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3.3.14	Concentration in vehicle	Not applicable due to subcutaneous administration
3.3.15	Exposure period / day	Not applicable due to subcutaneous administration
3.3.16	Controls	sham exposure or other **Intraperitoneal (not applicable due to subcutaneous administration)**
3.3.17	Vehicle	Not applicable due to subcutaneous administration
3.3.18	Concentration in vehicle	Not applicable due to subcutaneous administration
3.3.19	Total volume applied	Not applicable due to subcutaneous administration
3.3.20	Controls	Not applicable due to subcutaneous administration
3.4	**Examinations**	**Subcutaneous**
3.4.1	Body weight	Body weight were recorded before mating and in females on day 1, 6-16 and 20 of gestation.
3.4.2	Food consumption	Food consumption was visually inspected.
3.4.3	Clinical signs	Clinical signs were recorded daily after dosing. At least once a week examination, palpation and detailed health status were recorded.
3.4.4	Examination of uterine content	Uterine weight, implantations, per-implantation loss, resorptions, dead foetuses, late embryonic deaths, foetal deaths, living implants, corpora lutea
3.4.5	Examination of foetuses	Sex ratio, foetal and placental weight, visceral abnormalities, skeletal abnormalities
3.4.5.1	**General**	Number of dead foetuses, foetal weight, sex ratio
3.4.5.2	**Skelet**	Yes
3.4.5.3	**Soft tissue**	Yes
3.5	**Further remarks**	None

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Annex Point VI.6.8.1

Teratogenicity

4 RESULTS AND DISCUSSION

4.1 Maternal toxic Effects

There was a dose dependent decrease in weight gain of the dams. A pharmacological effect of the medetomedine, sedation was seen in dams at all levels. No abortions were seen at any dose level.

Dose group 30 µg/kg medetomedine

Pharmacological effects of medetomidine were found. Animals were slightly sedated after dosing. Sedation was usually disappeared at the second observation after about three hours from dosing.

Dose group 120 µg/kg medetomedine

Pharmacological effects of medetomidine were obvious. Animals were sedated at the first observation about an hour after dosing. Some animals had occasionally exophthalmos. Animals were normal or slightly sedated at the second observation. Slight piloerection was found occasionally in some animals.

Dose group 480 µg/kg medetomedine

Animals were sedated; piloerection and exophthalmos were found at the first observations. Sedation was also observed at the second observation and occasionally piloererction and exophthalmos still existed.

Summary

Decreased weight gain was found in the medium dose group 120 µg/kg and shortly after onset of dosing of the high dose groups 480µg/kg. On the 20th day of pregnancy the mean weight of medium dose group was significantly decreased compared to controls.

In the high dose group mean weight of dams was decreased in statistically tendency showing way on the 13th day of pregnancy and significantly on the 14th, 15th and 16th and highly significantly on the 20th day of pregnancy when compared to controls.

4.2 Teratogenic / embryotoxic effects

Foetal effects: dose dependent weight decrease of foetuses and placentae was found. There was increased number of resorptions in the highest dose group (480µg/kg). One late embryonic death was found in the medium dose group. One foetal death was found in the medium dose group. There were no differences in the number of living foetuses in any dose group compared to controls.

Soft tissue examination of foetuses:

There were no abnormalities which could be classified as drug induced malformations.

Skeletal examination: retardation of ossification was found at the highest dose group (480 µg/kg).

Occurence of one exencephalic foetus in the medium dose group was considered fortuitous.

4.3 Other effects

None

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Teratogenicity

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Teratogenicity of medetomidine was studied in rats by subcutaneous administration during organogenesis phase of pregnancy.

Dose groups:

Control b.w physiological NaCl solution.

Group2: 30 µg/kg medetomidine HCl

Group 3: 120 µg/kg medetomidine HCl

Group 4: 480 µg/kg medetomidine HCl

Number of animals:

Control: 20 dams, group 2: 24 dams, group 3: 23 dams, group 4: 27 dams

5.2 Results and discussion

Teratogenicity of medetomidine was studied by subcutaneous administration to rats during the organogenesis phase of pregnancy.

Medetomidine is a sedative used for sedation in cats and dogs. Sedative effects were also seen in dams during observations. Other pharmacological effects were piloerection and exophthalmos. Decrease in weight gain was seen at medium and high dose levels. During autopsy of dams no drug induced lesions were found. There were two dams with hydramnionic uteri in the medium dose group.

Slight embryo and fetotoxicity were found with a dose dependent weight decrease in foetuses and placentae. However, in more recent studies (IIIA6.8.1.2 effect is deemed secondary since it was caused by reduced food consumption in the gravid females due to sluggishness. The effects could also be caused by toxicity in the gravid females since the maximum tolerated dose for female rats have been reported to be below 120 µg/kg (group 3).

Early embryonic deaths were increased in the highest dose group. There were no increases in late embryonic deaths and foetal deaths. The found deaths were considered fortuitous, because they were incidental and no dose dependency was found. One exencephalic foetus found in the medium dose group is considered fortuitous and not drug induced.

In soft tissue examination by Wilson`s sectioning or evisceration no drug induced malformations were found. In skeleton examination no drug induced malformations were found. Medetomidine was found to correlate to induce retardation of ossification. This correlated well with weight decrease of foetuses.

The used doses were adequate for teratogenicity study of medetomedine. Early embryonic deaths were found to increase in the highest group. Therefore, it could not be possible to increase the dose. No effect level for medetomidine was found in this study, because medetomedine is a sedative and pharmacologically effective at low level.

5.3 Conclusion

Teratogenicity of medetomedine was studied in rats by subcutaneous administration during organogenesis phase of pregnancy. Secondary effects on offspring were observed due to possibly reduced food intake in the gravid females or overall toxic effects of the test substance. On the basis of this study medetomidine can not be regarded teratogenic at

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		these levels and at these experimental conditions.	
5.3.1	LO(A)EL maternal toxic effects	No information given in the study	X
5.3.2	NO(A)EL maternal toxic effects	No information given in the study	X
5.3.3	LO(A)EL embryotoxic / teratogenic effects	Dose dependent weight decrease of foetuses and placentae was found, There were increased number of resorptions in the highest dose group (480 µg/kg). Retardation of ossification was found in the highest dose group (480 µg/kg). No soft tissue abnormalities in the foetus found which could be classified as drug induced malformations.	X
5.3.4	NO(A)EL embryotoxic / teratogenic effects	Medetomedine was considered non-teratogenic in these experimental conditions and on the doses used (30 µg/kg, 120 µg/kg, 480 µg/kg medetomedine HCl)	X
5.3.5	Reliability	1	
5.3.6	Deficiencies	No	

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	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	1st October 2010
Materials and Methods	As stated by the applicant
Results and discussion	As stated by the applicant
Conclusion	Maternal LOAEL = 30 µg/kg bw/day Developmental LOAEL = 30 µg/kg bw/day
Reliability	1
Acceptability	Acceptable
Remarks	None.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

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Table A6_8_1_3(01)-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects.

Parameter	control data		30µg/kg	120 µg/kg	480 µg/kg	dose-response + / -
	historical	study				
Number of dams examined	n.a	20	24	23	27	n.a
Clinical findings during application of test substance	n.a	Slight sedation	Slight sedation	Slight sedation	Slight sedation	+
Mortality of dams *%*	n.a	0%	0%	0%	0%	-
Abortions		0	0	0	0	-
Food consumption	n.a	Ad libitum	Ad libitum	Ad libitum	Ad libitum	n.a
Water consumption *if test substance is applied with drinking water*	n.a	n.a	n.a	n.a	n.a	n.a
Pregnancies *%*	-	67%	80%	79%	87%	-
Necropsy findings in dams dead before end of test	n.a	n.a	n.a	n.a	n.a	n.a

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Table A6_8_1_3(01)-2. Table for Teratogenic effects (separate data for all dosage groups)
Litter response (Caesarean section data)

Parameter	control data		30µg/kg	120 µg/kg	480 µg/kg	dose-response + / -
	historical	study				
Corpora lutea state total/number of dams	n.a	16.5	16.8	17.3	17.2	-
Implantations state total/number of dams	n.a	12.1	12.6	11.5	13.6	-
Resorptions state total/number of dams	n.a	1.1	1.1	1.9	3.1	+
total number of fetuses	n.a	232	291	250	294	-
pre-implantation loss state %	n.a	4.4	4.1	5.8	3.7	-
post-implantation loss state %	n.a	n.a	n.a	n.a	n.a	n.a
total number of litters	n.a	20	24	21	26	-
fetuses / litter	n.a	4	4	3.8	3.5	-
live fetuses / litter *%*	n.a	100	100	99.6	100	-
Dead fetuses / litter *%*	n.a	0	0	0.4	0	-
fetus weight (mean) *[g]*	n.a	3.762	3.3368	3.070	2.450	+
placenta weight (mean) *[g]*	n.a	0.526	0.498	0.479	0.415	+
crown-rump length (mean) *[mm]*	n.a	n.a	n.a	n.a	n.a	n.a
Fetal sex ratio *[state ratio m/f]*	n.a	1.17	0.93	1.02	1.13	-

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Table A6_8_1_3(01)-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the foetuses

Parameter	control data		30µg/kg	120 µg/kg	480 µg/kg	dose-response + / -
	historical	study				
External malformations* *[%]*	n.a	0	0	1	0	-
External anomalies* *[%]*	n.a	0	0	0	0	-
Skeletal malformations* *[%]*	n.a	0	0	0.6	0	-
Skeletal anomalies* *[%]*	n.a	36.8	29.9	55.9	88.9	+ **
Skeletal variants* *[%]*	n.a	0	0	0	0	-
Visceral malformations* *[%]*	n.a	0	0	0	0	-
Visceral anomalies* *[%]*	n.a	5.1	5.3	3.8	12	-
Variants visceral* *[%]*	n.a	n.a	n.a	n.a	n.a	n.a

** Classified as signs of retardation of development and ossification

Table A6_8_1_3(01)-4. Number of dams in each dose group and pregnancy performance is:

	Control	30 µg/kg	120 µg/kg	480 µg/kg
Females mated	30	30	29	31
Pregnant	20	24	23	27
Sperm found, not pregnant	3	2	1	2
No sperm found	6	4	5	2
Unscheduled delivery	1*	0	0	0
Abortions	0	0	0	0

*Dam delivering her pups

Doc III A section 6.8.2(01)
Annex Point IIA VI.6.8.2

Multigeneration Reproduction Toxicity Study

Official use only

1 REFERENCE

1.1	**Reference**	[redacted], Fertility study (segment I study of medetomidine in rats by subcutaneous administration), [redacted] (Unpublished)
1.2	**Data protection**	Yes.
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data on new [a.s.] for [first approval / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	ECC 332/II 28.11, 1983 requirements. Performed according to FDA guidelines for Reproduction Studies for Safety Evaluation of drugs for human use (1966)
2.2	**GLP**	Yes, both according to OECD guidelines and FDA regulations.
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Medetomidine hydrochloride MPV-785
3.1.1	Lot/Batch number	24401
3.1.2	Specification	As given in section 2
3.1.2.1	**Description**	Medetomidine is a white to almost white crystalline powder that is freely soluble in water.
3.1.2.2	**Purity**	[redacted]
3.1.2.3	**Stability**	Ranging between [redacted] % and [redacted] %
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Sprague-Dawley
3.2.3	Source	[redacted]
3.2.4	Sex	Both sexes
3.2.5	Age/weight at study initiation	Males around 175 g and 45 days old, females about 220 g and 75 days old
3.2.6	Number of animals per group	24 males and 24 females per dose group
3.2.7	Mating	One female and one male were housed together.
3.2.8	Duration of mating	2 weeks
3.2.9	Deviations from standard protocol	None

Doc III A section 6.8.2(01) — Multigeneration Reproduction Toxicity Study

Annex Point IIA VI.6.8.2

3.2.10	Control animals	Yes. Dose group 0.
3.3	**Administration/ Exposure**	
3.3.1	Animal assignment to dosage groups	24 males and 24 females per dose group
3.3.2	Duration of exposure before mating	Males: daily for about 9 weeks (61 dosages) before mating until autopsy Females: daily for 2 weeks (15 dosages), before mating during mating and until autopsy
3.3.3	Duration of exposure in general P, F1, males, females	Males (P_0) were dosed daily for at least 60 days before mating, during mating and thereafter to the sacrifice of the offspring. Females (P_0) were dosed daily for at least 14 days before mating, during mating and after successful copulation to the day before sacrifice. The offspring (F_1- generation) were not dosed.
		Subcutaneous injection
3.3.4	Type	Subcutaneous injection to the shoulder region
3.3.5	Concentration	Dose groups: 0, 13.2, 40 and 120 µg/kg bodyweight
3.3.6	Vehicle	NaCl solution (natrosterile, medipolar)
3.3.7	Concentration in vehicle	Vehicle: 0.9% NaCl solution (natrosteril, medipolar)
3.3.8	Total volume applied	1 ml/kg
3.3.9	Controls	Yes. Dose group 0.
		Inhalation (not applicable since this study relates to subcutaneous administration)
3.3.10	Concentrations	Not applicable since this study relates to subcutaneous administration
3.3.11	Particle size	Not applicable since this study relates to subcutaneous administration
3.3.12	Type or preparation of particles	Not applicable since this study relates to subcutaneous administration
3.3.13	Type of exposure	Not applicable since this study relates to subcutaneous administration
3.3.14	Vehicle	Not applicable since this study relates to subcutaneous administration
3.3.15	Concentration in vehicle	Not applicable since this study relates to subcutaneous administration
3.3.16	Duration of exposure/day	Not applicable since this study relates to subcutaneous administration
3.3.17	Frequency of exposure	Not applicable since this study relates to subcutaneous administration
3.3.18	Controls	Not applicable since this study relates to subcutaneous administration
3.4	**Examinations**	
3.4.1	Clinical signs	Yes, daily watching including mortality. Once a week examination, palpation and a more detailed health status were recorded.
3.4.2	Body weight	Weekly, in addition females on days 0,7,14, 20 of gestation and 0,7,14, and 21 of lactation. Weight of offspring was recorded in days 1, 4, 14, and 21.

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Annex Point IIA VI.6.8.2

Multigeneration Reproduction Toxicity Study

3.4.3	Food/water consumption	Food consumption weekly during premating dosing period and in females during gestation.
3.4.4	Oestrus cycle	No information given in the study
3.4.5	Sperm parameters	No information available.
3.4.6	Offspring	Half of the P_0 females in all dose groups were allowed to litter. All pups (F_1) were weighed, examined for sex and abnormalities, survival recorded at day 1, 4, 14 and 21 of lactation. Postnatal development was examined and recorded on day 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21. The other half of the P_0 females in all dose groups was autopsied with Caesarean section on day 20 of the gestation. Live foetuses were weighed, sexed and examined for abnormalities. One third of the foetuses were selected for soft tissue analysis and preserved in Bouin´s fluid. Two thirds were preserved in alcohol for examination for skeletal abnormalities. Dead foetuses were counted, time of death was estimated and type of dead foetus was determined. Number and sexes of F_2 pups were recorded. All pups were sacrificed on day 4 after birth and abnormalities were recorded.
3.4.7	Organ weight	Organ weights were investigated.
3.4.8	Histopathology	Hispathology were performed on testes for P-generation males. Males and females which failed to copulate were autopsied and gross observations were made of organs and tissues with special emphasis on reproductive organs.

4 RESULTS AND DISCUSSION

4.1 Effects

4.1.1 Parent males

Except for pharmacological effects (sedation, piloerection and exophthalmos), there was no indication of treatment related clinical signs. Food consumption was reduced in all groups compared to the control group at the beginning and at the end of the dosing period. Weight gain was reduced in the highest dosed group and to some extent in the other dosed groups.

Actual weight of testis and epididymis were decreased dose dependently in all groups. Actual weight of prostate was decreased in low and high groups. However, the changes in reproduction organ weights are due to the reduced weight gain. The relative weight of testis and epididymis was increased in the high dose group. Because the number of successful matings was not decreased in any dose group compared to controls, it can be concluded that medetomidine had no on male fertility or reductive capacity of rats on the used doses.

4.1.2 Parent females

Except for pharmacological effects (sedation and piloerection) there was no indication of clinical signs induced by the drug treatment. Body weight of females was decreased in the high group on days 0, 14, and 20 of gestation and in the medium dose group on day 20 of gestation compared to the control group. During lactation, weight was decreased on day 7 and day 14 in the medium and high dose group compared to the control group. There were no changes in food consumption in any dose group compared to the controls during pre-mating dosing, pregnancy or lactation. No abortions were found.

4.1.3 F_1 males

Medetomidine had no effect on the fertility if the F_1 generation. The number of offspring was decreased in high dose group but the decrease is considered incidental and not drug induced.

4.1.4 F_1 females

Medetomidine had no effect on the fertility if the F_1 generation. The number of offspring was decreased in high dose group but the decrease is considered incidental and not drug induce

4.1.5 F_2 males

No differences from the control animals were observed.

4.1.6 F_2 females

No differences from the control animals were observed.

4.2 Other

Not applicable

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Fertility study of medetomidine in rats by subcutaneous administration. Performed according to a) FDA guidelines for Reproduction Studies for Safety Evaluation of drugs for human use (1966) and ECC 332/II 28.11,1983 requirements.

24 males and 24 females per dose group

Dose groups: 0, 13.2, 40 and 120 µg/kg bodyweight

5.2 Results and discussion

The effect of medetomidine on the fertility of male and female rats was studied by subcutaneous dosing before mating, during mating, pregnancy and lactation. Effects on fertility in the non-dosed F_1 generation were also observed.
Sedation was the main pharmacological effect during dosing. Other pharmacological effects were piloerection and exophthalmos

Decreased weight gain was seen in males during premating dosing period and in females during pregnancy and lactation. In males, decreased body weight gain correlated to decreased food consumption. In females, food consumption was comparable to controls. Medetomidine induces slight embryo and fetotoxicity in the P_0 generation high dose which manifested as increased number of early embryonic deaths, decreased weight of foetuses and placenta. Weight decrease of foetuses correlated with the retardation of ossification. However, since the maximum tolerated dose (MTD) for females is below the highest dose these effects might be due to poor status of the dams. Other fetal development studies of medetomidine contradict the lack of correlation between food consumption and weight gain.
No effects on weight were seen in the F_1 generation past lactation or at all in the F_2 generation.

No malformations were found in foetal examinations for the P_0 and F_1 generations. The number of delivered offspring was decreased at the beginning of lactation in the highest dose group due to the strong sedation of dams which caused aggressive behaviour and eating of offspring. Viability of small offspring in the highest dose group was reduced.

The doses were adequate for testing the effects of medetomidine on fertility of rats. Increasing the high dose could not have been possible because of strong sedation and tendency of dams to eat their young. In the low dose group, only minor effects were seen; slight decreased weight gain of males. In females, the lowest dose induced minor effects which were pharmacological. The non-effect dose level is in males and females somewhat less than 13.3 µg/kg. The maximum tolerated dose MTD is in males somewhat more than 120 µg/kg/day and in females ranges between 40 and 120 µg/kg/day.

5.3	**Conclusions**	Medetomidine had no effect on the fertility of male and female rats in the parent (P_0) or first generation offspring (F_1). A slight embryo and fetotoxicity manifested as increased number of early embryonic deaths, decreased weight of foetuses and placenta in the P_0 high dose group. Since that group is above the maximum tolerated dose this might be a secondary effect due to sever sedation in dams.
5.3.1	LO(A)EL	
5.3.1.1	**Parent males**	13.3 µg/kg
5.3.1.2	**Parent females**	13.3 µg/kg
5.3.2	NO(A)EL	
5.3.2.1	**Parent males**	Below 13.3 µg/kg
5.3.2.2	**Parent females**	Below 13.3 µg/kg
5.3.3	Reliability	1
5.3.4	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*21st October 2010*
Materials and Methods	*As stated by the Applicant.*
Results and discussion	*As stated by the Applicant.*
Conclusion	*As stated by the Applicant*
Reliability	*1*
Acceptability	*Acceptable*
Remarks	*This study closely resembles a two-generation study such as that described in OECD guideline 416.*
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_8_2(01)-1 Table for animal assignment for mating (modify as appropriate)

		Number of animals			
		Controls	**13.3 µg/kg**	**40 µg/kg**	**120 µg/kg**
Parents	**m**	24	24	24	24
	f	24	24	24	24
F_1	**m**	12	11	12	10
	f	12	11	12	10

Table A6_8_2(01)-2 Table for reproductive toxicity study (modify if appropriate)

If effects are found in one generation, the figures for the other generation(s) should be given as well (as shown as an example for mortality). Give only information on endpoints with effects, delete other endpoints.

Parameter			control		13.3 µg/kg		40 µg/kg		120 µg/kg			
		Generation	m	f	m	f	m	f	m	f		
Mortality	incidence	**P**	0	0	0	0	0	0	0	0		
		F_1	0	0	0	0	0	0	0	0		
		F_2	0	0	0	0	0	0	0	0		
Food consumption (week 9)	% of control		-	-	91		87		86			
Body weight gain (f at end of lactation)	% of control		-	-	96	100	90	96	85	96		
Reproductive Performance												
Mating index			0.88		0.96		1		1			
Fertility index			0.88		0.96		1		1			
Number of implantations	Mean		117		156		132		147			
Duration of pregnancy	Mean		22.1		22.1		22.2		23.0			
Birth index			-	.	-	.	-	.	-	.		
Live birth index			0.96		0.96		0.92		0.89			
Gestation index	(pups alive / pups born)		0.97		0.98		0.95		0.7			
Litter size	Mean		12.8		11.9		12.1		10.3			
Litter weight	Mean		47.0		44.2		39.4		39.2			
Pup weight	Mean day 1		6.689		6.160		5.527		4.584			
Sex ratio	Male/female		1.33		1.02		0.89		1.27			
Reproductive Performance F_1												
Fertility index			0.92		1		1		0.9			
Viability index			0.99		0.94		0.95		1			
Gestation index	(pups alive /pups born)		1		0.86		0.96		1			

Table A6_8_2(01)-3 Weight of male reproductive organs.

*p<0.05, **p<0.01, ***p<0.01

Dose group µg/kg	Control	13.3 µg/kg	40 µg/kg	120 µg/kg
Testis	4.255 ±0.307	4.181 ±0.263 (98)	3.992** ±0.292 (94)	3.963** ±0.307 (93)
Prostate	0.550 ±0.155	0.461* ±0.092 (84)	0.492 ±0.098 (89)	0.458* ±0.095 (83)

Seminal vesicle	1.423 ±0.255	1.251 ±0.246 (88)	1.253 ±0.251 (88)	1.245 ±0.295 (87)
Epididymis	1.480 ±0.093	1.427 ±0.087 (96)	1.397** ±0.307 (94)	1.342*** ±0.116 (91)

Table A6_8_2(01)-4 Organ weights P and F1 females

Dose group µg/kg	Control	13.3	40	120
Corpora lutea				
Total	127	167	174	170
Mean	14.1	13.9	14.5	14.2
S.D.	1.8	2.1	3.0	1.9
Implantations				
Total	117	156	132	147
Mean	13.0	13.0	11.0	12.3
S.D.	2.1	2.1	3.0	2.8
Pre implantation loss				
Total	10	11	42	23
Mean	1.1	0.9	3.5	1.9
S.D.	2.1	2.1	3.0	2.4
Weight of foetuses (g)				
Mean	3.872	3.632	3.059***	2.525***
S.D.	0.243	0.339	0.164	0.512
%		93	79	65
Weight of placentae (g)				
Mean	0.513	0.517	0.467	0.42**
S.D.	0.044	0.041	0.046	0.082
%		101	91	82
Number of male foetuses				
Total	55	66	60	69
Mean	6.1	5.5	5.0	5.8
S.D.	1.9	2.8	2.0	3.0
Number of female foetuses				
Total	57	83	61	62
Mean	6.3	6.9	5.1	5.2
S.D.	2.0	2.2	2.3	1.7
Sex ratio				
M/F	0.96	0.80	0.98	1.11

*p<0.05, **p<0.01, ***p<0.01

Table A6_8_2(01)-5 Soft tissue examination by "Wilson's sectioning"

Dose group µg/kg	Control	13.3	40	120
No of litters studied	9	12	12	11
No of foetuses studied	37	49	41	43
Normal foetuses	29	32	21	27
Litters with abnormal foetuses	6	10	9	10
Abnormal foetuses	8	17	20	16

III A Section 6.9 **Annex Point IIIA VI.I**	**Neurotoxicity Study**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	Medetomidine, an α_2-adrenoreceptor agonist, affect neurotransmitter levels in mammals. There is therefore a risk of neurotoxicity. The oral subchronic study that is submitted includes weekly behavioural observations and after a minimum of 11 weeks sensory reactivity were assessed. Scientific studies (Ma et al 2005, British Medical Bulletin 71: 77-92) do also indicate neuroprotecting functions of α_2-adrenoreceptors including dexmedetomidine instead of neurotoxicity. Further neurotoxicity studies are therefore not regarded as necessary at this point.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	22nd October 2010	
Evaluation of applicant's justification	OK, RMS agrees with the Applicant	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

III A Section 6.10 Annex Point IIIA VI.7	**Mechanistic study**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	Due to the very long experience of this substance as a sedative for humans and mammals like dogs and cats,no unexpected adverse events have been reported which should have justified a mechanistic study, hence no mechanistic study is enclosed.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	22nd October 2010	
Evaluation of applicant's justification	OK, RMS agrees with the Applicant	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

III A Section 6.11 Annex Point III-0§	Studies on other routes of administration	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	For other routes of administration, please review e.g. section A6.2.4 Introduction to metabolism in mammals Metabolism and excretion of ^{3}H-dexmedetomedine following intravenous or subcutaneous administration to chronically bile duct cannulated rats. And section A6.1.8 The acute subcutaneous toxicity of different doses of medetomedine MPV-785 in rat after a single subcutaneous injection. The LD50 value is approximately 20 mg/kg. More examples of different routes of exposure are found in the dossier related to the specific types of studies.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	22nd October 2010	
Evaluation of applicant's justification	OK, RMS agrees with the Applicant	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

III A Section 6.12.1 Annex Point IIA VI.9.1	**Medical surveillance data on manufacturing plant personnel if available**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [X]**	**Technically not feasible [X]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	Medical surveillance data on manufacturing plant personel of the active substance is not provided, as no such information is available to I-Tech AB, since the manufacturer is [redacted] and I-Tech AB buys the active substance from the manufacturer without having access to information on the medical surveillande of the manufacturing plant personel. I-Tech AB has enclosed a Material Safety Data Sheet on Medetomidine hydrochloride created by [redacted], which has been made available to I-Tech. The Material Safety Data Sheet provides hazard identification and instructions on how to handle human contact with the active substance and how to store the substance. For further information, please see Reference No. [redacted]	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Agree with applicant	
Conclusion	Applicants justification is acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Doc III A section 6.12.2.1 (01)

Annex Point VI.6.9.2

Human Case Report - overdose in the perioperative setting

Official use only

1 REFERENCE

1.1	**Reference**	Jorden V, 2004, Dexmedetomidine overdose in the perioperative setting Abbot Laboratories, Ohio, IL, USA, Ann Pharmacother **38** pages 803-7 (published)
1.2	**Data protection**	No
1.2.1	Data owner	Public domain

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Dexmedetomidine, which is white to nearly white crystalline
3.2	**Persons exposed**	*3 persons*
3.2.1	Sex	Male
3.2.2	Age/weight	1- 74 years 68 kg 2- 51 years 95 kg 3- 29 years 214 kg
3.2.3	Known Diseases	1burn injured, in need of skin grafting 2 atherosclerotic cardiovascular disease 3 diabetes mellitus
3.2.4	Number of persons	3
3.2.5	Other information	None
3.3	**Exposure**	Intravenous administration
3.3.1	Reason of exposure	Intensive care unit patients in need of short term sedation
3.3.2	Frequency of exposure	Single
3.3.3	Overall time period of exposure	1. 9 minutes in total 2. Approximately 30 minutes 3. Approximately 3 hours
3.3.4	Duration of single exposure	Please see 3.3.3.
3.3.5	Exposure concentration/dose	1. about 1 µg/kg/h plus 200 µg injected 2.about 2 µg/kg/h to 4 µg/kg/h 3. about 0.5 µg/kg/min

Doc III A section 6.12.2.1 (01)

Annex Point VI.6.9.2

Human Case Report - overdose in the perioperative setting

3.3.6	Other information	None
3.4	**Examinations**	Observations, physical stimulation
3.5	**Treatment**	Withdrawal of the dexmedetomidine
3.6	**Remarks**	None
		4 RESULTS
4.1	**Clinical Signs**	Lowered heart rate , unresponsive to stimulation, lowered breathing during overdose
4.2	**Results of examinations**	When overdoses were identified, dexmedetomidine was removed, patients were observed until they woke up. Physical stimulation tests were carried when patients woke up.
4.3	**Effectivity of medical treatment**	Not applicable
4.4	**Outcome**	The patients recovered uneventfully
4.5	**Other**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Report based on 3 cases of accidental dexmedetomidine overdose in the perioperative setting. The study was a review of the pathophysiology of alpha2 agonist overdose. Three patients accidentally received overdoses of dexmedetomidine , one intraoperatively (192 µg over 20 minutes) and 2 postoperatively (4 and 2 rather than 0.4 and 0.2 µg/kg/min, 0.5 µg/kg/min rather than 0.5 µg/kg/h).
5.2	**Results and discussion**	Dexmedetomidine dosing in excess of the labelled recommendation has been reported, but accidental dexmedetomidine overdose in clinical practice has not been described. Excessive levels of sedation were the only significant finding in all three patients. Dexmedetomidine has a short redistribution half-life of 6 minutes which should lead to rapid resolutions of over sedation induced by overdoses. While the patients reported here were hemodynamically stable, dexmedetomidine may endanger significant hemodynamic changes either because of symphatholysis at normal doses or vasoconstriction at higher recommended doses. The absence of a significant hypertensive response to high dexmedetomidine concentrations suggests that dexmedetomidine induced hypertension may be multifactorial, not simply related to plasma drug concentrations.
5.3	**Conclusion**	Practitioners presented with dexmedetomidine overdose should be prepared to manage over sedation. While haemodynamic alterations may be seen with dexmedetomidine use. Hypertension from high dexmedetomidine plasma concentrations is not consistent response. Practitioners using dexmedetomidine should carefully note that dosing for this agent is described by the manufacturer in µg/kg/h, not µg/kg/min.

Doc III A section 6.12.2.1 (01)

Annex Point VI.6.9.2

Human Case Report - overdose in the perioperative setting

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4th November 2010
Materials and Methods	As stated by the applicant.
Results and discussion	As stated by the applicant
Conclusion	As stated by the applicant
Remarks	None.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Doc III A section 6.12.2.2/01
Annex Point VI.6.9.2

Human Case Report

Pharmacological effects of medetomidine in humans

Official use only

1 REFERENCE

1.1	**Reference**	Scheinin H,1989, Farmous Group Ltd, Research Centre, Turku, Finland Pharmacological effects of medetomidine in humans, Acta vet. Scand. Volume **85**, pages 145-147. (published)

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Medetomidine, which is white to nearly white crystalline
3.2	**Persons exposed**	Healthy male volunteers in three clinical trials
3.2.1	Sex	Male
3.2.2	Age/weight	No information
3.2.3	Known Diseases	Healthy
3.2.4	Number of persons	No information
3.2.5	Other information	None
3.3	**Exposure**	Intravenous administration
3.3.1	Reason of exposure	Clinical trial phase I, acute single dose, clinical pharmacology
3.3.2	Frequency of exposure	Single
3.3.3	Overall time period of exposure	5 minutes of intravenous administration of drug and placebo
3.3.4	Duration of single exposure	5 minutes, at least 24 hours follow up
3.3.5	Exposure concentration/dose	25, 50 and 100 µg doses of medetomidine in physiological saline
3.3.6	Other information	None
3.4	**Examinations**	Vigilance, hemodynamic effects, saliva secretion, biochemical and hormonaleffects
3.5	**Treatment**	Withdrawal of the medetomidine
3.6	**Remarks**	None

4 RESULTS

4.1	**Clinical Signs**	Drug-sedative effects disappeared after 4 h, hypotension and dry mouth still there after 8 h.

Doc III A section 6.12.2.2/01

Annex Point VI.6.9.2

Human Case Report

Pharmacological effects of medetomidine in humans

4.2	**Results of examinations**	The highest dose tested was 120 µg. Medetomidine was well tolerated.
4.3	**Effectivity of medical treatment**	A clear dose-dependent sedative effect.
4.4	**Outcome**	The patients recovered uneventful
4.5	**Other**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Pharmacological effects of medetomidine in humans
5.2	**Results and discussion**	The highest dose tested was 120 µg. Medetomidine was well tolerated. Medetomidine caused adose-dependent decrease of blood pressure (max 22/14 mmHg) heart rate (max 14/min) and cardiac output (max 21%). A clear dose-dependent sedative effect.
5.3	**Conclusion**	The highest dose tested was 120 µg. Medetomidine was well tolerated.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4th November 2010
Materials and Methods	As stated by the applicant
Results and discussion	As stated by the applicant
Conclusion	As stated by the applicant
Remarks	None.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

III A Section 6.12.3 **Annex Point VI.6.9.3**	**Healthrecords**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	Even though the very long experience of this substance as a sedative for humans and mammals like dogs and cats, no unexpected adverse events have been reported , but no formal health records have been created, therefore no such data is enclosed. Please view section A6.12.4 with different epidemiological data for further information.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Applicants justification acceptable	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Doc III A Section 6.12.4.1(01)

Annex Point VI.6.9.4

Epidemiological Study

Cohort-study

Official use only

1 REFERENCE

1.1	**Reference**	Dasta J et al, 2004, Comparing Dexmedetomidine Prescribing Patterns and Safety in the Naturalistic Setting Versus, Abbott Laboratories, Ann Pharmacother volume 38 pages 1130-5 (published)
1.2	**Reference**	Hartwig SC et al., 1991, Severity indexed, incident report-based medication error-reporting program. Am J Hosp Pharm;48:2611-6 (published)
1.3	**Data protection**	No data protection claimed
1.3.1	Data owner	Public domain
1.3.2	Companies with letter of access	-
1.3.3	Criteria for data protection	Data on new [a.s.] for [first approval / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	Dexmedetomidine
3.1.1	Lot/Batch number	Not available
3.1.2	Specification	Not available
3.1.2.1	**Description**	Brand name: Precedex Active ingredient: dexmedetomidine hydrochloride Dosage form: intravenous injection Company name: Abbott Laboratories Available by prescription only, intensive care unit use only
3.1.2.2	**Purity**	Sterile
3.1.2.3	**Stability**	No information available
3.2	**Type of study**	Cohort study. Retro-perspective observational study
3.3	**Method of data collection**	Investigators reviewed the medical records daily to assess the presence, severity, causality and clinical outcome of adverse drug reaction and consulted with the prescriber, if necessary, for clarification.
3.4	**Test Persons / Study Population**	

Doc III A Section 6.12.4.1(01)

Annex Point VI.6.9.4

Epidemiological Study

Cohort-study

3.4.1	Selection criteria	**cohort study and cross sectional study:** Adults over 18 years of age, who were prescribed dexmedetomidine as part of routine care in an intensive care unit in the United States. Data were obtained irrespective of the dosage or duration of therapy. Ten sites from 8 US states were recruited to participate in this study to serve as convenience samples. Site selection included institutions having dexmedetomidine as medication with sufficient usage to generate data on 8-10 patients over a 4-to6-months period.
3.4.2	Number of test persons per group/cohort size	Ten sites from 8 US states were recruited to participate in this study to serve as convenience samples. Site selection included institutions having dexmedetomidine as medication with sufficient usage to generate data on 8-10 patients over a 4- to 6-months period.
3.4.3	Sex	Both sexes
3.4.4	Age	Over 18 years of age
3.4.5	Diseases	Intensive care unit patients
3.4.6	Smoking status	smokers or non-smokers
3.5	**Controls**	No
3.5.1	Type of control	cohort or cross-sectional study: National population from 8 states in the United States
3.5.2	Number of test persons per group/cohort size	In total 136 patients were enrolled
3.5.3	Sex	Both sexes
3.5.4	Age	Over 18 years of age
3.5.5	Diseases	Intensive care unit patients in need of short term use of sedative in initially intubated mechanistically ventilated critically ill patients. Thoracic surgery was the most common admitting services (46% of institutions).
3.5.6	Smoking status	smokers and non-smokers
3.6	**Administration/ Exposure**	
3.6.1	Exposure Route	Injection/infusion
3.6.2	Exposure Situation	Intensive care unit patients in need of short term use of sedative in initially intubated, mechanistically ventilated critically ill patients
3.6.3	Exposure concentration(s)	Information not available.
3.6.4	Method(s) to determine exposure	Blood samples
3.6.5	Postexposure period	Observation period 4-6 months.

Doc III A Section 6.12.4.1(01)
Annex Point VI.6.9.4

Epidemiological Study
Cohort-study

3.7	**Examinations**	
3.7.1	Type of disease	Intensive care unit patients in need of short term use of sedative in initially intubated mechanistically ventilated critically ill patients.
3.7.2	Parameters	Thoracic surgery was the most common admitting services (46% of institutions). The top tree reasons for prescribing dexmedetomidine were to assist in weaning (53%), reduce the use of other narcotic or sedative drugs (42.6%) and maintain the patients' alertness (25%).
3.8	**Further remarks**	
	4 RESULTS AND DISCUSSION	
4.1	**Exposure**	The duration of therapy averaged 25.4±21.4 hours (range 1-123.5). Dexmedetomidine was abruptly stopped in 96 (70.5%) patients and weaned in the remaining subjects over 4.5±4.3 hours. There were no reports of rebound symptoms in any patient. In 6 patients, investigators reported treatment failure at a dosage of 0.7 µg/kg/h. Fourty-six (33.8%) patients received dexmedetomidine >24 hours. Duration of therapy in these patients averaged 54 hours (range 24.5-123). Ten patients in this group received a maximum dose >0.7 µg/kg/h. Dexmedetomidine was abruptly stopped in 24 (52.2%) of these patients and was titrated to discontinuation in the remaining patients over 5.4±5.2 hours.
4.1.1.1	**Number of measurements**	Not stated in the study
4.1.1.2	**Average concentrations**	The initial dose averaged 0.32±0.13 µg/kg/h, the minimum dosage (lowest dosage for at least one hour) averaged 0.26 µg/kg/h, and the maximum dosage (highest dosage for at least one hour) averaged 0.53 µg/kg/h. Thirty-seven (27.2%) patients received a dexmedetomidine dose >0.7 µg/kg/h, with the highest being 1.4 µg/kg/h. Eighty-two percent of patients were mechanistically ventilated when dexmedetomidine was started, whereas 20 (14.7%) patients were never mechanically ventilated during dexmedetomidine administration. The drug was continued after exturbation on 81 (59.5%) patients for 11.3±13.5 hours (range0.1-55).
4.1.1.3	**Standard deviation**	Data was analysed using Excel, and descriptive statistics were reported, including mean ±SD.
4.1.1.4	**Date(s) of measurement(s)**	June 27, 2001 to May 31, 2002
4.1.2	Other	None

Doc III A Section 6.12.4.1(01)

Annex Point VI.6.9.4

Epidemiological Study

Cohort-study

4.2	**Number of cases for each disease / parameter under consideration**	136 patients enrolled
4.3	**SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)**	Not stated in the study
4.4	**Other Observations**	Not stated in the study

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

A retro perspective observational study evaluated adults (>18 years of age) who were prescribed dexmedetomidine as part of routine care in an intensive care unit. Data was obtained on these patients irrespective of the dosage or duration of therapy. Ten sites from 8 US states were recruited to participate in this study to serve as a convenience sample. Site selection included institutions having dexmedetomidine as medication with sufficient usage to generate data on 8-10 patients over a 4 to 6 moth period. Sites were nominally reimbursed for their participation and these are listed in Appendix 1 in the article.

Investigators at each site received approval from their respective institutional review board prior to data collection, which occurred from June 27, 2001 to May 31, 2002. Patient information was entered anonymously by the site investigator via the Internet to the study coordinator centre (The Ohio State University) on a secure server. The following data was collected: characteristics of the study site, patient demographics, admitting service and prescribing physician speciality, rationale for prescribing dexmedetomidine, detailed information on dosing and duration of therapy, and adverse drug reactions.

The adverse drug reactions are defined as an undesired or unintended effect of a drug. Investigators reviewed the medicinal records daily to assess the presence, severity, causality, and clinical outcome of adverse drug reactions and consulted with the prescriber, if necessary, for clarification. Adverse drug reactions were classified as highly probable, probable, possible and doubtful by clinical determination on causality on the basis of the patient's disease states and concurrent drugs administered. Severity of the adverse drug reactions was scored on a 6-point scale, modified from Hartwig et al (see reference 1.2). The categories of this scale were no change in clinical outcome; increased monitoring required; additional laboratory tests, change in vital signs, or discontinue drug; invasive procedure or increased hospital stay required; and contributed to fatal outcome. There were no predetermined definitions of hypotension and bradycardia. It was reported whether the institution submitted a Medwatch report to the Food and Drug Administration (FDA) during the administration of dexmedetomidine. The findings were compared with those listed in product labeling and findings of relevant clinical studies. Data was analysed using Excel, and descriptive statistics were reported, including mean ±SD.

5.2 Results and discussion

Summarize relevant results

70% of the US hospitals engaged had a multidisciplinary intensive care unit team, and 80% had dexmedetomidine-specific prescribing guidelines. A total of 136 patients received dexmedetomidine during the study time. Most sites indicated that data was obtained in all consecutive patients who were prescribed dexmedetomidine. Thoracic surgery was the most common admitting service (46% of institutions).

Dexmedetomidine was initiated most frequently in the surgical intensive care units (38%), followed by operating room (25%) medical/surgical /intensive care units and cardiothoracic intensive care units (10%).

The top three reasons for prescribing dexmedetomidine were to assist in weaning (53%), reduce the use of other narcotics or sedative drugs (42.6%) and to maintain the patient`s alertness(25%).

Only 33% of the patients received a loading dose. The most common reasons for not prescribing loading doses were the institution`s study protocol did not include a loading dose (11%) and loading doses have never been used at that institution (10.3 %).

The initial dose averaged 0.32±0.13 µg/kg/h, the minimum dosage (lowest dosage for at least one hour) averaged 0.26 µg/kg/h, and the maximum dosage (highest dosage for at least one hour) averaged 0.53 µg/kg/h. Thirty-seven (27.2%) patients received a dexmedetomidine dose >0.7 µg/kg/h, with the highest being 1.4 µg/kg/h. Eighty-two percent of patients were mechanistically ventilated when dexmedetomidine was started, whereas 20 (14.7%) patients were never mechanically ventilated during dexmedetomidine administration. The drug was continued after exturbation on 81 (59.5%) patients for 11.3±13.5 hours (range0.1-55).

The duration of therapy averaged 25.4±21.4 hours (range 1-123.5). Dexmedetomedine was abruptly stopped in 96 (70.5%) patients and weaned in the remaining subjects over 4.5±4.3 hours. There were no reports of rebound symptoms in any patient. In 6 patients, investigators reported treatment failure at a dosage of 0.7 µg/kg/h.

Fourty-six (33.8%) patients received dexmedetomidine >24 hours. Duration of therapy in these patients averaged 54 hours (range 24.5-123). Ten patients in this grouprecevied a maximum dose >0.7 µg/kg/h. Dexmedetomidine was abruptly stopped in 24 (52.2%) of these patients and was titrated to discontinuation in the remaining patients over 5.4±5.2 hours.

Adverse drug reactions were reported in 41 (31.1%) patients; 4 patients experienced 2 adverse drug reactions for a total of 45 occurrences. The overall causality of adverse drug reactions to dexmedetomidine were as follows: 15 highly probable, 17 probable, 11 possible, and 2 doubtful. The severity of adverse drug reactions was hypotension in 31 (22.7%) patients. Treatment of hypotension consisted of reducing the dose in 32.1% of the patients, discontinuing the drug in 21.4%, and administering either vasopressors or fluids in 7.1%. One patient (0.7%) experienced hypertension during the loading infusion. Bradycardia was reported in 6 (4.4%) patients. Other adverse drug reactions included atrial fibrillation (3 patients), unresponsiveness/oversedation (2 patients), hypoxia/shunt (1 patient) and Cheyne-Strokes respirations (1 patient).

5.3	**Conclusion**	Dexmedetomidine usage in the naturalistic settings concluded to mimic product labelling guidelines except for the low use of a loading infusion, higher doses given to some patients, and duration of therapy extending beyond 24 hours. In this setting, dexmedetomidine maintains its expected safety profile even when administered beyond 24 hours. Future prospective studies are needed to fully evaluate the long-term safety of dexmedetomidine.
5.3.1	Reliability	2
5.3.2	Validity	Less than 10% of all adverse drug reactions are reported via the US FDA Medwatch system, suggesting that inadequate reporting by clinicians may delay the detection of adverse drug reactions of newly marketed drugs. Furthermore, there is considerable delay when reports start appearing. This study was conducted within the first five years of dexmedetomidine approval and hence provides timely insights into the relevant usage and safety of this drug. The duration of therapy is limited to 24 hours; however, approximately one-third of the patients received dexmedetomidine beyond one day. In fact, the average duration of treatment in these patients was 54 hours. Concern of long term dexmedetomidine therapy includes the development in these patients.
5.3.3	Deficiencies	Yes The overall adverse drug reaction rate was 30%, and no US FDA Medwatch reports were generated. It is difficult to compare the adverse drug reaction rate with that of any other studies, since a total of adverse drug reactions rate is typically not reported. However, one randomized trial of bispectral index-guided dexmedetomidine versus placebo revealed that 47% of patients experienced at least one drug-related adverse reaction. That study also reported that 40% of patients randomized to receive placebo experienced an adverse drug reaction.
5.4	**Other**	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4th November 2010
Materials and Methods	As stated by the applicant
Results and discussion	As stated by the applicant
Conclusion	As stated by the applicant
Reliability	2
Acceptability	acceptable
Remarks	None.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_12_4_1(01)-1. Results of epidemiological study: Concentration dependency (modify if necessary

Not applicable since data was obtained on these patients irrespective of the dosage or duration of therapy.

Exposure	Disease A			Disease B			Disease C		
	observed cases	SMR	CI	observed cases	SMR	CI	observed cases	SMR	CI
low									
medium concentration									
high									
total									
duration: < x years									
duration: ≥ x years									
x .. years since first exposure									
y .. years since first exposure									
z .. years since first exposure									

Doc III A Section 6.12.4.2(01)

Annex Point VI.6.9.4

Epidemiological Study

Case report study

			Official use only
		1 REFERENCE	
1.1	Reference	Michael AE et al, 2004, Dexmedetomidine as a Total Intravenous Anestetic Agent, Anaesthesiology volume101 pages 787-90 (published)	X
1.2	Data protection	No	
1.2.1	Data owner	Public domain	
1.2.2	Companies with letter of access	None	
1.2.3	Criteria for data protection	Data on new [a.s.] for [first approval / authorisation] No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2 Dexmedetomidineis a highly selective alpha2 adrenoreceptor agonist that has sedative and analgesic properties with associated reduction on opioid and anaesthetic requirements..	
3.1.1	Lot/Batch number	Not available.	
3.1.2	Specification	Not available.	
3.1.2.1	**Description**	Brand name: Precedex Active ingredient: dexmedetomidinehydrochloride Strengths: 100mcg/ml Dosage form: intravenous injection Availability; prescription only, intensive care unit use only	
3.1.2.2	**Purity**	Sterile, non-pyrogenic solution suitable for intravenous infusion following dilution	
3.1.2.3	**Stability**	No data available	
3.2	**Type of study**	Case control study	
3.3	**Method of data collection**	This report describes three patients who were presented for surgery with potential airway management challenges. Dexmedetomidine was administered to these patients in increasing doses until general anaesthesia was attained. The effects of these high doses of dexmedetomidine on respiratory function and hemodynamics are described. The rate of dexmedetomdine infusion was administered based on patient body weights.	
3.4	**Test Persons / Study Population**	Non-entry field	
3.4.1	Selection criteria	This report describes three patients who presented for surgery with potential airway management challenges. Dexmedetomidine was administered to these patients in increasing doses of dexmedetomidine until general anaesthesia was attained.	

Doc III A Section 6.12.4.2(01)

Annex Point VI.6.9.4

Epidemiological Study

Case report study

3.4.2	Number of test persons per group/cohort size	3 patients in total
3.4.3	Sex	One woman and two men
3.4.4	Age	The woman was 66 years old, one man 65 years old and the other man was 50 years old.
3.4.5	Diseases	Mainly airway management challenges in combination with other diseases as described in each case: Case 1: 66 years old and 85 kg woman presented with inspiratory stridor and was found to have a severe subglottic stenosis of her trachea. Case 2: a 65 years old and 50 kg man with acute exacerbation of chronic failure secondary to emphysema. Case 3: one 50 years old, 80 kg man presented for an evaluation of an upper airway obstruction. He had an upper trachea in the form of a silastic Montgomery tracheal stent which had been replaced every year and which caused pain.
3.4.6	Smoking status	Not stated whether the subjects were smokers or non-smokers
3.5	**Controls**	No
3.5.1	Type of control	No controls were used.
3.5.2	Number of test persons per group/cohort size	No controls
3.5.3	Sex	Not applicable
3.5.4	Age	Not applicable
3.5.5	Diseases	Not applicable
3.5.6	Smoking status	Not applicable
3.6	**Administration/ Exposure**	
3.6.1	Exposure Route	Infusion
3.6.2	Exposure Situation	Intensive care unit at hospitals in the US
3.6.3	Exposure concentration(s)	Case 1: A loading dose of dexmedetomidine of 1 µg/kg was infused for 10 minutes and then an infusion of 0.7 µg/kg-1*h-1was delivered but rapidly increased over 10 minutes to 10 µg/kg-1*h-1 to attain acceptable level of anaesthesia. After 20 minutes the infusion was reduced to 5 µg/kg-1*h-1. Case 2: sedation with dexmedetomidine was attempted with a loading dose of 1 µg/kg followed by an infusion of 07 µg/kg-1*h-1. This did not provide adequate anaesthesia so the infusion was increased to 5 µg/kg-1*h-1. Case 3: dexmedetomidine was administered with a loading dose of 1 µg/kg, followed by infusion of 0.7 µg/kg-1*h-1. The infusion was increased over 5 minutes to 5 µg/kg-1*h-1 and maintained at this rate for a further 5 minutes before the patient would tolerate the surgery.

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Annex Point VI.6.9.4

Epidemiological Study

Case report study

3.6.4	Method(s) to determine exposure	The concentration of the infusion dose was calculated prior to infusion based on the body weight of each patient.
3.6.5	Postexposure period	Not available.
3.7	**Examinations**	
3.7.1	Type of disease	Mainly airway management challenges in combination with other diseases as described in each case: Case 1: 66 years old and 85 kg woman presented with inspiratory stridor and was found to have a severe subglottic stenosis of her trachea. Case 2: a 65 years old and 50 kg man with acute exacerbation of chronic failure secondary to emphysema. Case 3: a 50 years old, 80 kg man presented for an evaluation of an upper airway obstruction. He had an upper trachea in the form of a silastic Montgomery tracheal stent which had been replaced every year and which caused pain.
3.7.2	Parameters	Potential airway management challenges
3.8	**Further remarks**	None
		4 RESULTS AND DISCUSSION
4.1	**Exposure**	
4.1.1.1	**Number of measurements**	3 persons, one operation per person
4.1.1.2	**Average concentrations**	arithmetic, geometric mean or median and/or 95-Percentile Case 1: A loading dose of dexmedetomidine of 1 µg/kg was infused for 10 minutes and then an infusion of 0.7 µg/kg-1*h-1was delivered but rapidly increased over 10 minutes to 10 µg/kg-1*h-1 to attain acceptable level of anaesthesia. After 20 minutes the infusion was reduced to 5 µg/kg-1*h-1. Case 2: sedation with dexmedetomidine was attempted with a loading dose of 1 µg/kg followed by an infusion of 07 µg/kg-1*h-1. This did not provide adequate anaesthesia so the infusion was increased to 5 µg/kg-1*h-1. Case 3: dexmedetomidine was administered with a loading dose of 1µg/kg, followed by infusion of 0.7 µg/kg-1*h-1. The infusion was increased over 5 minutes to 5 µg/kg-1*h-1 and maintained at this rate for a further 5 minutes before the patient would tolerate the surgery
4.1.1.3	**Standard deviation**	Not stated, as the case study only includes 3 persons.
4.1.1.4	**Date(s) of measurement(s)**	Dates of measurement not specified, but possibly during 2004.
4.1.2	Other	

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Annex Point VI.6.9.4

Epidemiological Study

Case report study

4.2	**Number of cases for each disease / parameter under consideration**	3 cases in total
4.3	**SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)**	Not applicable
4.4	**Other Observations**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	This report describes three patients who presented for surgery with potential airway management challenges. Dexmedetomidine was administered to these patients in increasing doses until general anaesthesia was attained. The effects of these high doses of dexmedetomidine on respiratory function and hemodynamics are described. The rate of dexmedetomidine infusion was administered based on actual patient body weights.
5.2	**Results and discussion**	Previous studies on assessing dexmedetomidine as a general anaesthetic found that supplementary agents were necessary, but the doses of dexmedetomidine had not reached the high levels of administration. In the first case reported here, the dexmedetomidine was supplemented with topical anaesthesia before surgical intervention. In the second patient, postoperative analgesia was supplemented with infiltration of local anaesthesia, and no respiratory depression demonstrated at lower doses appeared to be sustained at anaesthetic doses.
5.3	**Conclusion**	High doses of dexmedetomidine could safely be used in severely ill patients.
5.3.1	Reliability	3
5.3.2	Validity	The preservation of respiratory drive offers the opportunity that this anaesthetic technique may present another method for providing anaesthesia for the patient with difficult airway. This needs to be studied further, as the data available on dexmedetomidine mainly realties to its use as an anaesthetic and opioid-sparing agent at much lower doses and when used in combination with other anaesthetic, sedative, and analgesic agents. At these doses there were no airway concerns other than one patient requiring a chin-lift and no opioids were needed even in the patient who was a chronic opioid user. Smoking was not mentioned in the study.
5.3.3	Deficiencies	None
5.4	**Other**	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4th Novemeber 2010
Reference	The correct name for the author of the study is Ramsay and NOT Michael.
Materials and Methods	As stated by the applicant
Results and discussion	As stated by the applicant
Conclusion	As stated by the applicant
Reliability	3
Acceptability	acceptable
Remarks	None.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_12_4_2(01)-1. Results of epidemiological study: Concentration dependency (modify if necessary)

Not applicable as high doses of dexmedetomidine could safely be used in severely ill patients.

Exposure	Disease A			Disease B			Disease C		
	observed cases	SMR	CI	observed cases	SMR	CI	observed cases	SMR	CI
low									
medium concentration									
high									
total									
duration: < x years									
duration: ≥ x years									
x .. years since first exposure									
y .. years since first exposure									
z .. years since first exposure									

Doc III A Section 6.12.4.3

Annex Point IIA VI.6.9.4

Epidemiological Study

Dexmedetomidine: an updated review

Official use only

1 REFERENCE

1.1	**Reference**	Gerlach A, 2007 Dexmedetomidine: an updated review. The Ohio State University, Ohio USA, Ann Pharmacother; **41** pages 245-254 (published)
1.2	**Data protection**	No, public domain
1.2.1	Data owner	The Ohio State University, Ohio USA,
1.2.2	Companies with letter of access	No, public domain
1.2.3	Criteria for data protection	Data on new [a.s.] for [first approval / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	Dexmedetomidine
3.1.1	Lot/Batch number	Not available
3.1.2	Specification	Not available
3.1.2.1	**Description**	White to nearly white crystalline powder
3.1.2.2	**Purity**	Not available
3.1.2.3	**Stability**	Not available
3.2	**Type of study**	Review
3.3	**Method of data collection**	Review of recent literature on the safety and efficacy of dexmedetomidine
3.4	**Test Persons / Study Population**	
3.4.1	Selection criteria	The study selection and data extraction was based on experimental and observational studies that focused on the safety and efficacy of dexmedetomidine in humans.
3.4.2	Number of test persons per group/cohort size	Cannot be specified
3.4.3	Sex	Both
3.4.4	Age	Cannot be specified
3.4.5	Diseases	Mostly Intensive Care Unit (ICU) patients in need of surgery (patients in need of mechanically ventilated surgery since they are critically ill)
3.4.6	Smoking status	Both smokers and non-smokers
3.5	**Controls**	No
3.5.1	Type of control	Not applicable

Doc III A Section 6.12.4.3

Annex Point IIA VI.6.9.4

Epidemiological Study

Dexmedetomidine: an updated review

3.5.2	Number of test persons per group/cohort size	Not applicable
3.5.3	Sex	Not applicable
3.5.4	Age	Not applicable
3.5.5	Diseases	Not applicable
3.5.6	Smoking status	Not applicable
3.6	**Administration/ Exposure**	
3.6.1	Exposure Route	Intravenous infusion
3.6.2	Exposure Situation	Intensive care units at hospitals
3.6.3	Exposure concentration(s)	Information available: mainly loading dose 1 µg/kg for 10 minutes, followed by intravenous administration between 02. – 0.7 µg/kg
3.6.4	Method(s) to determine exposure	Blood sample or observation of sedation
3.6.5	Postexposure period	Hospitalisation
3.7	**Examinations**	
3.7.1	Type of disease	Critically ill persons in need of mechanically ventilated surgery with short term sedation
3.7.2	Parameters	Short term sedation
3.8	**Further remarks**	None
		4 RESULTS AND DISCUSSION
4.1	**Exposure**	Mainly loading dose 1 µg/kg for 10 minutes, followed by intravenous administration between 02. – 0.7 µg/kg for a maximum of 24 hours
4.1.1.1	**Number of measurements**	No information
4.1.1.2	**Average concentrations**	No information
4.1.1.3	**Standard deviation**	No information
4.1.1.4	**Date(s) of measurement(s)**	No information
4.1.2	Other	None

Doc III A Section 6.12.4.3

Annex Point IIA VI.6.9.4

Epidemiological Study

Dexmedetomidine: an updated review

4.2	**Number of cases for each disease / parameter under consideration**	No information
4.3	**SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)**	No information
4.4	**Other Observations**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Articles were identified though searches of MEDLINE (1966-Jan 2007). Key words included dexmedetomidine, medetomidine, alpha2 agonist, and sedation. References from selected articles were reviewed for additional references. Experimental and observational studies that focused on safety and efficacy of dexmedetomidine in humans were selected.
5.2	**Results and discussion**	Dexmedetomidine is a selective central alpha2 sedative that does not depress respiratory drive, usually decreases opioid requirements and permits patient cooperation. For short term sedation, dexmedetomidine produces results similar to those with propofol in surgical ICU patients. Unfortunately, few well-designed trials have evaluated use of dexmedetomidine in populations other than surgical ICU patients. More data is needed to define the role of dexmedetomidine in populations other than surgical ICU patients. It may be a promising agent in this setting, especially if it is shown to decrease the incidence of delirium compared with benzodiazepines. Although dexmedetomidine is approved only for use less than 24 hours in the US, it has been safely administered for longer periods of time without apparently causing rebound hypertension or tachycardia. Adjunct use of dexmedetomdine during anaesthesia to optimize hemodynamics and decrease opioid use is promising, but more data is needed. Hypertension and bradycardia are common adverse events of dexmedetomidine that may be minimized with judicious dose adjustments and proper selection of patients who are not dependent on adrenergic response to maintain vascular tone.
5.3	**Conclusion**	Dexmedetomidine is a safe and effective agent for sedation in critically ill patients.
5.3.1	Reliability	3
5.3.2	Validity	Further, well designed studies are needed to define its role as a sedative for critically ill medical, neurosurgical and paediatric patients, as an adjunct to anaesthesia and as a sedative during procedures
5.3.3	Deficiencies	No
5.4	**Other**	None

Doc III A Section 6.12.4.3

Annex Point IIA VI.6.9.4

Epidemiological Study

Dexmedetomidine: an updated review

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4th November 2010
Materials and Methods	As stated by the applicant
Results and discussion	As stated by the applicant
Conclusion	As stated by the applicant
Reliability	3
Acceptability	Acceptable
Remarks	None.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Doc III A Section 6.12.4.3

Annex Point IIA VI.6.9.4

Epidemiological Study

Dexmedetomidine: an updated review

Table A6_12_4_3(01)-1. Results of epidemiological study: Concentration dependency (modify if necessary)

Not applicable since it was concluded that dexmedetomidine is a safe and effective agent for sedation in critically ill patients.

Exposure		Disease A			Disease B			Disease C		
		observed cases	SMR	CI	observed cases	SMR	CI	observed cases	SMR	CI
low	concentration									
medium										
high										
total										
duration:	< x years									
	≥ x years									
x	.. years since first exposure									
y										
z										

III A Section 6.12.5 Annex Point VI.6.9.5	**Diagnosis of poisoning**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	For diagnosis and case report on poisoning please view section A6.12.2.1 Human case report - overdose in the perioperative setting for further information.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Justification acceptable	
Conclusion	Justification aceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

III A Section 6.12.6 **Annex Point VI.6.9.6**	**Sensitation/allergenicity observation, if available.**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	No observations regarding sensitation or allergenicity have been reported. No signs of irritation or sensitation from over 20 years of use in veterinary and human medicine.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Justification acceptable	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12.7(01) **Human Case Report**

Annex Point VI.6.9.7 **Specific treatment in case of an accident or poisoning: antidote**

Official use only

1 REFERENCE

1.1	**Reference**	Sheinin, H., Antaa, R., Antilla, M., Hakola, P., Helminen, A., and Karhuvaara, S. (1998) Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific alpha2-adrenoceptor antagonist Atipamezole: A pharmacodynamic and kinetic study in healthy volunteers. Anesthesiology, **89** (3) pp 574-584.
1.2	**Reference**	Pertovaara, A., Haapalinna, A., Sirviö, J., and Virtanen, R. (2005). Pharmacological properties, central nervous system effects, and potential therapeutic application of Atipamezole, a selective alpha2-adrenoceptor antagonist. CNS Drug Reviews, Vol 11(3), pages 273-288.

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Atipamezole
3.2	**Persons exposed**	
3.2.1	Sex	Males
3.2.2	Age/weight	20-28 years/65-88 kg
3.2.3	Known Diseases	Healthy
3.2.4	Number of persons	14
3.2.5	Other information	
3.3	**Exposure**	Intramusculary injection.
3.3.1	Reason of exposure	Phase 1 safety study
3.3.2	Frequency of exposure	One single dose
3.3.3	Overall time period of exposure	A single injection
3.3.4	Duration of single exposure	Not applicable.
3.3.5	Exposure concentration/dose	15, 50 and 150 microgram/kg.
3.3.6	Other information	Double-blinded, cross-over study with one week interval.
3.4	**Examinations**	Clinical and laboratory samples 12 times during a 420 min period.
3.5	**Treatment**	
3.6	**Remarks**	The study investigated the reversibility of 2.5 µg/kg dexmedetomidine given intramusculary.

Section A6.12.7(01) **Human Case Report**

Annex Point VI.6.9.7 **Specific treatment in case of an accident or poisoning: antidote**

4 RESULTS

4.1	**Clinical Signs**	The highest dose, 150 microgram/kg caused a transient sympathoactivation. Subjective effect was shivering and motor restlessness.
4.2	**Results of examinations**	The clinical assessment methods were: Visual analogue scale for vigilance and anxiety, psychomotor performance using digit symbol substitution test, saliva secretion, electric activity of the heart (lead V), systolic and and diastolic blood pressure as well as heart rate. Adverse events were rigorously sought and recorded. Plasma levels of dexmedetomidine and atipamezole were measured. Also plasma levels of noradrenaline, adrenaline and their metabolite 3,4-dihydroxyphenylglycol was measured. All tables and results are presented in reference 1.
4.3	**Effectivity of medical treatment**	Effectively counteracted the effects of dexmedetomidine in a ratio of 60:1
4.4	**Outcome**	Not applicable. Phase 1 investigation.
4.5	**Other**	Bradycardia was noted as well as a short sinus arrest for about10 s.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The investigation had two purposes, one dose finding study (part 1) and a safety study (part 2) that was a placebo-controlled, double-blinded randomized cross-over study. A vast number of clinical signs were combined with pharmacokinetic analysis. The study started with a single injection of 2.5 microgram/kg dexmedetomidine. After 1 hour, the antidote, Atipamezole was injected. In part 1, the dose was 12.5 microgram/kg Atipamezole and in part 2, the doses were either 15, 50 or 150 microgram/kg.
5.2	**Results and discussion**	Atipamezole reversed the effect of dexmedetomidine with a ratio of 60:1. Transient sympathoactivation was seen after the highest dose. It may be avoided by using slower infusion rate.
5.3	**Conclusion**	Atipamezole is a possible antidote for medetomidine in humans. It has been used extensively in veterinary medicine but could also be applicable in humans.

Section A6.12.7(01) **Human Case Report**

Annex Point VI.6.9.7 **Specific treatment in case of an accident or poisoning: antidote**

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4th November 2010
Materials and Methods	As stated by the applicant
Results and discussion	As stated by the applicant
Conclusion	As stated by the applicant
Remarks	None.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

III A Section 6.12.8 Annex Point VI.6.9.8	**Prognosis following poisoning**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	For diagnosis and case report on poisoning please view section A6.12.2.1 Human case report - overdose in the perioperative setting for further information.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Justification acceptable	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

III A Section 6.13 **Annex Point IIIA VI.2**	**Toxic effect on livestock and pets**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	The active substance has been used for a long period of time in mammals like cats and dogs as well as for a long time in humans as sedative. Please see SPC EMEA Dexmedetomidine indicated as sedative for dogs and cats under section advesre events toxic effects are presented.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November	
Evaluation of applicant's justification	Agree with applicant	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

III A Section 6_14 Annex Point III-XI.2	**Other test(s) related to the exposure of human.**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [x]**	
Detailed justification:	There are numerous of studies related to the exposure of humans. A litterture search and the findings thereof is attached. The literature list can be found in section IV 6.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Agree with applicant	
Conclusion	Applicants justification is acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	

III A Section 6_14 Annex Point III-XI.2	Other test(s) related to the exposure of human.
Remarks	

III A Section 6.15 Annex Point IIIA VI.4	**Food and feedingstuff**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [X]**	**Technically not feasible [ ] Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	Medetomidine will not be distribured in terrestrial compartments. Medetomidine will be used in the marine environment. There are no risk for contamination of food and feedingstuff.	
Undertaking of intended data submission [ ]	No	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Applicant justification is not acceptable.	
Conclusion	There is the potential for residues of medetomidine used as antifoulant to occur in food and feed of marine origin. A preliminary dietary risk assessment will be performed by taking into account the predicted environmental concentration (PEC) of medetomidine in fish and seafood and by estimating how much fish/seafood needs to be consumed by the general public to achieve the relevant dietary reference value. Therefore, an ADI and ARfD have been derived. At product authorisation, a more refined risk assessment might be required. Also, if necessary, the establishment of maximum residue levels (MRLs) should be considered.	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		