Annex I

List of nationally authorised veterinary medicinal products

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Vana GmbH Wolfgang Schmälzl Gasse 6 1020 Vienna Austria	Vanapen 300 mg/ml Injektionssuspension für tiere	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular use
Austria	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Taneven 300 mg/ml Injektionssuspension für pferde, rinder, schafe, ziegen, hunde, katzen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular, subcutaneous use
Austria	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procain Penicillin G aniMedica 300 mg/ml Injektionssuspension für tiere	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Austria	Ogris Pharma Vertriebs GmbH Hinderhoferstraße 3 4600 Wels Austria	Livipen 300 mg/ml Injektionssuspension für rinder, schweine und pferde	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Belgium	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Peniyet vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use
Belgium	Kela nv Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Peni-Kel	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Belgium	V.M.D. nv Hoge Mauw 900 2370 Arendonk Belgïe	Deposil	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, sheep, pig, dog, cat	Intramuscular, subcutaneous use
Belgium	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Belgium	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Bulgaria	Provet S.A. Posidonos avenue 77 174 55 Alimos, Attiki, Greece	Pangolamin injectable	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Sheep, pig, dog, cat	Intramuscular use
Bulgaria	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Taneven 300 mg/ml suspension for injection for horses, cattle, sheep, goats, dogs and cats	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular, subcutaneous use
Bulgaria	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen 300 mg/ml, suspension for injection for cattle, pigs and horses	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Bulgaria	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml suspension for injection for cattle and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use
Bulgaria	Alfasan International B.V. Kuipersweg 9 3449 JA Woerden The Netherlands	Procpen 30 injectable suspension	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, calve, swine, dog, cat	Intramuscular use
Croatia	Alfasan International B.V. Kuipersweg 9 3449 JA Woerden The Netherlands	Procpen 30, 300 mg/ml, suspenzija za injekciju, za goveda, konje, svinje, ovce, koze, pse i mačke	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular use
Cyprus	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen, 300 mg/ml, Ενέσιμο εναιώρημα για βοοειδή, χοίρους και άλογα	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig (adult)	Intramuscular use
Czech Republic	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin 300 mg/ml injekční suspense	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Czech Republic	Kela nv Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Peni-Kel 300 mg/ml injekční suspenze	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig, dog	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Czech Republic	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen 300 mg/ml, injekční suspenze pro skot, prasata a koně	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig (adult)	Intramuscular use
Czech Republic	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen LA 300 mg/ml injekční suspenze	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use
Denmark	ScanVet Animal Health A/S, Kongevejen 66, 3480 Fredensborg, Denmark	Noropen Prolongatum Vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Pig	Intramuscular use
Denmark	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Primopen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Denmark	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Ethacilin Vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular use
Denmark	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52, Copenhagen Ø 2100 Denmark	Penovet Vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Denmark	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Denmark	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	SOlong Vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Pig	Intramuscular use
Denmark	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Syvacillin Vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use
Denmark	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil Vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Estonia	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Estonia	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Estonia	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Estonia	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Estonia	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen LA	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use
Finland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Finland	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52, Copenhagen Ø 2100 Denmark	Penovet vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use
Finland	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen Vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Finland	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Syvacillin Vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Finland	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Ethacilin vet	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use
France	Intervet Rue Olivier de Serres Angers Technopole Beaucouze Cedex 49071 France	Depocilline	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular use
France	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive suspension injectable pour bovins et porcins	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
France	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen suspension injectable pour bovins, ovins et porcins	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil suspension injectable pour bovins, ovins et porcins	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Germany	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procain-Penicillin-G ad us.vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse	Intramuscular, intramammary use
Germany	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany	Procillin 30%	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig, dog	Intramuscular use
Germany	Ceva Tiergesundheit GmbH Kanzlerstr. 4 40472 Düsseldorf Germany	Vetriproc 30%	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Germany	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Procpen WDT 300 mg/ml	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular, subcutaneous use
Germany	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Germany	Dechra Veterinary Products Deutschland GmbH Hauptstr. 6-8, 88326 Aulendorf Germany	Procain-Penicillin Susp.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular use
Germany	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml Injektionssuspension für rinder und schweine	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Germany	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Taneven	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular, subcutaneous use
Germany	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen 300mg/ml Injektionssuspension für rinder, schafe und schweine	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Germany	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml Injektionssuspension für rinder, schafe und schweine	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Greece	Intervet Hellas A.E., Ag. Dimitriou 63, 174 55 Alimos, Athens Greece	Depocillin	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular use
Greece	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Primopen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Greece	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Syvacillin	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Hungary	Kela nv Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Neopen szuszpenziós injekció A.U.V.	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, pig, dog, cat	Intramuscular, subcutaneous use
Hungary	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml szuszpenziós injekció szarvasmarhák és sertések számára A.U.V.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Hungary	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen 300 mg/ml szuszpenziós injekció szarvasmarhák, sertések és lovak számára A.U.V.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Hungary	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Taneven 300 mg/ml szuszpenziós injekció lovak, szarvasmarhák, juhok, kecskék, kutyák és macskák számára A.U.V.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular, subcutaneous use
Hungary	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen LA 300 mg/ml szuszpenziós injekció szarvasmarhák és sertések számára A.U.V.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use
Iceland	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52, Copenhagen Ø 2100 Denmark	Penovet vet.	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular, subcutaneous use
Ireland	Mevet, S.A.U. Polígono Industrial El Segre, parcela 409-410 25191 Lérida Spain	Probencil 300 mg/ml suspension for injection for cattle and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Ireland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Ireland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Ireland	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml suspension for injection for cattle and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Ireland	Intervet Ireland Ltd. Magna Drive Magna Business Park Citywest Road Dublin 24 Ireland	Depocillin 300 mg/ml suspension for injection	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use
Ireland	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin 300 mg/ml suspension for injection	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig	Intramuscular use
Ireland	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen LA 300 mg/ml	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Ireland	Chem-Pharm Ballyvaughan Co. Clare Ireland	Pharmacillin 300 mg/ml suspension for injection	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig	Intramuscular use
Ireland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procillin 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Ireland	Interchem Ireland Ltd 29 Cookstown Industrial Estate Dublin 24 Ireland	Propen 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Ireland	Univet Limited Tullyvin Cootehill Co. Cavan. Ireland	Unicillin 300 mg/ml suspension for injection	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Ireland	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Primopen 300 mg/ml suspension for injection for cattle, pigs and horses	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Italy	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Depocillina 300 mg/ml sospensione acquosa iniettabile per bovini, ovini, suini, equini, cani e gatti	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Prontocill 300.000 U.I./ml sospensione iniettabile per bovini, ovini, caprini, suini, equini, cani e gatti	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular, subcutaneous use
Italy	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Primopen 300 mg/ml sospensione iniettabile per bovini, suini e cavalli	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Italy	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml sospensione iniettabile per bovini e suini	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use
Italy	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Italy	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimpropen 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Italy	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen, 300 mg/ml, sospensione iniettabile per bovini, suini e cavalli	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Taneven 300 mg/ml	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular use
Latvia	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen LA	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use
Latvia	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Latvia	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Latvia	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Lithuania	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin 300 mg/ml, injekcinė suspensija	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Lithuania	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen 300 mg/ml, injekcinė suspensija galvijams, kiaulėms ir arkliams	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Lithuania	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen 300 mg/ml, injekcinė suspensija galvijams, avims ir kiaulėms	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Lithuania	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen LA 300 mg/ml, injekcinė suspensija	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use
Luxembourg	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Peniyet vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use
Luxembourg	Kela nv Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Peni-Kel	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use
Luxembourg	V.M.D. nv Hoge Mauw 900 2370 Arendonk België	Deposil	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, sheep, pig, dog, cat	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Luxembourg	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Luxembourg	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Malta	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen 300 mg/ml, suspension for injection for cattle, pigs and horses	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig (adult)	Intramuscular use
Norway	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52, Copenhagen Ø 2100 Denmark	Penovet vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular, subcutaneous, intraperitoneal, intrasynovial, intrauterine use
Norway	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Peniyet vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Norway	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Primopen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Norway	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Poland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimpropen 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Poland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Poland	ScanVet Polan Sp. z o.o. Skiereszewo, ul. Kiszkowska 9 62-200 Gniezno Poland	Longapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use
Poland	ScanVet Polan Sp. z o.o. Skiereszewo, ul. Kiszkowska 9 62-200 Gniezno Poland	Penillin 30%	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular use
Poland	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Penject	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Primopen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Poland	Mevet, S.A.U. Polígono Industrial El Segre, parcela 409-410 25191 Lérida Spain	Probencil	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Poland	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Poland	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Taneven	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat	Intramuscular, subcutaneous use
Portugal	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen, 300 mg/ml, suspension for injection for cattle, pigs and horses	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Portugal	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml suspension for injection for cattle and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml suspension for injection for cattle and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Portugal	MSD Animal Health, Lda.	Depocilina 300 mg/ml suspensão injetável para bovinos, ovinos, suínos, equinos, cães e gatos	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use
Portugal	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Romania	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Penject 30	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, horse, pig, dog, cat	Intramuscular use
Romania	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Romania	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Depocillin	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	WdT - Wirtschaftsgenossenschaft Deutscher Tierärzte eG Siemensstr. 14 30827 Garbsen Germany	Taneven	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, dog, cat	Intramuscular, subcutaneous use
Slovak Republic	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin 300 mg/ml injekčná suspenzia	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Slovak Republic	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen, 300 mg/ml, suspenzia na injekciu pre hovädzí dobytok, ošípané a kone	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig (adult)	Intramuscular use
Slovenia	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Livipen 300 mg/ml, suspenzija za injiciranje za govedo, prašiče in konje	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Slovenia	Alfasan International B.V. Kuipersweg 9 3449 JA Woerden The Netherlands	Procpen 297,7 mg/ml suspenzija za injiciranje za govedo, prašiče, pse in mačke	Procaine benzylpenicillin	297,7 mg/ml	Suspension for injection	Cattle, pig, dog, cat	Intramuscular use
Spain	Mevet, S.A.U. Polígono Industrial El Segre, parcela 409-410 25191 Lérida Spain	Probencil 300 mg/ml suspension inyectable para bovino y porcino	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml suspension inyectable para bovino y porcino	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Spain	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen 300 mg/ml suspension inyectable para bovino, porcino y caballos	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
Spain	Merck Sharp & Dohme Animal Health, S.L. Polígono Industrial El Montalvo I C/ Zeppelin, nº 6, parcela 38 37008 Carbajosa de la Sagrada Salamanca Spain	Depocillin	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, non-food-producing horse, sheep, pig	Intramuscular use
Spain	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen 300 mg/ml suspension inyectable para bovino, ovino y porcino	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Spain	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension inyectable para bovino, ovino y porcino	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Sweden	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52, Copenhagen Ø 2100 Denmark	Penovet vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, goat, pig, dog, cat	Intramuscular use
Sweden	Intervet International BV, P.O. Box 30 5830 AA Boxmeer, The Netherlands	Ethacilin vet.	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use
Sweden	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Peniyet vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
Sweden	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
Sweden	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil vet	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
The Netherlands	Intervet Nederland B.V. Wim de Körverstraat 35 5831 AN Boxmeer Netherlands	Depocilline, suspensie voor injectie	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, sheep, pig, dog, cat	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
The Netherlands	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin, 300.000 I.E. per ml suspensie voor injectie	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, sheep, pig, dog, cat	Intramuscular use
The Netherlands	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Pen 30 Inj., 300.000 IE/ml, suspensie voor injectie voor varkens	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Pig	Intramuscular use
The Netherlands	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel The Netherlands	Pen 30 Pro Inj., suspensie voor injectie	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Dog, cat	Intramuscular use
The Netherlands	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Penject 30, 300.000 IE/ml, suspensie voor injectie voor varkens	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Pig	Intramuscular use
The Netherlands	Kepro B.V. Maagdenburgstraat 17 7421 ZA Deventer The Netherlands	P.P. 30% Susp. Pro Inj., suspensie voor injectie voor honden en katten	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Dog, cat	Intramuscular use
The Netherlands	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Procpen 30, 300.000 I.E. per ml suspensie voor injectie	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Cattle, sheep, pig, dog, cat	Intramuscular use
The Netherlands	Alfasan Nederland B.V. Kuipersweg 9 3449 JA Woerden The Netherlands	Procaine penicilline "30" Pro Inj, 300.000 IE/ ml, suspensie voor injectie voor hond en kat	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Dog, cat	Intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
The Netherlands	Alfasan Nederland B.V. Kuipersweg 9 3449 JA Woerden The Netherlands	Procaine Penicilline "30" Pro Inj, 300.000 IE/ ml, suspensie voor injectie	Procaine benzylpenicillin	300,000 IU/ml	Suspension for injection	Pig, piglet, dog, cat	Intramuscular use
The Netherlands	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Peniyet vet 300 mg/ml suspensie voor injectie bij runderen en varkens	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig (> 25 kg)	Intramuscular use
The Netherlands	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen 300 mg/ml suspensie voor injectie voor runderen, schapen en varkens	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
The Netherlands	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Procapen, 300 mg/ml, suspensie voor injectie voor runderen, varkens en paarden	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
UK (Northern Ireland)	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Bimprocil 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
UK (Northern Ireland)	MSD Animal Health UK Limited Walton Manor Walton, Milton Keynes MK7 7AJ United Kingdom	Depocillin 300 mg/ml suspension for injection	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, sheep, pig, dog, cat	Intramuscular, subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
UK (Northern Ireland)	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Norocillin 30% w/v suspension for injection	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
UK (Northern Ireland)	Fatro S.p.A., Via Emilia, 285, 40064 Ozzano d'Emilia, Bologna, Italy	Primopen 300 mg/ml suspension for injection for cattle, pigs and horses	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, horse, pig	Intramuscular use
UK (Northern Ireland)	Laboratorios Syva, S.A.U. Avda. Párroco Pablo Diez, 49-57 24010 Leon Spain	Procactive 300 mg/ml suspension for injection for cattle and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, pig	Intramuscular use
UK (Northern Ireland)	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road, Tallaght Dublin 24 Ireland	Procipen 300 mg/ml suspension for injection for cattle, sheep and pigs	Procaine benzylpenicillin	300 mg/ml	Suspension for injection	Cattle, sheep, pig	Intramuscular use
UK (Northern Ireland)	Norbrook Laboratories Limited Rosmore Industrial Estate, H18 W620, Monaghan Ireland	Ultrapen LA 30% suspension for injection	Procaine benzylpenicillin	30% w/v	Suspension for injection	Cattle, pig	Intramuscular, subcutaneous use

Annex II

Scientific conclusions and grounds for amendment of the product information

Overall summary of the scientific evaluation of veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection (see Annex I)

Introduction

Procaine benzylpenicillin is a salt of benzylpenicillin which belongs to the group of natural, narrow-spectrum penicillins (β-lactamase-sensitive penicillins; AMEG category D). Veterinary medicinal products containing procaine benzylpenicillin have been widely used for decades in cattle, horses, sheep, goats, pigs, dogs and cats for the treatment of a variety of infections caused by bacteria susceptible to benzylpenicillin and affecting e.g., the urinary, respiratory or reproductive system.

Beta-lactam antibiotics like penicillin prevent the actively growing bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis. Penicillins exert a bactericidal action but cause lysis only of growing bacteria. In Gram-positive bacteria the β-lactams not only prevent final peptidoglycan cross-linking, but also stimulate lipoteichoic acid release, causing a suicide response by degradation of peptidoglycan by autolysins.

During recent decentralised procedures submitted in accordance with Article 13(1) of Directive 2001/82/EC, it has come to light that the treatment duration for procaine benzylpenicillin veterinary medicinal products (VMPs) are disharmonised across the EU.

Germany noted that for several VMPs authorised in the EU containing procaine benzylpenicillin as a single active substance presented as suspensions for injection, a treatment duration of 1 to 3 days or 3 to 5 days with one injection every 24 hours is recommended. Procaine benzylpenicillin products authorised by means of 'purely' national procedures in Germany mostly require a treatment duration of at least 3 days (injection every 24 hours) without an upper limit. For several products, continuation of treatment for two days beyond clinical signs is recommended. This heterogeneity is further underlined by veterinary medicinal products that are authorised for a maximum treatment duration of 3, 4 or 5 days, while other VMPs require a minimum treatment duration of 3 or 4 days.

Based on the available data, a treatment duration of 1 to 3 days may no longer be appropriate to treat all claimed indications effectively. Published literature (e.g., Smith *et al.,* 1998[1]; Scott *et al.,* 2013[2]; Ordell *et al.,* 2016[3]) suggesting that 3 days is the minimum treatment duration necessary, but a longer treatment duration may be required, adds to the concern that a treatment duration of fewer than 3 days could be insufficient. This is further supported by the fact that benzylpenicillin is a time-dependent antimicrobial substance, i.e., the driving factor for pharmacokinetic/pharmacodynamic (PK/PD) analysis is %T>MIC (fraction of time above the minimum inhibitory concentration [MIC], the period of time during which the concentration exceeds the MIC of target bacteria).

Furthermore, several publications underline that a treatment duration of 5 days or longer for procaine benzylpenicillin may be necessary, e.g., to treat infections caused by *Leptospira* spp. (Ross and Rentko, 2000[4]), *Clostridium* spp. (Greene, 1990[5]; Staempfli and Oliver, 1999[6]), or *Erysipelothrix rhusiopathiae* (Kunesh, 1999[7]).

[1] Smith BI, Donovan GA, Risco C, Littell R, Young C, Stanker LH, Elliott J. Comparison of various antibiotic treatments for cows diagnosed with toxic puerperal metritis. J Dairy Sci. 1998 Jun;81(6):1555-62.
[2] Scott P.R. Clinical presentation, auscultation recordings, ultrasonographic findings and treatment response of 12 adult cattle with chronic suppurative pneumonia: case study. Ir Vet J. 66(1): 5, 2013.
[3] Ordell, A., Unnerstad, H.E., Nyman, A. A longitudinal cohort study of acute puerperal metritis cases in Swedish dairy cows. Acta Vet Scand 58, 79 (2016).
[4] Ross L., Rentko V. Leptospirosis in: Kirk's Current Veterinary Therapy XIII - Small Animal Practice (Bonagura, J.). WB Saunders Company, Philadelphia 13. edition: pp 308-310, 2000.
[5] Greene C., Appel M., Straubinger R. Lyme borreliosis in: Infectious diseases in the dog and cat (Greene C.). WB Saunders Company, Philadelphia, 2. edition: pp 282-293, 1990.

Therefore, Germany considered it important that the treatment duration is sufficiently long to ensure an effective use of veterinary medicinal products containing procaine benzylpenicillin as a single active substance and to avoid an unnecessary risk of antimicrobial resistance development.

On the other hand, Germany also considered it necessary to limit the maximum treatment duration to the therapeutically required minimum in order to avoid any unnecessary exposure of animals to antibiotics, to reduce the risk for adverse effects, to avoid an unnecessary risk of antimicrobial resistance development and to prevent any unnecessary entry of penicillin into the environment leading to an avoidable risk of exposure for the environment, as well as for the consumer.

In conclusion, Germany considered that a review of the dosage regimen (i.e., dosage and treatment duration in each target species) for VMPs containing procaine benzylpenicillin as a single active substance presented as suspensions for injection is necessary to ensure a safe and effective use of those VMPs and to avoid an unnecessary risk of resistance development, for the environment and the consumer.

Overall summary of the scientific evaluation

In order for the CVMP to assess the dosage regimen, two more aspects needed to be considered: the dosing interval (which is interrelated to the dosage and is highly relevant for an antimicrobial like penicillin whose efficacy is dependent on the time over the MIC) and the target pathogens themselves for which the dosing regimen needs to be adequate.

A number of marketing authorisation holders provided proprietary preclinical and clinical data, data on susceptibility of target pathogens to procaine benzylpenicillin, PK/PD models, as well as published scientific literature to support the dosage regimens, the indications, and any impact on the development of antimicrobial resistance, the target animal safety, the environment and the consumer.

Since the concerned products have been authorised for a long time (starting from the 1960s) or are generics, the available data were sparse and often dated. Due to the limitations in available data (field studies as well as dose finding and dose confirmation studies), the CVMP had to largely base its assessment on the efficacy of procaine benzylpenicillin on the preclinical dataset (particularly pharmacodynamic and pharmacokinetic data). Four steps were taken during the assessment:

1. As a first step, a simplified approach was taken to preselect reasonable target bacteria and indications. Maximum plasma concentrations obtained from pharmacokinetic studies were used as a proxy to estimate whether achieved penicillin concentrations were likely to be sufficiently high to cover the MICs (i.e., C_{max}>MIC). As a consequence, target bacteria not covered by C_{max}>MIC were proposed to be deleted from the indications. When elevated MIC values or bi-modal distribution profiles suggested acquired resistance for specific bacteria, these target pathogens were maintained in the indications, but a related warning was proposed to be included in section 3.4 (QRD template v.9)/4.4(QRD template v.8.2) of the summary of product characteristics (SPC) and corresponding section of the package leaflet.
2. Then, in order to assess the dosage and the treatment intervals, the approach taken used a plasma concentration threshold of 0.06 µg/ml indicative of the most susceptible target pathogens that had to be covered by a minimum percentage of 50% of the dosing interval (50%T>MIC). This approach was used to define minimum dosages and maximum treatment intervals that eliminate those treatment strategies that are likely to fail even for the most susceptible bacteria.

[6] Staempfli H., Oliver O. Tetanus, Botulism and Blackleg in: Current Veterinary Therapy 4. Food Animal Practice (Howard, J.). WB Saunders Company, Philadelphia (USA), 4. Edition: pp 383-386, 1999.
[7] Kunesh J. Swine Erysipelas in: Current Veterinary Therapy 4. Food Animal Practice (Howard, J.). WB Saunders Company, Philadelphia (USA), 4. Edition: pp 395-396, 1999.

3. As a third step, to determine the treatment duration, the approach taken was mostly based on general principles and the mode of action of procaine benzylpenicillin. The few clinical studies which were available, scientific published literature and data available from human medicine were also taken into account. A harmonised minimum and maximum treatment duration were proposed balancing the aim to ensure efficacious treatment for the multitude of indications and the risk for resistance development by considering also prudent use principles.
4. Finally, based on the proposed changes to the list of indications, dosage regimen and treatment duration, considerations were given to an appropriate withdrawal period for food-producing species, to the potential impact on the target animal safety and to the environmental risk assessment of the products concerned. The potential impact on the risk of resistance development was also considered.

Indications

The primary sources of information used to assess the efficacy of procaine benzylpenicillin regarding approved product indications in this referral procedure consisted of preclinical data such as *in vitro* MIC data and penicillin plasma concentrations following injections of procaine benzylpenicillin, as provided by different MAHs.

For several target pathogens, the provided MIC data indicated low susceptibility or potential (microbiological) resistance to benzylpenicillin. This is reflected by elevated MIC values or bi-modal distribution profiles suggesting acquired resistance which may result in a lack of clinical efficacy when treated with benzylpenicillin. This applies for *Fusobacterium necrophorum* causing metritis, *Mannheimia haemolytica* (except isolates of Finnish origin), *Bacteroides* spp., *Staphylococcus chromogenes* in cattle; *Staphylococcus* spp. causing MMA/PPDS, *Glaesserella parasuis*, *Streptococcus* spp. and *S. suis* in pigs; *Staphylococcus aureus*, coagulase-negative *staphylococci* as well as *Enterococcus* spp. in dogs; and *Staphylococcus aureus* and *Staphylococcus felis* in cats. Further target pathogens with elevated MIC values were identified by case reports and thus resistant subpopulations are suspected for *Actinobacillus lignieresii* and *Trueperella pyogenes* in cattle. The CVMP recommended that target pathogens with elevated MIC values or bi-modal distribution profiles suggesting acquired resistance were maintained in the indications, but an advisory warning was proposed for inclusion in SPC section 3.4 (QRD template v9.0)/4.4(QRD template v8.2).

Enterobacterales order*,* particularly *Salmonella* spp*., Escherichia coli* and *Proteus* spp*.*, *Bacteroides fragilis*, most *Campylobacte*r spp., *Nocardia* spp. and *Pseudomonas* spp., particularly *Pseudomonas aeruginosa* as well as beta-lactamase–producing *Staphylococcus* spp. are inherently resistant to benzylpenicillin. The CVMP therefore recommended to delete these pathogens from all indications and corresponding information was included in the pharmacodynamics section (SPC section 4.2 (QRD template v9.0)/5.1 (QRD template v8.2)).

For *B. bronchiseptica*, *Staphylococcus intermedius* group, particularly *S. intermedius* and *S. pseudintermedius* monomodal distribution profiles with very high MIC values were reported. As this suggests resistance of the entire population, it is highly likely that these target pathogens cannot be treated effectively with benzylpenicillin, hence the CVMP recommended to delete them from the indications as well.

Due to penicillin's poor ability to enter the intracellular space, it is not expected to be present within mammalian cells in relevant concentrations to be able to treat infections caused by *Rickettsia* spp. which are obligate intracellular Gram-negative bacteria. Therefore, the CVMP recommended that *Rickettsia* spp. should also be deleted from the indications.

With regard to non-obligate intracellular bacteria as well as infections of the central nervous system, the CVMP recommended a warning to be included in SPC section 3.4/4.4: 'After absorption,

benzylpenicillin poorly penetrates biological membranes (e.g. blood-brain barrier) since it is ionised and poorly lipid soluble. Use of this product for treatment of meningitis or CNS infections due to e.g., *Streptococcus suis* or *Listeria monocytogenes* may not be efficacious. Furthermore, benzylpenicillin penetrates mammalian cells poorly and hence this product may have little effect in treating intracellular pathogens e.g. *Listeria monocytogenes*.'.

Lastly, the CVMP recommended the revision of all indications in line with current nomenclature of bacteria, as well as the deletion of the indications 'strangles' and 'withheld after birth' from all target species apart from horses, as they only occur in horses. In addition, 'withheld after birth' in horses should be substituted by 'prevention of acute septic metritis caused by retained fetal membranes' to reflect current terminology.

Dosage and treatment interval

There are a variety of approved dosages, respectively dose ranges, of procaine benzylpenicillin in different target animal species. The dosages vary from a minimum of approximately 5 mg/kg bw in cattle and horses, 6 mg/kg bw in pigs, 7 mg/kg bw in sheep, dogs and cats and 10 mg/kg bw in goats, respectively, to a maximum of approximately 60 mg/kg bw in all target animal species.

While the majority of products concerned by this referral are authorised for treatment intervals of 24 hours, there are four VMPs authorised for a treatment interval of 24 hours or 48. These products are hereafter referred to as 'short-acting'. Additionally, there are a few long-acting procaine benzylpenicillin products authorised for cattle and pigs which feature a repeated treatment after 72 hours, if animals are not cured at this time. These VMPs were included in the assessment and, where possible, conclusions were drawn on posology. However, unless explicitly stated otherwise, the calculations and explanations refer to those products without long-acting effect.

Overall, clinical data regarding efficacy were limited and none of the MAHs provided any proprietary study data regarding dose justification. Nevertheless, several MAHs critically discussed the approved dosing regimens in their responses and a few provided PK/PD models for target animal species for which sufficient data were available, i.e. cattle and pigs.

For benzylpenicillin as a time dependent antibiotic, the T>MIC is the PK/PD parameter best correlating with clinical efficacy. Dependent on the target bacteria and in line with published literature (Toutain *et al.*, 2002[8]; Turnidge, 1998[9]; Onufrak *et al.*, 2016[10]; Kowalska-Krochmal *et al.*, 2021[11]) plasma levels should be above the MIC for 50-70% of the dosing interval.

It should be noted however that using T>MIC for 50-70% of the dosing interval as the only criterion is not appropriate to ensure efficacy for the current dosages and intervals in respect to approved indications and target pathogens. On one hand, there are shortcomings of the methodology itself (e.g., missing target tissue concentrations, partitioning effect) and issues with the quality of available data (e.g., outdated analytical methods, missing conversion factors). On the other hand, at least part of the necessary data points for several dosages and target animal species are missing. In addition, there is a lack of MIC values for several of the target pathogens included in the list of indications.

Similar reasons also precluded the adaptation of the modelling approach presented by one of the MAHs.

[8] Toutain PL, del Castillo JR, Bousquet-Mélou A. The pharmacokinetic-pharmacodynamic approach to a rational dosage regimen for antibiotics. Res Vet Sci. 2002 Oct;73(2):105-14.
[9] Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis. 1998 Jul;27(1):10-22. doi: 10.1086/514622. PMID: 9675443.
[10] Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing. Clin Ther. 2016 Sep;38(9):1930-47.
[11] Kowalska-Krochmal B, Dudek-Wicher R. The Minimum Inhibitory Concentration of Antibiotics: Methods, Interpretation, Clinical Relevance. Pathogens. 2021 Feb 4;10(2):165.

In summary, since determining a dose range was not feasible, the CVMP was able only to define minimum dosages and maximum treatment intervals which would eliminate those treatment strategies that are likely to fail even for the most susceptible bacteria, in order to reduce the risk of treatment failure due to insufficient dosages. Therefore, the approach that was applied used a plasma concentration threshold of 0.06 µg/ml indicative of the most susceptible target pathogens. This value was proposed by different MAHs and substantiated by reference to data and literature and was considered acceptable by CVMP. It should be covered by a minimum percentage of 50% of the dosing interval (50%T>MIC). While those minimum dosages and maximum treatment intervals are defined on the basis of PK/PD considerations, they have been cross-checked for this assessment with all available clinical data, in order to confirm that none of these showed efficacy for a dose lower than the proposed minimum dosage in any of the target species or for a treatment interval longer than the ones proposed.

Based on the PK data for different dosages and treatment intervals cited above, the following minimum dosages and maximum treatment intervals were recommended by the Committee for short-acting procaine benzylpenicillin products for the different target animal species:

Target animal species	Minimum dosage	Maximum dosage interval
Cattle, sheep, goat, pig	10 mg/kg	24h
Horses	12 mg/kg 20 mg/kg	24h 48h
Dog, cat	20 mg/kg	24h

The Committee also recommended that for the VMPs authorised for a 24- as well as a 48-hour treatment interval, the option to extend the treatment interval to 48 hours should be deleted for target species other than horses. The submitted PK/PD data as well as the clinical data suggested that a dosing interval of 24 hours as well as 48 hours should be efficacious for the treatment of horses, provided that a minimum dosage of 20 mg/kg bw is administered to animals treated every 48 hours.

Finally, regarding the long-acting formulations, based on the available efficacy studies and PK studies, there is no evidence leading to the assumption that a 72-hour dosing interval in connection with a dosage of 20 mg/kg bw would be insufficient in cattle and pigs. Therefore their dosage regimens remain unchanged.

Treatment duration

The authorised treatment durations for procaine benzylpenicillin products concerned by this referral procedure ranged between 1 day and an indefinite upper limit. Additionally, in several SPCs the stated treatment duration seemed inconclusive and there were also some VMPs for which it was not explicitly specified.

No preclinical and very limited clinical data was provided to substantiate any treatment duration for procaine benzylpenicillin.

It is assumed that the necessary treatment duration for a disease with a certain active substance does not largely differ between products with the same route of administration. Thus, as indications of the products concerned by this referral procedure are often similar, it is considered reasonable to harmonise the treatment duration across all products. Given the long list of diseases and target pathogens for which procaine benzylpenicillin is authorised, but also given the broad and very non-specific indications, the CVMP considered it necessary to specify a treatment duration span. A time span allows the responsible veterinarian to adapt the treatment duration according to clinical needs and individual recovery of a specific case. It furthermore ensures that the wide spectrum of pathogens

for which procaine benzylpenicillin is authorised can be treated adequately, including highly susceptible pathogens and mild infections potentially requiring a shorter treatment duration, as well as less susceptible and more severe or chronic infections potentially requiring longer treatment.

When considering adequate lower and upper limits for the treatment duration span, CVMP took into account the following general principles. Considering that benzylpenicillin is a time-dependent antibiotic (i.e., antibacterial activity correlates with the time that the 'free' (unbound) antibiotic concentration is maintained above the minimum inhibitory concentration (f T>MIC) of the pathogen) with a slow mode of action, insufficient treatment durations can cause treatment failure. This in turn can increase the risk for AMR development, firstly due to the selection pressure on surviving bacterial population(s) which have been exposed to penicillin, and secondly due to the increased probability of re-treatment with antimicrobials. On the other hand, unnecessarily prolonged treatment duration may increase the risk for adverse events, may cause higher antimicrobial entry into the environment and may increase the risk of antimicrobial resistance development. In addition, to ensure consumer safety an upper limit of treatment duration is needed.

Based on considerations on the mode of action of procaine benzylpenicillin and the available data, CVMP proposed a lower limit of 3 days as there is no clinical evidence that a shorter treatment with benzylpenicillin is effective for any indication. Moreover, a minimum 3-day treatment is in line with the 72 hours as suggested by some MAHs.

Besides this lower limit of 3 days, CVMP considered that a limitation to a maximum treatment duration of 7 days represents the best balance between the need to treat mild, acute infections and more moderate to severe infections to full resolution and account for a reduced efficacy in chronic infections.

It is important to point out that although an upper limit of 7 days is proposed, it is at the discretion (clinical judgement) of the responsible veterinarian to terminate a treatment earlier (e.g., after 3 or 5 days) if the clinical condition of the animal allows for this. In order to address concerns that products are used for 7 days indiscriminately in the field, advice should be given to the responsible veterinarian on the appropriate treatment duration. Thus, the CVMP recommended to add advice in SPC section 3.9 (QRD template v9.0)/4.9 (QRD template v8.2).

Regarding the few long-acting procaine benzylpenicillin products concerned by this referral, a treatment duration of 1 to 2 applications with a 72-hour treatment interval was proposed by CVMP. This treatment duration corresponds to the 3–7 days proposed for the short-acting procaine benzylpenicillin products, as long-acting formulations on average achieve sufficient plasma levels for approximately 72 hours.

Impact on withdrawal periods

The duration of treatment may have an impact on the withdrawal period. Therefore, for those products where a higher maximum treatment duration is recommended, it was considered necessary to review the possible consequences for the withdrawal period. For those products for which no adjustment of the treatment duration is considered necessary, it was consequently not considered necessary to review the withdrawal periods, which remain as authorised.

The residue depletion studies available are heterogeneous in terms of their general quality, applied dosages (6-30 mg procaine benzylpenicillin/kg bw), treatment durations (1-5 consecutive days at 24-hour intervals and twice at a 72-hour interval in case of a long-acting product), study designs and analytical test methods used. In addition, the conclusions on the establishment of withdrawal periods drawn from these data vary for identical products that are authorised in different Member States, e.g., due to the addition of different safety spans. While currently authorised withdrawal periods have been established based on data that may not fulfil current regulatory expectations, these withdrawal periods

are not questioned since no indication of a risk to the consumer has been identified during the many years that these products have been on the market.

For the products whose dose was adjusted, in the absence of a standard data package to establish safe withdrawal periods for the individual products that are subject to this referral procedure, the CVMP had to consider other approaches, with a view to ensure consumer safety.

Extrapolation of withdrawal periods across different products may only be considered if the differences in formulations, but also particle sizes and potential differences in crystallization, are compared and carefully considered, which was not possible in this referral procedure.

PK/PD and physiologically based pharmacokinetic (PBPK) models were considered, however, the CVMP did not consider the available modelling approaches suitable for the establishment of new withdrawal periods for this referral procedure.

As none of the approaches described above was considered appropriate to establish updated withdrawal periods, the CVMP based their decision on pharmacokinetic principles and knowledge on properties of the substance procaine benzylpenicillin, supported by the totality of the data available.

In summary, the available evidence does not point towards a systemic accumulation of procaine benzylpenicillin after repeated injections. Nevertheless, due to the data limitations and the resulting uncertainty, the CVMP considered it prudent to add a safety span to the currently authorised withdrawal periods to ensure consumer safety. Therefore, a safety span of 2 days should be added to the approved withdrawal periods of products whose maximum treatment duration will be extended from 3 or 5 days to 7 days. In this respect, it should be pointed out that the approved withdrawal periods were considered safe for their authorised posology – this is also supported by the fact that no signals have been reported to EU Member States of major penicillin residue violations in food stuffs following use of procaine benzylpenicillin containing VMPs as authorised. Therefore, the safety span is an additional precautionary measure.

Concerning milk, the CVMP concluded that the available data up to 5 days of treatment demonstrated that 'steady-state' penicillin concentrations in milk occur after the second day. Thus, no increased penicillin residue concentrations in milk would be expected with a treatment duration of up to 7 days at the same dose and the withdrawal periods for milk do not need to be amended in order to ensure consumer safety.

Impact on environmental safety

The CVMP updated the calculation of the predicted concentration in soil to reflect the proposed 7-day treatment period for cattle, pigs, and sheep (foot rot) using the default values and calculations of the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005-Rev.1- Corr.1).

At most doses authorised, the PECsoil for cattle, pigs, and for foot rot in sheep exceed the action limit of 100 µg/kg. This is the concentration at which the VICH GLs consider that a potential risk for the environment exists and triggers an experimental Phase II environmental risk assessment. As a Phase II assessment is not available, a conclusion on the risk (or not) of procaine benzylpenicillin to the environment when used in cattle, pigs, and foot-rot in sheep could not be drawn. However, some products within the scope of this referral are already authorised with a treatment duration of 7 days or more. Thus, the increase in treatment duration for the remaining products to 7 days would only lead to the same potential environmental risks on a field level that currently exist following use in cattle, pigs, or sheep (foot rot only) from use of the products already authorised with a treatment duration of 7 days.

The CVMP noted that the existing products with treatment duration of 7 days and above have initially been authorised before the need for an environmental risk assessment in line with the VICH GLs was implemented and it is unlikely that the potential risk for the environment following the use of these products has been assessed. However, the assessment of the environmental risk of authorised products was not within the scope of this referral procedure and no concrete evidence of environmental risk from the products has been identified for the existing products which were already authorised with a treatment duration of 7 days.

For horses, goats and most indications for sheep, equally no further risk assessment is needed irrespective of the treatment duration due to the assumption that only individual animals are treated and thus exposure of the environment is limited.

For cats and dogs an environmental risk assessment is also not considered necessary.

Impact on target animal safety

A comparably large data set on target animal safety and local tolerance was submitted by the MAHs including target animal safety studies and combined studies investigating pharmacokinetics and/or residues and local tolerance for all target animal species except goats.

Besides providing proprietary data, most MAHs also referred to published literature and provided a comprehensive summary addressing potential target animal safety concerns. In brief, despite a lack of reproductive toxicity studies, it is well documented that procaine benzylpenicillin is neither embryotoxic nor mutagenic or cancerogenic. Moreover, according to published literature, besides local reactions at the injection site, any other adverse reactions are very rare, the few known effects mostly belong to the hypersensitivity complex including any kind of allergic reaction such as respiratory distress, oedema or urticaria.

Overall, based on the studies provided, the CVMP concluded that systemic adverse effects are very rare and that procaine benzylpenicillin has a wide margin of safety. Injection site reactions occurred in different target animal species but were mostly mild and transient.

Regarding the impact of the suggested amendments on target animal safety, the following can be concluded:

Any proposed amendments and deletion of indications or target pathogens would not concern target animal safety.

The implementation of a minimum dosage, of 10, 12 or 20 mg/kg bw in the different target animal species would not pose any target animal safety concern.

Available target animal safety studies covered single injections of up to 40 mg/kg and repeated administrations of 30 mg/kg in cattle, repeated administrations of 30 mg/kg bw over 5 days in sheep and of 60 mg/kg over 5 days in pigs, dogs and cats with no or no major adverse effects. For horses, target animal safety studies covered repeated administrations of up to 60 mg/kg over 5 days with only mild and transient adverse effects reported for this dosage.

Treatment intervals of 24 hours for the short-acting VMPs in all target animal species as well as 72 hours for the long-acting procaine benzylpenicillin formulations in cattle and pigs were covered by the available target animal safety data.

The implementation of a treatment duration of 3-7 days was not considered to pose any target animal safety concern. On one hand, it is highly unlikely that an administration of a VMP for 7 days would cause severe adverse reactions, as no adverse effects were reported in studies with a 2-fold dose over 5 days. On the other hand, some of the VMPs containing procaine benzylpenicillin have been

authorised for treatment duration of 7 days and longer for many decades, without notable disproportionate risks being revealed by pharmacovigilance reporting.

Neither the treatment duration, nor the dosage appear to affect injection site safety as those local reactions may occur already after the first injection and are not related to the administered dose. This was demonstrated in two studies in cattle with a limitation in injected volume per injection site to 20 ml and where local reactions occurred in animals treated with 20 mg/kg that mostly received 1 or 2 injections as well as in animals treated with 40 mg/kg that mostly received 3 or 4 injections.

However, to account for the systemic toxic effects in young piglets, which are transient but can be considered to be potentially lethal, especially at higher doses, the CVMP recommended that a related warning should be included in SPC section 3.6 (QRD template v9.0)/ 4.6 (QRD template v8.2) and the corresponding section of the package leaflet.

Impact on risk of development of antimicrobial resistance

The implementation of warnings regarding the susceptibility situation of target pathogens in the product information and the deletion of resistant target pathogens following the recommendations made above will have a positive impact on the risk of AMR development. Raising attention in the product information to specific pathogens with an already precarious susceptibility situation for which the use of procaine benzylpenicillin might result in a lack of clinical efficacy will support veterinarians in making treatment decisions in accordance with prudent use.

The implementation of a lower dose limit following the approach explained in detail in the chapter on dosage and treatment interval contributes to the reduction of the risk of AMR development. The elimination of doses below individual thresholds for which there is no demonstrated efficacy, even for the most susceptible target pathogens in the different target species, would represent a significant improvement in terms of AMR risk.

Additionally, the deletion of 48-hour treatment intervals for target species other than horses is a further improvement to lower the AMR risk. By ensuring adequate dosing intervals, reaching relevant tissue concentrations above MIC for an adequately long time is more likely.

The risk of resistance development is considered to be reduced by the implementation of a treatment duration of 3-7 days. Firstly, the risk of AMR development following treatment failure because of an insufficient treatment duration would be minimised. Also, prolonged treatments above 7 days, which increase the entry of antimicrobials into the environment and e.g., wastewater, which promotes the development of resistance, would be prevented. In addition, prolonged treatment required due to reduced susceptibility of treated pathogens favours the development of AMR, so the duration of treatment should always be limited to the minimum necessary.

Benefit risk balance

Direct therapeutic benefit

Benzylpenicillin is a narrow-spectrum first-line antibiotic belonging to the AMEG category D. It is most active against Gram-positive bacteria and has a limited activity against Gram-negative bacteria. Veterinary medicinal products containing procaine benzylpenicillin within the scope of this referral have been used for decades in cattle, horses, sheep, goats, pigs, dogs and cats to effectively treat a wide range of infections caused by bacteria susceptible to benzylpenicillin and affecting different organ systems.

Additional benefits

Veterinary medicinal products containing procaine benzylpenicillin are well-tolerated, causing mostly only mild local reactions at the injection site and no serious systemic adverse events in the target animals.

Antimicrobial resistance to benzylpenicillin is well described. However, several target pathogens, particularly Gram-positive bacteria remain susceptible to benzylpenicillin.

Risk assessment

Quality and user safety were not within the scope of this referral procedure and therefore were not specifically assessed.

For some products involved in this referral procedure, a risk has been identified indicating an inappropriate dosage regimen, i.e., too low dosages, too short as well as too long treatment durations, and too long treatment intervals related to their indications.

The risk of an inappropriate dosing regimen is interconnected with an increased risk of antimicrobial resistance development. With respect to the latter, specific target pathogens were recognised showing acquired resistance, low susceptibility, or even inherent resistance.

Besides, indications were identified which are not in line with current scientific knowledge.

Apart from systemic toxic effects in young piglets, no other risks with regards to target animal health were identified.

A potential risk for consumer safety with regard to withdrawal periods has been identified for those products for which the treatment duration is extended up to 7 days.

For products used in cats, dogs, horses, goats, and most indications for sheep, the exposure of the environment is low and therefore no risk for the environment is expected. Due to higher exposure, a potential risk for the environment could theoretically exist for products used in cattle, pigs, and foot rot in sheep.

Risk management or mitigation measures

The risks related to efficacy and antimicrobial resistance development will be mitigated by adjustment of the minimum dosage limit to 10 mg/kg bw in cattle, sheep, goats and pigs, 12 mg/kg bw in horses, 20 mg/kg bw in dogs and cats, and by deletion of 48-hour dosing intervals in all target animal species except horses and for horses if dosages are below 20 mg/kg bw, as well as by harmonising the treatment duration to 3 to 7 days for all products.

Further risk management measures are the deletion of some indications and several target pathogens as well as the inclusion of warnings in the product information to indicate resistance or decreased susceptibility in specific target pathogens.

Indications and target pathogens which are not in line with the current scientific knowledge or current nomenclature need to be reworded or deleted, respectively.

The risk related to safety in young piglets will be mitigated by inclusion of a warning in the product information.

The risk for the consumer when the maximum treatment duration is harmonised to 7 days will be managed by adding a second withdrawal period for edible tissues. The first withdrawal period represents the already established one for the originally approved treatment duration, whereas the second one is applicable for the extension of the treatment duration from 3 or 5 days to 7 days and is

characterised by an additional safety span of 2 days. Furthermore, the CVMP decided that the withdrawal periods for milk do not need to be amended in order to ensure consumer safety.

As the risk for the environment has not been assessed within this referral because some products already exist on the market with a treatment duration of 7 days or more with no proven safety risk, no additional risk mitigation measures to protect the environment will be included. Any risk mitigation measures in existing products will remain.

Evaluation of the overall benefit-risk balance

Injectable procaine benzylpenicillin products are considered to be effective medicinal products against various disease complexes caused by susceptible bacteria in the target species cattle, sheep, goats, horses, pigs, dogs and cats. Benzylpenicillin is an AMEG category D antibiotic that should be used as a first line treatment, whenever possible.

As with any other antibiotic, benzylpenicillin should be used prudently and only when medically needed. Moreover, any unnecessary use, overly long treatment periods, and under-dosing should be avoided as stated by AMEG.

Assessment of the dosage, dosage interval and treatment duration revealed for some products concerned by this referral too low dosages, too short as well as too long treatment durations, and too long treatment intervals. Accordingly, the dosage regimen of these products needs to be adjusted to ensure an effective use for the proposed indications by minimising the risk of antimicrobial resistance development at the same time. In addition, indications of the VMPs need revisions particularly with respect to the current susceptibility situation of the target pathogens.

The treatment duration has been further evaluated with respect to the risks for the target animal safety, environment and consumer safety related to withdrawal periods. The benefit risk balance remains unchanged in terms of target animal safety and the environment. With regard to withdrawal periods, the proposed additional withdrawal periods for edible tissues, as well as the maintenance of the currently authorised withdrawal periods for milk were considered to ensure consumer safety.

Conclusion on the benefit-risk balance

Having considered the grounds for the referral and the data provided by the MAHs, the CVMP concluded that for the products concerned, the overall benefit-risk balance remains positive, subject to the recommended changes stated in the product information (see Annex III).

Grounds for amendment of the product information (summary of product characteristics, labelling and package leaflet)

Whereas:

- The CVMP considered the referral procedure under Article 82 of Regulation (EU) 2019/6 for veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection for intramuscular and subcutaneous administration routes.
- The CVMP reviewed the available data in support of the indications, dosage (including dosage interval), duration of treatment, residue depletion, environmental risk, target animal safety and risk to antimicrobial resistance for public health.
- The CVMP noted that veterinary medicinal products containing procaine benzylpenicillin have been authorised for decades, under previous regulatory and scientific frameworks.
- The CVMP considered that procaine benzylpenicillin is an antimicrobial agent with a narrow spectrum of activity and a wide safety margin that is still generally effective against a number of

common diseases in food-producing animals. The CVMP considered it important to provide practicing veterinarians with the necessary tools to correctly use procaine benzylpenicillin as a first-choice antimicrobial, in line with AMEG recommendations, guidelines and national policies.

- In view of the above considerations and based on the available data, the CVMP concluded that the indications and dosage regimens (dose rate and treatment duration) of the concerned veterinary medicinal products need to be revised.
- For products whose dosage regimen was amended, the CVMP concluded that the withdrawal periods for meat and offal from treated animals should be revised as well by adding a safety span of 2 days in order to ensure consumer safety. The CVMP considered that the withdrawal periods for milk already provide sufficient assurance of consumer safety and do not need to be amended.
- The CVMP considered it beneficial to include additional information in the product information regarding the mode of action of procaine benzylpenicillin and current susceptibility of target pathogens to support efficacious use of the concerned products for specific indications.

CVMP opinion

The CVMP, as a consequence, considered that the benefit-risk balance of veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection for intramuscular and subcutaneous administration routes remains favourable subject to the amendments to the product information as described in Annex III.

Therefore, the CVMP recommended the variation to the terms of the marketing authorisations for veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection.

Annex III

Amendments to relevant sections of the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

Amendments to relevant sections of the product information

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below, for the intramuscular and subcutaneous routes of administration only.

A. Summary of Product Characteristics

3.2 Indications for use for each target species (QRD template v9.0) **/ 4.2 Indications for use, specifying the target species** (QRD template v8.2)

Delete, where applicable, the following pathogens:

All species belonging to the Enterobacterales order, particularly *Salmonella* spp., *Escherichia coli* and *Proteus* spp.
Bacteroides fragilis
Bordetella bronchiseptica
Campylobacter spp.
Nocardia spp.
Pseudomonas spp., particularly *Pseudomonas aeruginosa*
Rickettsia spp.
Species belonging to the *Staphylococcus intermedius* group, particularly *S. intermedius* and *S. pseudintermedius*
Beta-lactamase–producing *Staphylococcus* spp.

Delete, where applicable:
- Any indication for Salmonellosis.
- 'Strangles' in all target animal species except horses.
- 'Withheld after birth' in all target animal species except horses.

Replace, where applicable:
- *'Staphylococcus aureus* (resistant to penicillin G)' by '*Staphylococcus aureus'*.
- 'Withheld after birth' by 'Prevention of acute septic metritis caused by retained fetal membranes' in horses.

Revise, where applicable, the following nomenclature:
'Glaesserella parasuis' instead of *'Haemophilus parasuis'.*
'Mannheimia haemolytica' instead of '*Pasteurella haemolytica'.*
'Trueperella pyogenes' instead of '*Actinomyces pyogenes', 'Arcanobacterium pyogenes', 'Corynebacterium pyogenes'.*

3.4 Special warnings (QRD template v9.0) **/ 4.4 Special warnings for each target species** (QRD template v8.2)

Add the following advice to all veterinary medicinal products:
After absorption, benzylpenicillin poorly penetrates biological membranes (e.g., blood-brain barrier) since it is ionised and poorly lipid soluble. Use of the product for treatment of meningitis or CNS infections due to e.g., *Streptococcus suis* or *Listeria monocytogenes* may not be efficacious. Furthermore, benzylpenicillin penetrates mammalian cells poorly and hence this product may have little effect in treating intracellular pathogens e.g., *Listeria monocytogenes*.

Add the following wording, as applicable, taking into account the target pathogens authorised in the target species within individual marketing authorisations:
Elevated MIC values or bi-modal distribution profiles suggesting acquired resistance have been reported for the following bacteria:
- *Glaesserella parasuis*, *Staphylococcus* spp. causing MMA/PPDS, *Streptococcus* spp. and *S. suis* in pigs;
- *Fusobacterium necrophorum* causing metritis and *Mannheimia haemolytica* (only in some member states), as well as *Bacteroides* spp., *Staphylococcus chromogenes*, *Actinobacillus lignieresii* and *Trueperella pyogenes* in cattle;
- *S. aureus,* coagulase negative *Staphylococci* and *Enterococcus* spp. in dogs;
- *Staphylococcus aureus* and *Staphylococcus felis* in cats.

Use of the veterinary medicinal product may result in a lack of clinical efficacy when treating infections caused by these bacteria.

3.6 Adverse events (QRD template v9.0) **/ 4.6 Adverse reactions (frequency and seriousness)** (QRD template v8.2)

Add, to all veterinary medicinal products authorised for use in piglets, the following wording:
Systemic toxic effects have been observed in young piglets, which are transient but can be potentially lethal, especially at higher doses.

3.9 Administration routes and dosage (QRD template v9.0) **/ 4.9 Amounts to be administered and administration route** (QRD template v8.2)

Replace, in all veterinary medicinal products, the current treatment duration recommendation with the following statement:
The treatment duration is 3 to 7 days.

Add the following advice to all veterinary medicinal products:
The appropriate treatment duration should be chosen based on the clinical needs and individual recovery of the treated animal. Consideration should be given to the accessibility of the target tissue and characteristics of the target pathogen.

Delete, where applicable, any reference to a 48-hour treatment interval:
- in other target animal species than horses;
- in horses, if dosages are below 20 mg/kg bw.

Replace, where lower dosages are authorised, the lower dosage limit by:
10 mg/kg bw in cattle, sheep, goats and pigs;
12 mg/kg bw in horses;
20 mg/kg bw in dogs and cats.
Specific dosage recommendations higher than those listed above, and dose ranges should be maintained.

3.12 Withdrawal periods (QRD template v9.0) **/ 4.11 Withdrawal period(s)** (QRD template v8.2)

The meat and offal withdrawal periods should be amended as follows:

[Species]
Meat and offal: x days[1] for treatment duration <3 days> <3-5 days>[2]
y days[3] for treatment duration <4-7 days> <6-7 days>[4]

[1] originally approved withdrawal period in days
[2] originally approved treatment duration
[3] originally approved withdrawal period in days + safety span of 2 days
[4] extended treatment duration from 3 or 5 days to 7 days

[text]: Information to be filled in
<text>: Options to be chosen as appropriate

4.2 Pharmacodynamics (QRD template v9.0) **/ 5.1 Pharmacodynamic properties** (QRD template v8.2)

The following wording should be added to all veterinary medicinal products:
Enterobacterales, *Bacteroides fragilis*, most *Campylobacter* spp., *Nocardia* spp. and *Pseudomonas spp*. as well as beta-lactamase–producing *Staphylococcus* spp. are resistant.

Delete, where applicable:
Any target bacteria present in this section but not mentioned in the indication.

Delete, where applicable, the following pathogens:
All species belonging to the Enterobacterales order, particularly *Salmonella* spp., *Escherichia coli* and *Proteus* spp.
Bacteroides fragilis
Bordetella bronchiseptica
Campylobacter spp.
Nocardia spp.
Pseudomonas spp., particularly *Pseudomonas aeruginosa*
Rickettsia spp.
Species belonging to the *Staphylococcus intermedius* group, particularly *S. intermedius* and *S. pseudintermedius*
Beta-lactamase–producing *Staphylococcus* spp.

Replace, where applicable:
'*Staphylococcus aureus* (resistant to penicillin G)' by '*Staphylococcus aureus*'.

Revise, where applicable, the following nomenclature:
'Glaesserella parasuis' instead of *'Haemophilus parasuis'.*
'Mannheimia haemolytica' instead of '*Pasteurella haemolytica'.*
'Trueperella pyogenes' instead of '*Actinomyces pyogenes', 'Arcanobacterium pyogenes', 'Corynebacterium pyogenes'.*

B. Labelling

Outer package

7. WITHDRAWAL PERIODS (QRD template v9.0) **/ 8. WITHDRAWAL PERIOD(S)** (QRD template v8.2)

The meat and offal withdrawal periods should be amended as follows:

[Species]
Meat and offal: x days[1] for treatment duration <3 days> <3-5 days>[2]
y days[3] for treatment duration <4-7 days> <6-7 days>[4]

[1] originally approved withdrawal period in days
[2] originally approved treatment duration
[3] originally approved withdrawal period in days + safety span of 2 days
[4] extended treatment duration from 3 or 5 days to 7 days

[text]: Information to be filled in
<text>: Options to be chosen as appropriate

Immediate package

5. WITHDRAWAL PERIODS (QRD template v9.0) **/ 5. WITHDRAWAL PERIOD(S)** (QRD template v8.2)

The meat and offal withdrawal periods should be amended as follows:

[Species]
Meat and offal: x days[1] for treatment duration <3 days> <3-5 days>[2]
y days[3] for treatment duration <4-7 days> <6-7 days>[4]

[1] originally approved withdrawal period in days
[2] originally approved treatment duration
[3] originally approved withdrawal period in days + safety span of 2 days
[4] extended treatment duration from 3 or 5 days to 7 days

[text]: Information to be filled in
<text>: Options to be chosen as appropriate

C. Package Leaflet

4. Indications for use (QRD template v9.0) **/ 4. INDICATION(S)** (QRD template v8.2)

Delete, where applicable, the following pathogens:

All species belonging to the Enterobacterales order, particularly *Salmonella* spp., *Escherichia coli* and *Proteus* spp.
Bacteroides fragilis
Bordetella bronchiseptica
Campylobacter spp.
Nocardia spp.
Pseudomonas spp., particularly *Pseudomonas aeruginosa*

Rickettsia spp.
Species belonging to the *Staphylococcus intermedius* group, particularly *S. intermedius* and *S. pseudintermedius*
Beta-lactamase–producing *Staphylococcus* spp.

Delete, where applicable:
- Any indication for Salmonellosis.
- 'Strangles' in all target animal species except horses.
- 'Withheld after birth' in all target animal species except horses.

Replace, where applicable:
- '*Staphylococcus aureus* (resistant to penicillin G)' by '*Staphylococcus aureus'*.
- 'Withheld after birth' by 'Prevention of acute septic metritis caused by retained fetal membranes' in horses.

Revise, where applicable, the following nomenclature:
'Glaesserella parasuis' instead of *'Haemophilus parasuis'.*
'Mannheimia haemolytica' instead of *'Pasteurella haemolytica'.*
'Trueperella pyogenes' instead of *'Actinomyces pyogenes', 'Arcanobacterium pyogenes', 'Corynebacterium pyogenes'.*

6. Special warnings (QRD template v9.0) **/ 12. SPECIAL WARNING(S)** (QRD template v8.2)
Special warnings: (QRD template v9.0) / Special warnings for each target species: (QRD template v8.2)

Add the following advice to all veterinary medicinal products:
After absorption, benzylpenicillin poorly penetrates biological membranes (e.g., blood-brain barrier) since it is ionised and poorly lipid soluble. Use of the product for treatment of meningitis or CNS infections due to e.g., *Streptococcus suis* or *Listeria monocytogenes* may not be efficacious. Furthermore, benzylpenicillin penetrates mammalian cells poorly, hence this product may have little effect in treating intracellular pathogens e.g., *Listeria monocytogenes*.

Add the following wording, as applicable, taking into account the target pathogens authorised in the target species within individual marketing authorisations:
Elevated MIC values or bi-modal distribution profiles suggesting acquired resistance have been reported for the following bacteria:
- *Glaesserella parasuis*, *Staphylococcus* spp. causing MMA/PPDS, *Streptococcus* spp. and *S. suis* in pigs;
- *Fusobacterium necrophorum* causing metritis and *Mannheimia haemolytica* (only in some member states), as well as *Bacteroides* spp., *Staphylococcus chromogenes*, *Actinobacillus lignieresii* and *Trueperella pyogenes* in cattle;
- *S. aureus,* coagulase negative *Staphylococci* and *Enterococcus* spp. in dogs;
- *Staphylococcus aureus* and *Staphylococcus felis* in cats.

Use of the veterinary medicinal product may result in a lack of clinical efficacy when treating infections caused by these bacteria.

7. Adverse events (QRD template v9.0) **/ 6. ADVERSE REACTIONS** (QRD template v8.2)

Add, to all veterinary medicinal products authorised for use in piglets, the following wording:
Systemic toxic effects have been observed in young piglets, which are transient but can be considered potentially lethal, especially at higher doses.

8. Dosage for each species, routes and method of administration (QRD template v9.0) **/ 8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION** (QRD template v8.2)

Replace, in all veterinary medicinal products, the current treatment duration recommendation with the following statement:
The treatment duration is 3 to 7 days.

Add the following advice to all veterinary medicinal products:
The appropriate treatment duration should be chosen based on the clinical needs and individual recovery of the treated animal. Consideration should be given to the accessibility of the target tissue and characteristics of the target pathogen.

Delete, where applicable, any reference to a 48-hour treatment interval:
- in other target animal species than horses;
- in horses, if dosages are below 20 mg/kg bw.

Replace, where lower dosages are authorised, the lower dosage limit by:
10 mg/kg bw in cattle, sheep, goats and pigs;
12 mg/kg bw in horses;
20 mg/kg bw in dogs and cats.
Specific dosage recommendations higher than those listed above, and dose ranges should be maintained.

10. Withdrawal periods (QRD template v9.0) **/ 10. WITHDRAWAL PERIOD(S)** (QRD template v8.2)

The meat and offal withdrawal periods should be amended as follows:

[Species]
Meat and offal: x days[1] for treatment duration <3 days> <3-5 days>[2]
y days[3] for treatment duration <4-7 days> <6-7 days>[4]

[1] *originally approved withdrawal period in days*
[2] *originally approved treatment duration*
[3] *originally approved withdrawal period in days + safety span of 2 days*
[4] *extended treatment duration from 3 or 5 days to 7 days*

[text]: Information to be filled in
<text>: Options to be chosen as appropriate