Annex I

List of the names, pharmaceutical form, strengths of the veterinary medicinal products, animal species, route of administration, marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Ceva Santé Animale 10 Avenue de la Ballastiere 33500 Libourne France	Enzaprost Bovis 12.5 mg/ml Injektionslösung für Rinder	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Austria	Zoetis Österreich GmbH Floridsdorfer Hauptstraße 1 1210 Vienna Austria	Dinolytic 5 mg/ml - Injektionslösung für Tiere	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Austria	Ceva Santé Animale 10 Avenue de la Ballastiere 33500 Libourne France	ENZAPROST T 5 mg/ml Injektionslösung für Rinder und Schweine	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Belgium	Ceva Santé 10 Avenue de la Ballastiere Libourne, Gironde 33500 France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Belgium	Zoetis Belgium s.a. Rue Laid Burniat, 1 B-1348 Louvain-La-Neuve Belgium	Dinolytic, 5 mg-ml	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Belgium	Ceva Santé Animale N.V. Metrologielaan 6 1130 Brussel Belgium	Enzaprost	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Bulgaria	Ceva Animal Health Bulgaria Ltd str. Elemag 26Б, app. 1, fl. 1 1113 Sofia Bulgaria	Enzaprost bovis 12.5 mg/ml solution for injection for cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Bulgaria	Ceva Animal Health Bulgaria Ltd str. Elemag 26Б, app. 1, fl. 1 1113 Sofia Bulgaria	ENZAPROST T 5 mg/ml solution for injection for cattle and pig	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Croatia	Ceva Sante Animale 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost Bovis, 12,5 mg/mL, otopina za injekciju, za goveda	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Croatia	Ceva Sante Animale 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost, 5 mg/mL, otopina za injekciju, za goveda i svinje	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Croatia	Zoetis B.V., Podružnica Zagreb za promidžbu Petra Hektorovića 2 10000 Zagreb Croatia	DINOLYTIC, 5 mg/mL, otopina za injekciju, za goveda, konje i svinje	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Cyprus	Ceva Santé Animale 10 avenue de la Ballastiere Libourne Gironde, 33500 France	Enzaprost Bovis 12.5 mg/ml solution for injection for cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Czech Republic	Ceva Santé Animale, 10 avenue de la Ballastiere 33500 Libourne Cedex France	Enzaprost Bovis 12.5 mg/ injekční roztok pro skot	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Czech Republic	Zoetis Česká republika s. r. o. Náměstí 14. října 642/17 150 00 Praha 5 Czech Republic	Dinolytic 5 mg/ml injekční roztok	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Czech Republic	Ceva Animal Health Slovakia s.r.o., Račianska 153 Bratislava, 831 53 Slovakia	ENZAPROST T 5 mg/ml injekční roztok	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Denmark	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde 33500 France	Enzaprost	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Denmark	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde 33500 France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Estonia	Zoetis Belgium S.A. Rue Laid Burniat 1, 1348 Louvain-la-Neuve, Belgium	Dinolytic 12.5 mg	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Estonia	Zoetis Belgium S.A. Rue Laid Burniat 1, 1348 Louvain-la-Neuve, Belgium	Dinolytic	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Estonia	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde 33500 France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Finland	Ceva Santé Animale 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Finland	Ceva Santé Animale 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Finland	Zoetis Finland Oy Tietokuja 4 00330 Helsinki Finland	Dinolytic vet.	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Finland	Zoetis Finland Oy Tietokuja 4 00330 Helsinki Finland	Dinolytic vet.	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
France	Zoetis France 10 Rue Raymond David 92240 Malakoff France	DINOLYTIC 12,5 MG/ML Solution Injectable pour bovins	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
France	Ceva Sante Animale 10 Avenue de la Ballastiere 33500 Libourne France	ENZAPROST BOVIS 12,5 mg/ml Solution injectable pour bovins	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
France	Zoetis France 10 Rue Raymond David 92240 Malakoff France	DINOLYTIC	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Ceva Sante Animale 10 Avenue de la Ballastiere 33500 Libourne France	ENZAPROST T	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Germany	Ceva Sante Animale 10 avenue de la Ballastiere F-33500 Libourne France	Enzaprost Bovis 12,5 mg/ml solution for injection for cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Germany	Zoetis Deutschland GmbH Schellingstr. 1 D-10785 Berlin Germany	Dinolytic Forte 12,5 mg/ml	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Germany	Zoetis Deutschland GmbH Schellingstr. 1 D-10785 Berlin Germany	Dinolytic	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Germany	Ceva Tiergesundheit GmbH Kanzlerstr. 4 D-40472 Düsseldorf Germany	Enzaprost T	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Greece	Ceva Hellas LLC, 15, Agiou Nikolaou str. Alimos, 17455 Greece	Enzaprost Bovis inj. Sol 12,5 mg/ml	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Greece	Ceva Hellas LLC, 15, Agiou Nikolaou str. Alimos, 17455 Greece	Cevaprost 5 mg/ml	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Zoetis Hellas S.A. Frangokklisias 7 151 25, Maroussi Attica Greece	Dinolytic Inj. Sol 5 mg/ml	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Hungary	Zoetis Hungary Kft. 1123. Budapest Alkotás u. 53. Hungary	Dinolytic injekció A.U.V.	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Hungary	Ceva-Phylaxia Zrt., 1107 Budapest Szállás u. 5. Hungary	Enzaprost T 5 mg/ml oldatos injekció szarvasmarhák és sertések részére A.U.V.	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Hungary	Ceva-Phylaxia Zrt., 1107 Budapest Szállás u. 5. Hungary	Enzaprost Bovis 12,5 mg/ml oldatos injekció szarvasmarhák részére A.U.V.	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Iceland	Ceva Santé Animale, 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Ireland	Zoetis Belgium S.A. 2nd Floor, Building 10 Cherrywood Business Park, Loughlinstown Co Dublin Ireland	Lutalyse	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Ireland	Ceva Santé Animale 10 avenue de la Ballastiere 33500 Libourne, France	Enzaprost 5 mg/ml Solution for injection for cattle and pig	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Ireland	Ceva Santé Animale 10 avenue de la Ballastiere 33500 Libourne, France	Enzaprost Bovis 12.5 mg/ml Solution for Injection for Cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Ireland	Zoetis Belgium S.A. 2nd Floor, Building 10, Cherrywood Business Park, Loughlinstown, Co Dublin, Ireland	Lutalyse High Concentration 12.5 mg/ml solution for injection for cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Italy	Zoetis Italia S.r.l. Via Andrea Doria, 41 M 00192 Roma Italy	DINOLYTIC 5 mg/ml soluzione iniettabile per bovini, equini e suini	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Italy	Zoetis Italia S.r.l. Via Andrea Doria, 41 M 00192 Roma Italy	DINOLYTIC 12,5 mg/ml soluzione iniettabile per bovini	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Italy	Ceva Salute Animale S.p.A. Viale Bartolomeo Colleoni 15 20864 Agrate Brianza (MB) Italia	Enzaprost 5 mg/ml Soluzione iniettabile per bovini e suini	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Italy	Ceva Salute Animale S.p.A. Viale Bartolomeo Colleoni 15 20864 Agrate Brianza (MB) Italia	Enzaprost Bovis 12,5 mg/ml soluzione iniettabile per bovini	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Latvia	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	Dinolytic 12,5 mg/ml šķīdums injekcijām	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Latvia	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	Dinolytic 5 mg/ml šķīdums injekcijām	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Latvia	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde, 33500 France	Enzaprost Bovis 12,5 mg/ml šķīdums injekcijām	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Latvia	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde, 33500 France	Enzaprost 5 mg/ml šķīdums injekcijām	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Lithuania	Zoetis Belgium S.A., Rue Laid Burniat 1, 1348 Louvain-la-Neuve Belgium	DINOLYTIC 12,5 mg/ml injekcinis tirpalas galvijams	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Lithuania	Zoetis Belgium S.A., Rue Laid Burniat 1, 1348 Louvain-la-Neuve Belgium	DINOLYTIC, 5 mg/ml injekcinis tirpalas galvijams, arkliams ir kiaulėms	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Lithuania	Ceva Sante Animale, 10 avenue de la Ballastiere Libourne, Gironde 33500 France	Enzaprost Bovis 12.5 mg/ml solution for injection for cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Lithuania	Ceva Sante Animale Z.I. 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost 5 mg/ml injekcinis tirpalas galvijams ir kiaulėms	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Luxembourg	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde 33500 France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Luxembourg	Zoetis Belgium s.a. Rue Laid Burniat, 1 B-1348 Louvain-La-Neuve Belgium	Dinolytic, 5 mg-ml	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Luxembourg	Ceva Santé Animale N.V. Metrologielaan 6 1130 Brussel Belgium	Enzaprost	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Norway	Ceva Santé Animale 10 avenue de la Ballastiere Libourne 33500 France	Enzaprost	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Norway	Ceva Santé Animale 10 avenue de la Ballastiere Libourne 33500 France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Poland	Ceva Animal Health Polska Sp. z o.o., Okrzei Street 1A 03-715 Warsaw Poland	Enzaprost Bovis 12,5 mg/ml roztwór do wstrzykiwań dla bydła	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Zoetis Polska Sp. z o.o. ul. Postępu 17B 02-676 Warsaw Poland	Dinolytic Forte	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Poland	Ceva Animal Health Polska Sp. z o.o., Okrzei Street 1A 03-715 Warsaw Poland	ENZAPROST 5 mg/ml, roztór do wstrzykiwań dla bydła i świń	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Poland	Zoetis Polska Sp. z o.o. ul. Postępu 17B 02-676 Warsaw Poland	Dinolytic	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Portugal	Ceva Saúde Animal Rua Dr. António Loureiro Borges, 9/9A - 9ºA, Miraflores, 1495-131 Algés – Portugal	ENZAPROST T 5 mg/ml Solução injectável para bovinos e suínos	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Portugal	Ceva Saúde Animal Rua Dr. António Loureiro Borges, 9/9A - 9ºA, Miraflores, 1495-131 Algés – Portugal	Enzaprost Bovis 12.5 mg/ml Solution for Injection for Cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Portugal	Zoetis Portugal Lda. Lagoas Park, Edifício 10 2740-271 Porto Salvo Portugal	DINOLYTIC 5 mg/ml Solução injectável para bovinos, siunos e equinos	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Ceva Sante Animale 10 Avenue De La Ballastiere, 33500 Libourne Gironde, France	Enzaprost Bovis 12,5 mg/ml	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Romania	Ceva Sante Animale, 10 Avenue De La Ballastiere 33500 Libourne Gironde France	Enzaprost T 5 mg/ml	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Romania	Zoetis Belgium SA, Rue Laid Burniat 1, 1348 Louvain-la-Neuve, Belgium	Dinolytic 5 mg/ml	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Slovak Republic	Zoetis Česká republika, s.r.o., náměstí 14. října 642/17, 150 00 Praha 5 Česká republika	Dinolytic 5 mg/ml injekčný roztok	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Slovak Republic	Ceva Animal Health Slovakia s.r.o., Račianska 153 Bratislava, 831 53 Slovakia	Enzaprost T 5 mg/ml injekčný roztok	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Slovak Republic	Ceva Animal Health Slovakia s.r.o., Račianska 153 Bratislava, 831 53 Slovakia	Enzaprost Bovis 12.5 mg/ml Solution for Injection for Cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Slovenia	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde, 33500 France	Enzaprost Bovis 12.5 mg/ml solution for injection for cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovenia	Ceva Santé Animale 10 avenue de la Ballastiere Libourne, Gironde, 33500, France	Enzaprost 5 mg/ml raztopina za injiciranje za govedo in prašiče	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Slovenia	Zoetis Belgium SA, Rue Laid Burniat 1, 1348 Louvain-la-Neuve, Belgium	Dinolytic 5 mg/ml raztopina za injiciranje za govedo, konje in prašiče	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Spain	Zoetis Spain, SL Avda. de Europa 20-B Parque Empresarial la Moraleja 28108 Alcobendas (Madrid) Spain	Dinolytic 12,5 mg/ml solución inyectable para bovino	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Spain	Ceva Salud Animal, S.A. Avda. Diagonal 609-615 Barcelona 08028 Spain	Enzaprost Bovis 12.5 mg/ml solution for injection for cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Spain	Zoetis Spain, SL Avda. de Europa 20-B Parque Empresarial la Moraleja 28108 Alcobendas (Madrid) Spain	DINOLYTIC 5 mg/ml solución inyectable para bovino, porcino y caballos	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Spain	Ceva Salud Animal, S.A. Avda. Diagonal 609-615 Barcelona 08028 Spain	Enzaprost T 5 mg/ml solución inyectable para bovino y porcino	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Sweden	Zoetis Finland Oy Tietokuja 4 00330 Helsingfors Finland	Dinolytic vet.	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Sweden	Ceva Santé Animale 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost Bovis	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
Sweden	Zoetis Finland Oy Tietokuja 4 00330 Helsingfors Finland	Dinolytic® vet.	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
Sweden	Ceva Santé Animale 10 avenue de la Ballastiere 33500 Libourne France	Enzaprost	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
The Netherlands	Zoetis B.V. Rivium Westlaan 74, 2909 LD Capelle a/d Ijssel, The Netherlands	Dinolytic hoge conenctratie 12,5 mg/ml oplossing voor injectie voor runderen	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
The Netherlands	Ceva Santé 10 avenue de la Ballastiere Libourne, Gironde 33500 France	Enzaprost Bovis 12,5 mg/ml oplossing voor injectie voor runderen	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
The Netherlands	Zoetis B.V. Rivium Westlaan 74, 2909 LD Capelle a/d Ijssel, The Netherlands	Dinolytic 5 mg/ml oplossing voor injectie voor runderen, varkens en paarden	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
The Netherlands	Ceva Santé Animjale B.V Tiendweg 8c, 2671 SB, Naaldwijk, The Netherlands	Enzaprost 5 mg/ml Solution for injection for cattle and pig	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
United Kingdom	Ceva Animal Health Ltd, Unit 3, Anglo Office Park, White Lion Road, Amersham, Buckinghamshire, HP7 9FB, United Kingdom	Enzaprost Bovis 12.5 mg/ml Solution for Injection for Cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
United Kingdom	Zoetis UK Limited, 5th Floor, 6 St. Andrew Street, London, EC4A 3AE, United Kingdom	Lutalyse 12.5 mg/ml Solution for Injection for Cattle	Dinoprost	12.5 mg/ml	Solution for injection	Cattle	Intramuscular
United Kingdom	Ceva Animal Health Ltd, Unit 3, Anglo Office Park, White Lion Road, Amersham, Buckinghamshire, HP7 9FB, United Kingdom	Enzaprost 5 mg/ml Solution for Injection for Cattle and Pig	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular
United Kingdom	Zoetis UK Limited, 5th Floor, 6 St. Andrew Street, London, EC4A 3AE, United Kingdom	Lutalyse 5 mg/ml Solution for Injection	Dinoprost	5 mg/ml	Solution for injection	Cattle	Intramuscular

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics

Overall summary of the scientific evaluation of Dinolytic 12.5 mg/ml and 5 mg/ml solutions for injection and associated names, and generic products thereof (see Annex I)

1. Introduction

The veterinary medicinal products Dinolytic and associated names, and generic products thereof are solutions for injection containing 12.5 mg and 5 mg of dinoprost (as dinoprost tromethamine) per ml. Dinoprost tromethamine is a synthetic analogue of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), used in cattle for its luteolytic and/or oxytocic effects. This substance is only effective in case of an active corpus luteum.

For cattle, the recommended dose for all indications is 25 mg of dinoprost per animal (equivalent to 2 ml of the 12.5 mg/ml products and 5 ml of the 5 mg/ml products).

An application was submitted under Article 13(1) of Directive 2001/82/EC, i.e. a generic application for a marketing authorisation under the decentralised procedure for the veterinary medicinal product Enzaprost Bovis 12.5 mg/ml solution for injection for cattle, with the Netherlands as reference Member State (NL/V/0256/001/DC). The reference product is Dinolytic Hoge Concentratie 12.5 mg/ml oplossing voor injectie voor runderen, marketed by Zoetis and authorised under the national procedure in various Member States since 2015, as a line extension of the original full dossiers of Dinolytic products registered with a strength of 5 mg/ml since 1986.

During the aforementioned decentralised procedure, although bioequivalence between Enzaprost Bovis 12.5 mg/ml solution for injection for cattle and the reference product was accepted, France and other Member States disagreed with the zero-day withdrawal period for cattle (meat and offal). The active substance dinoprost tromethamine has a 'no maximum residue limit (MRL) required' status, but an acceptable daily intake (ADI) of 0.83 µg dinoprost per kg body weight (bw) (equivalent to 50 µg per 60 kg person) has been previously established by the CVMP[1]. Considering the consumption of 0.3 kg muscle (injection site), this corresponds to a maximum allowable level of 167 µg/kg muscle. Residue levels above the maximum allowable level were observed in a residue depletion study 24 hours after treatment. France considered that the overall information available show that a withdrawal period of zero days may not be sufficient to ensure consumer safety.

In addition, it has been noted that for the veterinary medicinal products of the same strength (12.5 mg/ml and 5 mg/ml) and marketing authorisation holder (MAH) Zoetis, the Member States across the EU have established different withdrawal periods for cattle meat and offal, i.e. between zero and three days.

France considered that it is in the interest of protecting consumer safety in the Union to review the adequacy of the withdrawal periods for cattle meat and offal and referred the matter to the Committee for Medicinal Products for Veterinary Use (CVMP).

Therefore, on 3 September 2019, France initiated a procedure under Article 35 of Directive 2001/82/EC, for the veterinary medicinal products Dinolytic and associated names, and generic products thereof, containing 12.5 mg and 5 mg of dinoprost per ml presented as solutions for injection for intramuscular use in cattle. The CVMP was requested to review all available residue depletion data and recommend withdrawal periods for meat and offal derived from treated cattle.

[1] CVMP MRL Summary report for dinoprost tromethamine – link

2. Discussion of data available

Data provided by the MAHs

The composition of the products used in the different studies conducted by Zoetis has been provided, as well as the composition of the products registered by Ceva Santé Animale. The formulations being very similar, the CVMP considered that a common withdrawal period could be applicable to all veterinary medicinal products involved in this referral procedure.

Seven residue studies in cattle were made available to the Committee. Two studies were conducted with a solution of radiolabelled dinoprost ($PGF_{2\alpha}$). Five studies were conducted with Lutalyse 5 mg/ml which is the same product as Dinolytic 5 mg/ml, two of which were Good Laboratory Practice (GLP)-compliant.

Five studies were conducted before 1982 and two GLP-compliant studies were conducted in 2007 and 2009 (both reported in 2009).

Dinoprost tromethamine was administered intramuscularly at 25 mg per animal (the recommended dose), except for in the 2 studies conducted with radiolabelled dinoprost tromethamine that were considered to be informative only.

Dinoprost tromethamine residues were measured either by radioactivity (2 studies, 1976 and 1977), by radioimmunoassay (RIA) (3 studies, 1978, 1979 and 1982), by enzyme linked immunoassay (ELISA) (1 study, conducted in 2007 and reported in January 2009) or by liquid chromatography–mass spectrometry (LC-MS) (1 study, April 2009).

Also, one GLP-compliant *in vivo* bioequivalence study conducted with Lutalyse 5 mg/mL and Lutalyse 12.5 mg/ml, and a GLP-compliant tolerance study performed with Lutalyse 12.5 mg/ml were provided. In both studies a dose of 25 mg of dinoprost was administered by intramuscular route.

MRL Status

Since the active substance dinoprost tromethamine has a 'no MRL required' status, the ADI value is used as a reference value. An ADI of 0.83 µg per kg bw (corresponding to 50 µg for a 60 kg person) was established by the CVMP[1].

According to the CVMP MRL Summary Report[1], dinoprost tromethamine has an extremely short half-life of only a few minutes, is almost completely cleared following one or two passages through the liver and/or lungs and no accumulation of dinoprost or residues thereof has been detected in blood following repeated daily injection to cattle. Therefore, only injection site tissue is considered in the assessment of the withdrawal period.

For the establishment of withdrawal periods, a limit at 167 µg/kg injection site tissue was set based on the ADI of 50 µg per person per day and an intake of 300 g injection site tissues
(50 µg/0.3 kg = 167 µg/kg).

Residue depletion data in cattle meat and offal

The MAH Zoetis provided two non- GLP-compliant residue studies that were conducted with a solution of ^{3}H-$PGF_{2\alpha}$ in 1976 and 1977, respectively. In both studies, the product was administered twice by intramuscular route to one cow at doses slightly below the recommended dose (25 mg per animal), at an interval of 11 days.

The CVMP considered these two old residue studies as informative only, since they were not conducted in accordance with current standards and were poorly reported.

Zoetis also provided a residue depletion study, conducted in 1982 with the product 'Pronalgon F injection solution for animals', which corresponds to Lutalyse 5 mg/ml according to the MAH.

Twelve animals were treated by a single intramuscular injection at a dose of 25 mg of $PGF_{2\alpha}$ and were slaughtered at 12, 24, 48, 72 hours post treatment. Muscle, liver, kidney, fat, small intestine, heart and injection site were analysed using a RIA method. Among edible tissues, $PGF_{2\alpha}$ residues were highest at the site of injection at 12 hours post treatment and above the maximum allowable level of 167 µg/kg. After 24 hours, in all individual animals, $PGF_{2\alpha}$ residues at the injection site were below this limit of 167 µg/kg.

The CVMP considered that no reliable withdrawal period could be established from this residue depletion study. The study presents some shortcomings (the GLP status is not specified, the number of animals per time point of slaughter and the sampling procedures for the injection sites do not follow the recommendations of VICH GL48[2], the duration of storage before analysis and the stability of $PGF_{2\alpha}$ in frozen tissue samples are unknown). However, this study remains supportive for the establishment of a withdrawal period since it illustrates the generally rapid depletion of residues and also the significant inter-individual variability in the depletion kinetics in cattle.

Two GLP-compliant residue depletion studies were provided by Zoetis.

One of the studies was conducted in 2009 with a controlled intravaginal drug release (CIDR) insert (1.94 g progesterone/device), and Lutalyse 5 mg/ml. The product was administered by a single intramuscular injection to 25 cows at a dose of 25 mg of $PGF_{2\alpha}$. Among these 25 animals, 13 animals were treated with a CIDR insert 7 days before dinoprost administration.

Animals were slaughtered at approximately 10 hours after removal of the CIDR insert and administration of dinoprost. Injection sites were analysed using an LC-MS method.

Approximately 10 hours after $PGF_{2\alpha}$ injection, residues at the injection sites were highly variable and in the range of 2.29–497 µg/kg (CIDR + Lutalyse group) and 2.04–2620 µg/kg (Lutalyse group). In conclusion, 10 hours post administration, $PGF_{2\alpha}$ residues at the injection site were above the maximum allowable level of 167 µg/kg in 6 animals out of 25.

The CVMP considered this residue study as informative only, as it presents some shortcomings. The sampling of injection site is not in line with the recommendations of VICH GL48[2]. Although the weights of injection site core samples are in line with the guideline, surrounding tissue weighing ± 300 g was not collected. Hence, it is not possible to ensure that the collected samples represent tissue samples from the region where the maximum residue concentrations occur. The duration of storage of tissue samples before analysis and the stability of $PGF_{2\alpha}$ in frozen tissue samples are unknown. Moreover, at the only slaughter time point (10 hours), some residues are higher than the maximum allowable level of 167 µg/kg and no reliable withdrawal period can thus be drawn from this study. Nevertheless, it illustrates the significant inter-individual variability in the depletion of residues at the injection site.

Another GLP-compliant residue depletion study was conducted with Lutalyse 5 mg/ml in 2007 and reported in January 2009. Twelve cows divided into 3 groups with 4 animals in each group were treated by two intramuscular injections at a dose of 25 mg $PGF_{2\alpha}$, 12 hours apart. Animals received the double of the recommended dose which is not expected to affect the depletion results at the injection site which is the aim of this study. Animals in groups T01, T02 and T03 were sacrificed at 24 hours, 48 hours and 72 hours, respectively, after the first injection and both injection sites were collected for assay. As such, data were obtained at 12 hours and 24 hours post-treatment for T01, 36 hours and 48 hours post-treatment for T02 and 60 hours and 72 hours post-treatment for T03. A validated ELISA

[2] VICH topic GL48 Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods (EMEA/CVMP/VICH/463199/2009) - link

method was used to determine the concentration of $PGF_{2\alpha}$ in the injection site and in the immediate surrounding tissue. The weights of injection site samples are in line with the recommendations in VICH GL48[2]. Not all of the individual assay runs met the complete validation criteria specified in the protocol with respect to accuracy and precision. However, sufficient data were obtained from accepted runs to define the depletion profile of $PGF_{2\alpha}$ at the injection site.

Based on validated results, $PGF_{2\alpha}$ residues were higher than the maximum allowable level of 167 µg/kg after 12 hours in 2 injection sites out of 4 (245 and 647 µg/kg). After 24 hours, $PGF_{2\alpha}$ residues (8.01, 9.36, 12.6 and 17.5 µg/kg) in all four animals were below this limit. After 36 and 48 hours, only one $PGF_{2\alpha}$ residue value per group was validated out of 4 samples and was below 167 µg/kg. The other non-validated results were also below 167 µg/kg. After 60 hours, the 4 non-validated results (max: 13.9 µg/kg) were below 167 µg/kg. In conclusion, 24 hours after administration is the first time where $PGF_{2\alpha}$ residues were below the maximum allowable level of 167 µg/kg at the injection site.

The CVMP considered that this study is pivotal for the establishment of a withdrawal period. However, some shortcomings (stability of active substance in frozen samples, lack of analysis of most animals' samples at subsequent time points following the 24 hour samples) raise the need to consider also the other studies available, which indicate a high inter-individual variability and the possibility for some individual samples to contain residues above the 167 µg/kg threshold.

The statistical method cannot be used as at timepoints 36 and 48 hours, there were not enough validated residue concentrations. The Committee considered that a withdrawal period of 48 hours could be derived from this GLP-compliant residue study, i.e. 24 hours plus a safety span of 30% (based on the semi-quantitative analytical method, with lack of validated results in the last timepoints and high variability in individual animals at 12 hours timepoint) according to the CVMP guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012)[3].

The CVMP also considered two further studies which had been included in the MRL assessment.

One study was conducted in 1978 with the product Lutalyse 5 mg/ml with twelve treated animals (4 animals/treated group) and a control group consisting of 6 animals. Twelve cows were treated by a single intramuscular injection at a dose of 25 mg of dinoprost.

Animals were slaughtered at 24, 48 and 72 hours post treatment and injection sites (100 g) were analysed using a RIA. 24 hours after $PGF_{2\alpha}$ injection, residues at the injection sites were in the range of 6.1–198.1 µg/kg (Lutalyse group) and 1.2–2.9 µg/kg (control group), illustrating significant inter-individual variability. Injection site residues returned to baseline level by 48 hours post injection.

In one animal, the residue level at the injection site 24 hours after administration was 198.1 µg/kg and therefore consumption of an injection site derived from that animal would exceed the maximum allowable level of 167 µg/kg. At 48 hours after administration, the residues in all 4 animals were below 167 µg/kg. According to the CVMP guideline on determination of withdrawal periods for edible tissues[3], the statistical method would lead to a withdrawal period of 38.25 hours, rounded to 48 hours. However, the homogeneity of variance is not met, which is expected for injection residues at a time point so close to the administration.

The CVMP considered that this residue study is supportive but not pivotal since it presents some shortcomings ($PGF_{2\alpha}$ residues were measured only at the injection site, sampling of injection site is not in agreement with the recommendations of VICH GL48[2] and the stability of $PGF_{2\alpha}$ in frozen tissue samples before analysis is unknown). Nevertheless, results from this study supporting a withdrawal period of at least 48 hours should be considered for the establishment of the withdrawal period.

[3] CVMP guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012-Rev. 1) – link

The second residue study drawn from the MRL documentation was conducted in 1979 with Lutalyse 5 mg/ml. Six cows were treated by a single intramuscular injection at a dose of 25 mg of dinoprost. Animals were slaughtered at 24, 48 and 72 hours post treatment and injection sites and non-injection site muscle were analysed using a RIA. 24 hours after the administration of Lutalyse 5 mg/ml, the residue level at the injection site was below the maximum allowable level of 167 µg/kg.

The CVMP considers that this old residue study is informative only, as it presents some shortcomings such as the number of animals, the sampling of the injection site and the stability of residues.

Establishment of a withdrawal period

Altogether, studies show that residues at the injection site are higher than the maximum allowable level of 167 µg/kg at timepoints before 24 hours after treatment. Some studies highlight a significant inter-individual variability (1982, April 2009) in the absorption, distribution and depletion of the active substance over up to 48 hours after injection. At 24 hours, residues were below the maximum allowable level of 167 µg/kg in all studies, except in one study conducted in 1978 where one sample displayed a concentration of 198.1 µg/kg, thus higher than the maximum allowable limit at 24 hours post injection. From the samples analysed at 48 hours post treatment, injection site residues were always below this limit.

Based on the pivotal study (conducted in 2007 and reported in January 2009) and the other studies provided by the MAH Zoetis as well as those drawn from the MRL documentation, a withdrawal period of 48 hours could be established. This proposal considers the facts that:

- in the GLP-compliant study of January 2009 performed by Zoetis, no residues above the limit of 167 µg/kg derived from the ADI were observed from 24 hours post injection;
- a safety span of 30% is necessary due to the significant inter-individual variability (studies 1982 and April 2009);
- in one study from the MRL documentation (1978), one animal was found with residues at injection site above the limit of 167 µg/kg derived from the ADI (with 198,1 µg/kg) at 24 hours after administration. According to the CVMP guideline on determination of withdrawal periods for edible tissues[3], the alternative method would lead to a withdrawal period of 48 hours plus a safety span, resulting in a withdrawal period of 3 days. Nevertheless, the CVMP considered that such safety span is not necessary to be added to the 48-hour withdrawal period, since, at 24 hours, only one value was just above the limit of 167 µg/kg and the absorption half-life from the injection site is approximately 2 hours.

  Moreover, both the statistical method from the CVMP guideline on determination of withdrawal periods for edible tissues[3], with some limits, and a statistical approach inspired from the 'safe concentration per milking (SCPM) method' and based on the upper tolerable limit (UTL) at 95/95, are supportive of a withdrawal period of 48 hours when applied to the results from this study;
- the available studies show that residues at injection site at 48 hours are far below the limit of 167 µg/kg whereas at 10 and 12 hours, residues are highly variable and exceed the maximum allowable level of 167 µg/kg. The UTL 95/95 (similar statistical approach as for the SCPM method in milk) applied to all studies is largely above the limit of 167 µg/kg at 10 hours (with 25 individual residue values at 10 hours). For the later timepoints, the UTL 95/95 calculation lacks power as there are not enough residue values available per time point.

Although dinoprost tromethamine has no numerical MRL, the CVMP considered that a withdrawal period is necessary, based on the data from the residue studies provided and in line with the CVMP

guideline on injection site residues (EMEA/CVMP/542/03-FINAL)[4] and the CVMP guideline on the determination of withdrawal periods for edible tissues[3].

The CVMP acknowledged that the consumption of an injection site would be a rare event since animals treated with Dinolytic/Lutalyse are intended for reproduction purposes and are not routinely sent to slaughter. While emergency slaughter within 3 hours after administration and a concomitant accident is not considered realistic, the possibility of slaughter at 12 to 24 hours, as per VICH GL48[2] section 2.3.7.1, is realistic in case of an accident during/immediately following the administration (worst case). It is to be noted that in a number of Member States, cattle can be sacrificed by the veterinary surgeon at the farm for emergency slaughter reasons. Moreover, these veterinary medicinal products are used in a large number of animals, which enhances the probability that injection sites containing $PGF_{2\alpha}$ residues may be consumed.

The ADI is based on uterine contractions, which can be very painful and represent a potential serious risk (miscarriages and premature birth) over the entire pregnancy in those cases where the pregnancy is already at threat of premature delivery.

Considering the high variability in the absorption of the active substance observed in the various residues depletion studies in the early hours after injection, the large number of animals treated annually and since any risk of exposure of the consumer to levels of residues above the safe concentration must be prevented, there is a need for the setting of an appropriate withdrawal period to prevent possible consumer risks after oral intake of injection site tissue.

3. Benefit-risk assessment

Introduction

The CVMP was requested to review all available residue depletion data for the veterinary medicinal products Dinolytic 12.5 mg and 5 mg solutions for injection and associated names, and generic products thereof and to recommend appropriate withdrawal periods for meat and offal derived from treated cattle.

Benefit assessment

While the efficacy of the concerned products in cattle has not been specifically assessed as part of this referral, the veterinary medicinal products under assessment are considered to be effective in cattle for their luteolytic effects, provided an active corpus luteum is present. The recommended dose for all indications in cattle is 25 mg dinoprost per animal.

Risk assessment

Quality, target animal safety, user safety, and the environmental risk for the concerned veterinary medicinal products have not been assessed in this referral procedure.

A risk has been identified regarding the length of the authorised withdrawal periods for cattle (meat and offal). For some veterinary medicinal products, the current withdrawal period may be insufficient to allow residues of dinoprost to fall below the established ADI in edible tissues, thereby posing a risk to consumers after oral intake of injection site tissue from cattle treated with these products.

Risk management or mitigation measures

Dinoprost tromethamine was previously evaluated by the CVMP[1] and while it was considered that a MRL is not required, an ADI of 0.83 µg/kg body weight (corresponding to 50 µg for a 60 kg person) was established.

[4] CVMP guideline on injection site residues (EMEA/CVMP/542/03-FINAL) – link

To ensure the safety of consumers of food and food products derived from animals treated with these products, and in order for dinoprost tromethamine-derived residues to deplete below the ADI, a sufficient time between treatment and slaughter must be allowed.

On the basis of residue depletion studies in cattle tissues, a withdrawal period for cattle meat and offal of 2 days has been derived for all products. This withdrawal period is considered adequate to ensure consumer safety.

Evaluation and conclusions on the benefit-risk balance

Having considered the grounds for referral and the available data, the CVMP concluded that the withdrawal period for meat and offal derived from treated cattle should be amended as recommended to provide assurance for consumer safety.

The overall benefit-risk balance for the veterinary medicinal products Dinolytic 12.5 mg/ml and 5 mg/ml solutions for injection and associated names, and generic products thereof remains positive subject to the recommended changes in the product information.

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

Whereas

- on the basis of the available residue depletion data, the CVMP considered that the withdrawal periods for meat and offal derived from treated cattle should be amended to provide assurance for consumer safety;
- the CVMP considered that the overall benefit-risk balance for the products under this procedure remains positive subject to amendments in the product information;

the CVMP has recommended the amendment of the marketing authorisations for Dinolytic 12.5 mg/ml and 5 mg/ml solutions for injection and associated names, and generic products thereof as referred to in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

Summary of product characteristics

4.11 Withdrawal period(s)

Cattle:

Meat and offal: 2 days.

Labelling

8. WITHDRAWAL PERIOD(S)

Cattle:

Meat and offal: 2 days.

Package leaflet

10. WITHDRAWAL PERIOD(S)

Cattle:

Meat and offal: 2 days.