
	T7062784	corn oil
	T6071558	0.5% aqueous CMC suspension
	T9062786	0.5% aqueous CMC suspension
	T3063590	demineralised water / 83.5% polyethylene glycol 6000
	T5063600	0.5% aqueous tylose suspension
2003	T7063008	0.5% aqueous CMC suspension
	T7062955	aerosol
	T0063010	1% HPM cellulose / 2% solutol / demineralised water
	T6062954	0.5% aqueous tylose suspension
	T7072620	aerosol
	T1062959	0.5% aqueous tylose suspension

CMC = carboxymethylcellulose
tylose = methylhydroxyethylcellulose

Historical Data of Control Groups (2004 - 2006)

Vehicle

Species: Rat Strain: Hsd Cpb:WU

Year	Study	Vehicle
2004	T0073280	0.5% aqueous tylose suspension
	T4062961	0.5% aqueous CMC suspension
	T0073271[1)]	demineralised water / Polyvinylpyrrolidon 25
	T6062963	ethanol:solutol:demineralized water (1:4:5)
2005	T1062968	0.5% aqueous CMC suspension
2006	T8062974	0.9% aqueous NaCl solution
	T1062977[c]	95% PEG 400(Lutrol) / 5% glycerol suspension
	T5062971[c]	0.5% aqueous CMC suspension
	T3074525	0.5% aqueous tylose suspension

[1] not checked by QAU
[c] not reported yet

CMC = carboxymethylcellulose
tylose = methylhydroxyethylcellulose
PEG = polyethylene glycol