ANNEX I

COUNTRY, PRODUCT INVENTED NAME, ACTIVE SUBSTANCE MARKETING AUTHORISATION NUMBER, MARKETING AUTHORISATION HOLDER CONCERNED BY THE PROCEDURE

Country	Product invented name	Active substance	Marketing Authorisation number	Marketing Authorisation Holder
AT	Rompun	Xylazine	14840	Bayer Austria GmbH
AT	Chanazine 2%	Xylazine	8-00448	Chanelle Pharmaceuticals Manufacturing Ltd., Dublin Road, Loughrea Co. Galway, IRELAND
AT	Domosedan	Detomidine	8-00128	Pfizer Animal Health BV, Postbus 37, 2900 AA Capell a/d Ijssel, THE NETHERLANDS
AT	Domitor	Medetomidine	8-00144	Pfizer Animal Health BV Postbus 37, 2900 AA Capell a/d Ijssel, THE NETHERLANDS
BE	Rompun 2%	Xylazine hydrochloride	0187IS0155F012	BAYER N.V., Louizalaan 143, 1050 Brussel, BELGIUM
BE	Rompun Droge Stof	Xylazine hydrochloride	0187IS0120F012	BAYER N.V., Louizalaan 143, 1050 Brussel, BELGIUM
BE	Domosedan 10mg/ml	Detomidine hydrochloride	0419IS0001F012	PFIZER ANIMAL HEALTH S.A. Rue Laid Burniat 1, 1348 Louvain La Neuve, BELGIUM
BE	Domitor 1mg/ml	Medetomidine hydrochloride	0419IS0003F012	PFIZER ANIMAL HEALTH S.A., Rue Laid Burniat 1, 1348 Louvain La Neuve, BELGIUM
BE	Sedivet 10mg/ml	Romifidine hydrochloride	0205IS0127F012	SCS BOEHRINGER INGELHEIM COMM.V, Vesalius Science Park, Avenue, Ariane, 16, 1200 Bruxelles, BELGIUM
CY	Sedivet 1% Solution for injection 10mg/ml	Romifidine	CY004V-E	Boehringer Ingelheim Vetmedica GmbH
CZ	Domitor	Medetomidine hydrochloride	96/731/96-C	Pfizer Animal Health S.A., Rue Laid Burniat 1, 1348 Louvain-la-Neuve, BELGIUM
CZ	Xylazine 2% Alfasan	Xylazine hydrochloride	96/025/00-C	ALFASAN INTERNATIONAL B.V., P.O. BOX 78, 3440 AB Woerden, THE NETHERLANDS
CZ	Sedivet 1%	Romifidine hydrochloride	96/039/01-C	BOEHRINGER INGELHEIM VETMEDICA GMBH, Binger Strasse 173, 55216 Ingelheim am Rhein, GERMANY
CZ	Domosedan inj.	Detomidine hydrochloride	96/730/96-C	Pfizer Animal Health S.A., Rue Laid Burniat 1, 1348 Louvain-la-Neuve, BELGIUM
DE	Sedivet	Romifidine hydrochloride	23715.00.00	BOEHRINGER INGELHEIM VETMEDICA GMBH, Binger Str. 173, 55218 Ingelheim, GERMANY
DE	Rompun TS	Xylazine hydrochloride	6293723.00.00	Bayer Vital Gmbh, 51368 Leverkusen, GERMANY
DE	Rompun 2%	Xylazine hydrochloride	6293841.00.00	Bayer Vital GmbH, 51368 Leverkusen, GERMANY
DE	Domosedan	Detomidine hydrochloride	15912.00.00	Pfizer GmbH, Pfizerstr. 1, 76139 Karlsruhe, GERMANY

Country	Product invented name	Active substance	Marketing Authorisation number	Marketing Authorisation Holder
DE	Domitor	Medetomidine hydrochloride	32457.00.00	Pfizer GmbH, Pfizerstr. 1, 76139 Karlsruhe, GERMANY
DE	Xylazin 2%	Xylazine hydrochloride	6324464.00.00	CEVA TIERGESUNDHEIT GmbH, Kanzlerstr. 4, 40472 Düsseldorf, GERMANY
DK	Sedivet Vet.	Romifidine	14896	Boehringer Ingelheim Vetmedica GmbH, Binger Str. 173, 55218 Ingelheim, GERMANY
DK	Rompun Vet.	Xylazine	05669	Bayer A/S, Bayer HealthCare
ES	Rompun	Xylazine	7532 A	Química Farmacéutica Bayer
ES	Sedivet	Romifidine	1107 ESP	Boehringer Ingelheim España S.A., Prat de la Riva s/n., 08190 Sant Cugat del Valles. Barcelona, SPAIN
ES	Domosedan	Detomidine hydrochloride	9059 I	Pfizer S.A. Avda. Europa, 20 B. Parque Empresarial La Moraleja, 28108 Alcobendas (Madrid), SPAIN
ES	Domitor	Medetomidine hydrochloride	933 ESP	Pfizer S.A. Avda. Europa, 20 B. Parque Empresarial La Moraleja, 28108 Alcobendas (Madrid), SPAIN
FI	Rompun vet	Xylazine hydrochloride	6047	Bayer HealthCare AG, Animal Health Division, 51368, Leverkusen, GERMANY
FI	Domosedan	Detomidine hydrochloride	8546	Orion oyj, P.O. Box 65, 02201 Espoo, FINLAND
FI	Domitor vet	Medetomidine hydrochloride	9501	Orion oyj, P.O. Box 65, 02201 Espoo, FINLAND
FR	Rompun 2%	Xylazine chlorhydrate	255	BAYER SANTE
FR	Rompun Lyophilise	Xylazine chlorhydrate	8061	BAYER SANTE
FR	Domosedan	Detomidine chlorhydrate	10076	PFIZER
FR	Sedivet	Romifidine Chlorhydrate	11004	BOEHRINGER INGELHEIM FRANCE
FR	Domitor	Medetomidine Chlorhydrate	10718	PFIZER
GR	Domitor	Medetomidine	46335/ 06-12-00	PFIZER HELLAS
GR	Rompun 2%	Xylazine	19605/23-06-93	ALAPIS
GR	Chanazine	Xylazine	11188/30-03-99	FARMAZAC SYNVET
GR	Sedivet	Romifidine	44613/22-11-00	BOEHRINGER INGELHEIM VETMEDICA GMBH., GERMANY
HU	Rompun	Xylazine	411/1991.	Bayer Hungária Ltd., 1123 Budapest, Alkotás u. 50, HUNGARY
HU	Domosedan	Detomodine hydrochloride	2079/2006.	Pfizer Co. Ltd., 1123 Budapest, Alkotás u. 53, HUNGARY

Country	Product invented name	Active substance	Marketing Authorisation number	Marketing Authorisation Holder
HU	Domitor	Medetomidine hydrochloride	891/1999.	Pfizer Co. Ltd., 1123 Budapest, Alkotás u. 53, HUNGARY
HU	Primazin 2 % injection	Xylazine	743/1997.	Alfasan International B.V., 3449 JA Woerden, THE NETHERLANDS
IE	Sedivet	Romifidine	10007/023/001	Boehringer Ingelheim Ltd, Ellesfield Avenue Bracknell, Berkshire RG12 8YS, UNITED KINGDOM
IE	Chanazine 2% Solution for Injection	Xylazine	10987/030/001	Chanelle Pharmaceuticals Manufacturing Ltd., Loughrea, Co. Galway, IRELAND
IE	Chanazine 10% Solution for Injection	Xylazine	10987/031/001	Chanelle Pharmaceuticals Manufacturing Ltd., Loughrea, Co. Galway, IRELAND
IE	Domosedan Injection	Detomidine hydrochloride	10019/025/001	Pfizer Animal Health, Ringaskiddy, Co. Cork, IRELAND
IE	Domitor Injection	Medetomodine hydrochloride	10019/026/001	Pfizer Animal Health, Ringaskiddy, Co. Cork, IRELAND
IS	Domosedan, vet.	Detomidine	890003	Orion Corporation, Orionintie 1, FUB-0220 Espoo, FINLAND
IS	Chanazine 2%, vet.	Xylazine	IS/2/01/003/02	Icepharma hf., Lynhálsi 13, 110 Reykjavík, ICELAND
IS	Chanazine 10%, vet.	Xylazine	IS/2/01/003/01	Icepharma hf., Lynhálsi 13, 110 Reykjavík, ICELAND
IS	Rompun, vet.	Xylazine	691254	Bayer HealthCare AG, Animal Health Division, 51368, Leverkusen, GERMANY
IT	Sedivet	Romifidine	102196	Boehringer Ingelheim, Località Prulli 103/c, 50066 Regello, FINLAND
IT	Rompum	Xylazine	100390032	Bayer, Viale Certosa 130, 20156 Milano, ITALY
IT	Rompum 2%	Xylazine	100390018	Bayer, Viale Certosa 130, 20156 Milano, ITALY
IT	Domosedan	Detomidine	100102	Orion
IT	Domitor	Medetomidine	100103	Orion Corporation animal health
LV	Xylazine 2%	Xylazine	NRP/VFP-00544-05	Alfasan International B.V., Kuipersweg 9, P.O. Box 78, NL-3440 AB Woerden, THE NETHERLANDS
LV	Domitor	Medetomidine	NRP/VFP-01453-07	Alfasan International B.V., Kuipersweg 9, P.O. Box 78, NL-3440 AB Woerden, THE NETHERLANDS
NL	Sedivet	Romifidine	7232	Boehringer Ingelheim, Postbus 8037, 1802 KA Alkmaar, THE NETHERLANDS

Country	Product invented name	Active substance	Marketing Authorisation number	Marketing Authorisation Holder
NL	Xylalin	Xylazine	3886	CEVA Santé BV, Tiendweg 8c ,2671 SB Naaldwijk, THE NETHERLANDS
NL	Rompun droog	Xylazine	5407	Bayer BV Animal Health, Postbus 80, 3640 AB Mijdrecht, THE NETHERLANDS
NL	Rompun	Xylazine	5409	Bayer BV Animal Health, Postbus 80, 3640 AB Mijdrecht, THE NETHERLANDS
NL	Xylazine 5'+mg	Xylazine	7695	Dopharma Research BV, Postbus 205, 4940 AE Raamsdonksveer, THE NETHERLANDS
NL	Aescoket Plus	Xylazine, Ketamine, Atropine	7986	Aesculaap BV, Mijlstraat 35, 5281 LJ Boxtel, THE NETHERLANDS
NL	Sedazine 20 Inj.	Xylazine	8066	A.S.T. Farma BV, Willeskop 206a, 4321 GW Oudewater, THE NETHERLANDS
NL	Rompun 2% Injectievloeistof	Xylazine	8210	Bayer BV Animal Health, Postbus 80, 3640 AB Mijdrecht, THE NETHERLANDS
NL	A.A. Xylazine P.I.	Xylazine	9759	CEVA Santé BV, Tiendweg 8c, 2671 SB Naaldwijk, THE NETHERLANDS
NL	Xylazine 20 Inj.	Xylazine	10080	Kepro BV, Maadgenburgstraat 38, 7421 ZE Deventer, THE NETHERLANDS
NL	Xylasan 2% Pro Inj.	Xylazine	10253	Alfasan Nederland BV, Postbus 78, 3440 AB Woerden, THE NETHERLANDS
NL	Chanazine 2%	Xylazine	7756	Chanelle Pharmaceuticals Manufacturing Ltd., Dublin Road, Loughrea Co. Galway, IRELAND
NL	Domosedan	Detomidine	2973	Pfizer Animal Health BV, Postbus 37, 2900 AA Capell a/d Ijssel, THE NETHERLANDS
NL	Domosedan	Detomidine	9713	Equi Products Holland BV, Hermelijnkoog 44, 1822 CB Alkmaar, THE NETHERLANDS
NL	Domosedan	Detomidine	10032	Equi Products Holland BV, Hermelijnkoog 44, 1822 CB Alkmaar, THE NETHERLANDS
NL	Domosedan	Detomidine	10131	Equi Products Holland BV, Hermelijnkoog 44, 1822 CB Alkmaar, THE NETHERLANDS
NL	Domosedan	Detomidine	10295	Novivet BV, Albert Cuyplaan 2B, 7482 JA Haaksbergen, THE NETHERLANDS
NL	Domosedan	Detomidine	10403	Wirtz Farma BV, Albert Cuyplaan 2B, 7482 JA Haaksbergen, THE NETHERLANDS
NL	Domitor	Medetomidine	7823	Pfizer Animal Health BV, Postbus 37, 2900 AA Capell a/d Ijssel, THE NETHERLANDS

Country	Product invented name	Active substance	Marketing Authorisation number	Marketing Authorisation Holder
NL	Domitor	Medetomidine	10354	Wirtz Farma BV, Albert Cuyplaan 2B, 7482 JA Haaksbergen, THE NETHERLANDS
NO	Sedivet vet	Romifidine	0000/7913	Boehringer Ingelheim Vetmedica GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, GERMANY
NO	Rompun vet	Xylazine	0000/05588	Bayer Healthcare AG, Animal Health Division, 51368 Leverkusen, GERMANY
PL	Sedivet 1%	Romifidine	P-1257/02	Boehringer Ingelheim Vetmedica GmbH, Binger Str. 173, 55218 Ingelheim, GERMANY
PL	Domosedan	Detomidine hydrochloride	P3-0505/98	Orion Corporation Orion Pharma, Tengstromink 8, Box 65, Turku, 0101, FINLAND
PL	Domitor	Medetomidine hydrochloride	P2-0118/95	Orion Corporation Orion Pharma, Tengstromink 8, Box 65, Turku, 0101, FINLAND
PT	Romidys 1 mg/ml Solução Injectável para cães e gatos	Romifidine	51498	Virbac S.A., 1ère avenue, 2065 m, L.I.D., 06516 Carros Cedex, FRANCE
PT	Domitor	Medetomidine	50855P	Laboratórios Pzifer, AS Laboratórios Pfizer, Lda Lagoas Park, Edifício 10, 2740-271 Porto Salvo, PORTUGAL
PT	Domosedan	Detomidine	50820P	Laboratórios Pzifer, AS Laboratórios Pfizer, Lda Lagoas Park, Edifício 10, 2740-271 Porto Salvo, PORTUGAL
PT	Chanazine 2%	Xylazine	51188	Agrovete, Organização Técnica Agro Pecuária, S.A R. Alto B Vista Pavilhão 40 Agualva-Cacém, 2735-340 Agualva, Cacém, Lisbon, PORTUGAL
PT	Rompun	Xylazine	4770	Bayer Portugal, S.A Rua da Quinta do Pinheiro 5, 2794-003 Carnaxide PORTUGAL
RO	Xylazine 2% xylazine	Xylazine	161895/3 of 06.12.2002 (expired)	ALFASAN INTERNATIONAL B.V. Kuipersweg 9, 3449 Ja Woerden, THE NETHERLANDS
RO	Domosedan	Detomidine	221972/2 of 23.01.2004 (valid until 23.01.2009)	PFIZER GLOBAL MANUFACTURING, Rue Laid Burniat 1, 1348 Louvain La Nueve, BELGIUM (Variation IA,1 – pending Pfizer Animal Health MA EEIG Ramsgate Road, Sandwich, Kent CT13 9NJ UNITED KINGDOM)
RO	Domitor	Medetomidine	221972/3 of 23.01.2004 (valid until 23.01.2009)	PFIZER GLOBAL MANUFACTURING, Rue Laid Burniat 1, 1348 Louvain La Nueve, BELGIUM (Variation IA,1 – pending Pfizer Animal Health MA EEIG Ramsgate Road, Sandwich, Kent CT13 9NJ UNITED KINGDOM)

Country	Product invented name	Active substance	Marketing Authorisation number	Marketing Authorisation Holder
SE	Sedivet vet.	Romifidine hydrochloride	11753	Boehringer Ingelheim Vetmedica GmbH, Binger Str. 173, 55218 Ingelheim, GERMANY
SE	Rompun vet.	Xylazine hydrochloride	8534	Bayer HealthCare AG
SE	Domosedan vet.	Detomidine hydrochloride	10243	Orion Corporation, Box 65, 02101 Esbo, FINLAND
SE	Domitor vet.	Medetomidine hydrochloride	10574	Orion Corporation, Box 65, 02101 Esbo, FINLAND
SK	Chanazine 2%	Xylazine	96/174/00-S	Chanelle Pharmaceuticals Manufacturing Ltd., Dublin Road, Loughrea Co. Galway, IRELAND
SL	Chanazine 2%	Xylazine	323-03-8/01-42	VET4VET, Gerbičeva 50, 1000 Ljubljana, SLOVENIA
SL	Domitor	Medetomidine	5363-783/2005	Pfizer Luxembourg SARL PFIZER, podružnica Ljubljana, Letališka 3 c, 1000 Ljubljana, SLOVENIA
SL	Domosedan	Detomodine	5363-959/2004	Pfizer Luxembourg SARL PFIZER, podružnica Ljubljana, Letališka 3 c, 1000 Ljubljana, SLOVENIA
UK	Sedivet 10 mg/ml Solution for Injection	Romifidine	00015/4033	Boehringer Ingelheim Ltd, Ellesfield, Avenue Bracknell, Berkshire RG12 8YS, UNITED KINGDOM
UK	Domosedan 10 mg/ml Injection	Detomidine hydrochloride	03649/4000	Orion Corporation Orion Pharma, Tengstromink 8, Box 65, Turku 20101, FINLAND
UK	Domosedan 10 mg/ml Injection	Detomidine hydrochloride	24939/4001	Globalmed Ltd, Ground Floor, 134 Church Hill, Loughton, Essex IG10 1LH, UNITED KINGDOM
UK	Domosedan 10 mg/ml Injection	Detomidine hydrochloride	20860/4005	Quvera Ltd, Unit 8, Brember Road, Harrow, Middlesex HA2 8AX, UNITED KINGDOM
UK	Domitor 1 mg/ml Solution for Injection	Medetomidine hydrochloride	03649/4001	Orion Corporation Orion Pharma, Tengstromink 8, Box 65, Turku 20101, FINLAND
UK	Domitor Injection (Strength 1 mg/ml)	Medetomidine hydrochloride	20860/4002	Quvera Ltd, Unit 8, Brember Road, Harrow, Middlesex HA2 8AX, UNITED KINGDOM
UK	Chanazine 10% Solution for Injection	Xylazine	11990/4006	Chanelle Animal Health Ltd, 7 Rodney Street, Liverpool L1 9HZ, UNITED KINGDOM
UK	Chanazine 2 % Solution for Injection	Xylazine	11990/4005	Chanelle Animal Health Ltd, 7 Rodney Street, Liverpool L1 9HZ, UNITED KINGDOM
UK	Rompun 2% w/v Solution for Injection	Xylazine	00010/4093	Bayer plc, Animal Health Division, Bayer House, Strawberry Hill Newbury, Berkshire RG14 1JA, UNITED KINGDOM

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

1. Introduction and background

The Products listed in Annex I are approved in various MS for use via the parental route, containing alpha2-adrenoreceptor agonists romifidine, xylazine, detomidine, medetomidine.

These products are used for sedation or analgesia in various species. Most of these products are presented as solutions for injection, and some are presented as powders to be dissolved in water for solution for injection.

The competent regulatory authority for medicinal products for veterinary use of the Netherlands *College Ter Beoordeling van Geneesmiddelen* (Medicines Evaluation Board) *Bureau Diergeneesmiddelen*, notified the EMEA on 21 August 2006 in accordance with Article 78(1) of Directive 2001/82/EC, as amended by Directive 2004/28/EC, of its intention to vary 21 marketing authorisations These authorisations are for veterinary medicinal products containing an alpha2-adrenoreceptor agonist (romifidine, xylazine, detomidine or medetomidine) as the active substance and approved for use via a parenteral (injectable) route. The objective of the variations was to add a set of new precautionary measures concerning user safety, and information on human adverse reactions, to the product literature.

The pharmacovigilance data evaluated by the Dutch competent regulatory authority that resulted in its intention to vary the authorisations is a published suspected adverse reaction (SAR) in a human being, reporting cardiovascular and central nervous system effects over a period of 3 days after accidental self-injection of Sedivet (Reference: Hoyer, Mark J. *Alpha2-agonisten, alledaagse verdovingsmiddelen in de diergeneeskunde praktijk, maar verre van ongevaarlijk – de gevolgen van een accidentele zelfinjectie*. Tijdsch.for Diergeneeskunde deel 131 Maart aflevering 6 2006. EudraVigilance Veterinary Case Ref No NLBBD 1368).

On the basis of the notification sent by the Dutch competent regulatory authority, the matters considered by the Committee for Medicinal Products for Veterinary Use (CVMP) were the following proposed precautionary measures:

Precautionary measures:

1. In the case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.
2. Avoid skin contact and wear impermeable gloves when handling the product
3. Wash the exposed skin immediately after exposure with large amounts of water.
4. In the case of accidental projection of the product into the eyes, rinse abundantly with fresh water. If irritation persists, seek the advice of a physician.
5. Remove contaminated clothes.
6. Pregnant women should not handle the product.
7. ADVICE TO DOCTORS: <The substance> is an alpha2-adrenoreceptor agonist whose toxicity may cause clinical effects including sedation, respiratory depression and coma, bradycardia and hypotension and hyperglycaemia. Ventricular arrhythmias have also been reported. Treatment should be supportive with appropriate intensive therapy.

In addition, the following information concerning human adverse reactions was considered by the CVMP:

- Irritation, sensitisation, contact dermatitis and systemic effects cannot be excluded after skin contact.

The CVMP during its meeting of 12-14 September 2006 initiated a procedure for evaluating the matter under Article 78(3) of Directive 2001/82/EC for these products. The CVMP agreed on 14 September 2006 to communicate the proposed precautionary measures and information on human adverse reactions to the concerned Marketing Authorisation Holders (MAHs). The MAHs were invited to comment and justify any counterproposals by 16 October 2006.

The pharmacovigilance data evaluated included the published suspected adverse reaction (SAR) in a human being, reporting cardiovascular and central nervous system effects (Hoyer, M.J., 2006). In addition, any proprietary data submitted by MAHs was evaluated in support of the products investigated in those studies. Furthermore, the results of the outcome of a European survey for alpha2-adrenoreceptor agonists were considered.

The CVMP also considered other publicly available data for the scientific evaluation.

On 3 June 2008 the European Commission requested the Committee to complete the procedure to take into account all marketing authorisations of the 21 notified products throughout the EU.

Following this request, the CVMP during its meeting of 15-17 July 2008 restarted the procedure for evaluating the products indicated by the Member States. The MAHs were invited to comment and submit any counterproposals by 16 September 2008. No new substantial data were submitted.

Therefore, the CVMP in the July 2008 plenary meeting agreed on 16 July 2008 to complete the procedure under Article 78 of Directive 2001/82/EC, as amended, for all marketing authorisations held in the EU for the 21 products containing alpha2-adrenoreceptor agonists initially notified and to revise the initial previous opinion accordingly.

A revised list of questions addressed to the Marketing Authorisation Holders concerned was adopted on 16 July 2008.

2. Discussion

The proposed precautionary measures relate to different user safety concerns. Aimed at the user are systemic sedative and hypotensive effect, skin contact, eye contact and risks for pregnant women. The advice to doctors lists the potential clinical effects and suggested treatment.

In the mutual recognition procedure concerning another product - Sedaxylan - containing an alpha2-adrenoceptor agonist, a user safety evaluation was performed. This resulted in a set of precautionary measures, which was agreed by all concerned Member States and the applicant at the time.

The set of precautionary measures then served as basis for the proposals made by the Dutch competent regulatory authority for this procedure under Article 78 of Directive 2001/82/EC, as amended.

In the following, each of the proposed precautionary measures and information on human adverse reactions is evaluated separately.

2.1 Systemic effect on sedation and hypotension

Although the exact accidental injected exposure (dose) of the reported human adverse reaction (Hoyer, M.J., 2006) was unknown, it was concluded that the observed clinical effects - *on day 1 being loss of consciousness (arousable), hallucinations, low heart rate and low blood pressure, vasoconstriction, and vasodilation; and on day 2 drowsiness, mild headache, loss of memory and tiredness* – can be attributable to the product (Sedivet). The maximal exposure was estimated to 0.3 ml Sedivet (3 mg romifidine). Oral exposure was not reported.

The CVMP further considered the published Maximum Residue Limit (MRL) Summary Reports for xylazine, detomidine and romifidine. Since systemic effects may occur in rather low doses of romifidine in humans (0.2 mg/person), the CVMP concluded that the effects experienced by a person accidentally having injected a maximum of 0.3 ml Sedivet (3 mg romifidine) could be related to the active substance of the product. Xylazine induced sedation, muscle relaxation and analgesia after a single intravenous dose of 0.27 or 0.68 mg/kg bw or after a single oral dose of 0.54 mg/kg bw. Medetomidine, structurally related to detomidine, at an intravenous dose 0.67 µg/kg bw caused hypotension and sedation that lasted for at least 8 hours, as reported in the MRL Summary Report for detomidine.

The CVMP considered the extrapolation of the proposed warnings to other alpha2-adrenoreceptor agonists justified, as all these substances have the same pharmacological mode of action and since several of the substances have shown similar effects in humans.

The proposed precautionary measures were considered relevant and proportionate, since it relates to the clinical effects, which may be expected depending on the amount injected or ingested, and because it highlights one of the main dangers for a veterinary practitioner after a self-injection or ingestion of such a product, i.e. a sedative effect in combination with driving.

Therefore, the CVMP concluded upon the following recommendation:

In the case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.

2.2 Skin contact

No information on skin exposure was available in the reported human adverse reaction (Hoyer, M.J., 2006).

In the mutual recognition procedure concerning Sedaxylan, a user safety evaluation was performed. In general, it was concluded that xylazine hydrochloride is moderately irritating to the human skin after prolonged exposure although no reports on skin irritation were, however, available nor were reports on sensitisation of xylazine. It was concluded that systemic effects after dermal exposure could not be excluded. This resulted in the wording as proposed, which was agreed by all concerned Member States and the applicant.

In the MRL Summary Reports for xylazine and romifidine, it is stated that the compounds have not been tested for skin sensitising potential. The MRL Summary Report for detomidine does not mention this item. In the Summary of Product Characteristics (SPC) for a medicinal product for use in humans, Catapresan, containing the alpha2-adrenoreceptor agonist clonidine (injectable and tablets), the dermal adverse reactions after an unknown route of exposure are listed as skin-rash, urticaria, pruritus, and hairloss with an incidence rate of 1/100 – 1/10000 in patients.

The CVMP considered information provided by one MAH concerning the product's characteristics in relation to sensitisation and contact dermatitis. Such effects had never been reported after use of the product (detomidine). In reference to information on contact hypersensitivity to detomidine and to 10 studies after subcutaneous, intramuscular, or intravenous exposure, the MAH concluded that the risk of sensitisation and contact dermatitis is minimal.

The CVMP further considered proprietary data provided by another MAH concerning three of the products.

Having considered all available data, the CVMP concluded that the proposed precautionary measures regarding skin contact seem appropriate. In the absence of sufficient data concerning the human adverse reactions studies the CVMP did not support a recommendation concerning addition of information on irritation, sensitisation, contact dermatitis and systemic effects after skin contact. In addition, Article 78 of Directive 2001/82/EC applies only to the addition of precautionary measures in this procedure.

The recommendation to wear gloves when handling such a product was considered impractical for the veterinarian. The recommendation to wash exposed skin immediately was, however, considered a rational and proportionate measure, as was the advice to remove contaminated clothes in the absence of long term exposure studies in humans.

In conclusion, the CVMP agreed on the following recommendation:

Avoid skin, eye or mucosal contact.

Wash the exposed skin immediately after exposure with large amounts of water.

Remove contaminated clothes that are in direct contact with skin.

2.3 Eye contact

No information on eye exposure was available in the reported human adverse reaction (Hoyer, M.J., 2006).

The CVMP considered publicly available data on systemic toxicity after ocular exposure to xylazine hydrochloride in a human; corneal toxicity of xylazine and clonidine, in combination with ketamine, in the rat; and acute reversible cataract induced by xylazine and by ketamine-xylazine anesthesia in rats and mice.

Systemic absorption of xylazine was reported in a human after ocular exposure by irrigating the eyes with xylazine. The findings were considered relevant for the more normal exposure occurring in a situation where medicine may accidentally splash into the eyes, e.g. when a syringe detaches from the needle.

It was considered difficult to assess whether the results on corneal effects of xylazine in the studies using mice and rats are relevant for humans. The findings were, however, considered sufficient to support a warning against eye exposure and advice on how to act in the case of accidental eye exposure.

Having considered the data and the comments from the MAHs, the CVMP agreed on the following recommendation:

In the case of accidental contact of the product with eyes, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

2.4 Risks for pregnant women

No information on the risks for pregnant women was available in the reported human adverse reaction (Hoyer, M.J., 2006).

The CVMP considered published data on the effects of xylazine hydrochloride on intrauterine pressure in the cow, the oxytocic effect of xylazine on the canine uterus, effects of detomidine, romifidine and xylazine on intrauterine pressure and sedation in horses, and the effects of xylazine on intrauterine pressure, uterine blood flow, maternal and foetal cardiovascular and pulmonary function in pregnant goats.

An oxytocin-like effect of xylazine on the uterus is well-known. The effect is reflected in the SPC of Sedaxylan, as a warning against the use in late pregnant animals, in particular cows and cats. In addition, the SPC for Sedaxylan states that no teratogenic or foetotoxic effects have been shown.

In reference to the MRL Summary Report for detomidine, the effects of detomidine on pregnant cows seemed less than those described for xylazine, but in horses treated with 20 µg/kg bw, 4 out of 10 pregnancies showed diverse abnormalities with unclear significance. In the MRL Summary Report for detomidine, two oral teratology studies were reported (rat and rabbit). In the rabbit study, detomidine was non-teratogenic and non-foetotoxic up to 2 mg/kg bw. The NOEL was 0.5 mg/kg bw/day based on maternal toxicity. In the rat study, a NOEL of 0.1 mg/kg bw/day was based on foetal and maternal toxicity and teratogenicity. Both these dose levels are above the NOEL for acute pharmacologic effects.

In the SPC for the medicinal product, Catapresin, it is stated that the active substance passes the blood-placenta barrier. Precedex is a product containing dexmedetomidine, the active enantiomer of medetomidine, that is approved for use in humans in the United States. The information on the approved United States New Drug Application (NDA) label for Precedex was considered, stating that dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the foetus. There are no adequate and well-controlled studies in pregnant women. The safety of Precedex during labour and delivery has not been studied. Teratogenic effects were, however, not observed following administration of dexmedetomidine at subcutaneous doses up to 200 µg/kg in rats from day 5 to day 16 of gestation and intravenous doses up to 96 µg/kg in rabbits from day 6 to day 18 of gestation. However, foetal toxicity, as evidenced by increased postimplantation losses and reduced live pups, was observed in rats at subcutaneous dose of 200 µg/kg. In another reproductive study when dexmedetomidine was administered subcutaneously to pregnant rats from gestation day 16 through nursing, it caused lower pup weights at 8 and 32 µg/kg as well as foetal and embryocidal toxicity of second generation offspring at a dose of 32 µg/kg. Furthermore, it is stated that it is not known whether Precedex is excreted in human milk.

Following consideration of the data available, the CVMP agreed on the relevance of this precautionary measure, recommending the following:

If pregnant women handle the product, special caution should be observed not to self-inject as uterine contractions and decreased foetal blood pressure may occur after accidental systemic exposure.

2.5 Advice to doctors

The CVMP considered that the proposed advice to doctors lists the most common pharmacological effects of alpha2-adrenoreceptor agonists, as could also be extracted from the MRL Summary Reports cited under section 2.1.

Ventricular arrhythmias are stated to have been reported, probably after accidental self-injection, but such was not reported in the published report on the human adverse reaction (Hoyer, M.J., 2006). The sentence was clearly considered a precautionary measure applicable to all alpha2-adrenoreceptor agonists and therefore not related to one specific product or substance. This is considered to be the appropriate way of expressing such an advice to doctors.

It was considered that the term toxicity implies an overdose and since that will not always be the case, a modification was agreed upon.

The CVMP further considered a recommendation to include a suggested antidote (atipamezole) not approved for use in humans, and, while not being in favour of recommending a treatment used only experimentally, concluded that symptoms should be treated symptomatically.

Having considered the matter, the CVMP concluded on the following recommendation:

<The substance> is an alpha2-adrenoreceptor agonist, symptoms after absorption may involve clinical effects including dose-dependent sedation, respiratory depression, bradycardia, hypotension, a dry mouth, and hyperglycaemia. Ventricular arrhythmias have also been reported.

Respiratory and haemodynamic symptoms should be treated symptomatically.

3. Conclusions

The CVMP, having considered the risk to human health, the proposed precautionary measures and information on human adverse reactions in light of the data available, concluded that the following information should be reflected in the product literature of the concerned products within a reasonable timeframe:

1. In the case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.
2. Avoid skin, eye or mucosal contact.
3. Wash the exposed skin immediately after exposure with large amounts of water.
4. Remove contaminated clothes that are in direct contact with skin.
5. In the case of accidental contact of the product with eyes, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.
6. If pregnant women handle the product, special caution should be observed not to self-inject as uterine contractions and decreased foetal blood pressure may occur after accidental systemic exposure.
7. Advice to doctors:
   <The substance> is an alpha2-adrenoreceptor agonist, symptoms after absorption may involve clinical effects including dose-dependent sedation, respiratory depression, bradycardia, hypotension, a dry mouth, and hyperglycaemia. Ventricular arrhythmias have also been reported. Respiratory and haemodynamic symptoms should be treated symptomatically.

The CVMP concluded that the recommended general statements on precautionary measures are final recommendations given in response to the notification received from the Netherlands. In conclusion, the precautionary measures should be reflected in the product literature of the concerned veterinary medicinal products containing alpha2-adrenoreceptor agonists.

Furthermore, the CVMP recommends inclusion of the agreed statements on precautionary measures for alpha2-adrenoreceptor agonists in the relevant guideline on Summary of Product Characteristics, to be implemented in accordance with the national regulatory framework.

The CVMP concluded that these scientific recommendations concerning the precautionary measures apply also to other injectable products containing alpha2-adrenoreceptor agonists.

Finally, having considered the urgency of the matter, the CVMP concluded that since products containing alpha2-adrenoreceptor agonists have been on the market for a long time, although these new statements are clearly needed, urgent measures were not considered proportional.