EUROPEAN COMMISSION

Brussels, 1.7.2010
C(2010)4676

COMMISSION DECISION

of 1.7.2010

concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations for Gadolinium-containing contrast agents for human use which contain one or more of the active substances "gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoteridol, gadobutrol and gadoteric acid"

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THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[1], and in particular Article 34(1) thereof,

Having regard to the opinion of the European Medicines Agency, formulated on 18 March 2010 by the Committee for Medicinal Products for Human Use,

Whereas:

(1) Medicinal products for human use authorised by the Member States must meet the requirements of Directive 2001/83/EC.

(2) On 6 November 2008, the Kingdom of Denmark referred a question to the Committee for Medicinal Products for Human Use under Article 31(1) of Directive 2001/83/EC, pursuant to which, in specific cases where the interests of the Union are involved, a matter may be referred to that Committee before a decision is reached on a request for a marketing authorisation or on the suspension or withdrawal of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary.

(3) The scientific assessment by the Committee, the conclusions of which are set out in Annex II to this Decision, shows that, in the interests of the Union, a decision should be taken amending the marketing authorisations for the medicinal products concerned.

(4) The measures provided for in this Decision are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use,

[1] OJ L 311, 28.11.2001, p. 67

HAS ADOPTED THIS DECISION:

Article 1

The Member States concerned shall amend national marketing authorisations for the medicinal products referred to in Annex I on the basis of the scientific conclusions set out in Annex II.

Article 2

The national marketing authorisations referred to in Article 1 shall be based on the summary of the product characteristics, the labelling and the package leaflet set out in Annex III and, in accordance with Article 32(4) of Directive 2001/83/EC, shall be subject to the conditions set out in Annex IV to this Decision.

Article 3

This Decision is addressed to the Member States.

Done at Brussels, 1.7.2010

For the Commission
Paola Testori Coggi
Director-General

CERTIFIED COPY
For the Secretary - General

Jordi AYET PUIGARNAU
Director of the Registry

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
AT - Austria	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem - Injektionslösung	279,32 mg/ml	solution for injection	intravenous use
AT - Austria	**Insight Agents GmbH** Ringstrasse 19 B 69115 Heidelberg Germany	Gadopentetsäure Insight 500 Mikromol/ml Injektionslösung	469 mg/ml Gadopentetat-Dimeglumin (78,63 mg/ml Gadolinium)	solution for injection	intravenous use
AT - Austria	**Bayer Austria GmbH** Herbststrasse 6-10 1160 Wien Austria	Gadovist 1,0 mmol/ml Injektionslösung in Fertigspritzen/Patronen	604,72 mg/ml Gadobutrol (157,25 mg/ml Gadolinium)	solution for injection	intravenous use
AT - Austria	**Bayer Austria GmbH**, Herbststrasse 6-10 1160 Wien Austria	Gadovist 1,0 mmol/ml - Injektionslösung	604,72 mg/ml Gadobutrol (157,25 mg/ml Gadolinium)	solution for injection	intravenous use
AT - Austria	**Insight Agents GmbH** Ringstrasse 19 B 69115 Heidelberg Germany	Magnegita 500 Mikromol/ml Injektionslösung	469 mg/ml Gadopentetat-Dimeglumin (78,63 mg/ml Gadolinium)	solution for injection	intravenous use
AT - Austria	**Bayer Austria GmbH**, Herbststrasse 6-10 1160 Wien Austria	Magnevist 0,5 mmol/ml - Injektionslösung	469 mg/ml Gadopentetsäure Dimeglumin	solution for injection/infusion	intravenous use
AT - Austria	**Bracco S.p.A**. Via Egidio Folli, 50 20134 Milano Italy	MultiHance 0,5 M - Injektionslösung	334 mg/ml Gadobensäure Dimeglumin	solution for injection	intravenous use
AT - Austria	**Bracco S.p.A**. Via Egidio Folli, 50 20134 Milano Italy	MultiHance 0,5 mmol/ml Injektionslösung in einer Fertigspritze	334 mg/ml Gadobensäure Dimeglumin	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
AT - Austria	**GE Healthcare Handels GmbH** Europlaza Gebäude E Technologiestr. 10 1120 Wien Austria	Omniscan 0,5 mmol/ml - parenterale Kontrastmittellösung	287 mg/ml Gadodiamid	solution for injection	intravenous use
AT - Austria	**Bayer Austria GmbH**, Herbststrasse 6-10 1160 Wien Austria	Primovist 0,25 mmol/m Injektionslösung in einer Fertigspritze	181,43 mg/ml Gadoxetsäure-Dinatrium	solution for injection	intravenous use
AT - Austria	**Bayer Austria GmbH**, Herbststrasse 6-10 1160 Wien Austria	Primovist 0,25 mmol/ml Injektionslösung in einer Durchstechflasche	181,43 mg/ml Gadoxetsäure-Dinatrium	solution for injection	intravenous use
AT - Austria	**Bracco S.p.A**. Via Egidio Folli, 50 20134 Milano Italy	Prohance - Injektionslösung	279,3 mg/ml Gadoteridol (78,61 mg/ml Gadolinium)	solution for injection	intravenous use
BE - Belgium	**Codali S.A.** Avenue Henri Dunant 31 1140 Bruxelles Belgium	DOTAREM	0,5 mmol/ml	Solution for injection	intravenous use
BE - Belgium	**Insight Agents GmbH** Ringstrasse 19 B 69115 Heidelberg Germany	GADOPENTETATE CURAGITA 500MICROMOL/ML	500 micromol/ml	Solution for injection	intravenous use
BE - Belgium	**Bayer SA-NV** J.E. Mommaertslaan 14 1831 Diegem Belgium	GADOVIST	1,0 mmol-ml	Solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
BE - Belgium	**Insight Agents GmbH** Ringstraat 19 B 69115 Heidelberg Germany	MAGNEGITA	500 micromol-ml	Solution for injection	intravenous use
BE - Belgium	**Bayer SA-NV** J.E. Mommaertslaan 14 1831 Diegem Belgium	MAGNEVIST	0,5 mmol-ml	Solution for injection	intravenous use
BE - Belgium	**BRACCO Imaging Deutschland GmbH** Max-Stromeyer-Strasse 116 D - 78467 Konstanz Germany	MULTIHANCE	0,5 M	Solution for injection	intravenous use
BE - Belgium	**GE HEALTHCARE BVBA** Koutervelstraat 20 1831 DIEGEM Belgium	OMNISCAN	0,5 mmol-ml	Solution for injection	intravenous use
BE - Belgium	**Bayer SA-NV** J.E. Mommaertslaan 14 1831 Diegem Belgium	PRIMOVIST	0,25 mmol-ml	Solution for injection	intravenous use
BE - Belgium	**BRACCO Imaging Deutschland GmbH** Max-Stromeyer-Strasse 116 D - 78467 Konstanz Germany	PROHANCE	279,3 mg-ml	Solution for injection	intravenous use
BG - Bulgaria	**Bayer Schering Pharma AG** Muellerstrasse 178 13353 Berlin Germany	Gadovist	604.72 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
BG - Bulgaria	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Primovist	181,43 mg/ml	solution for injection	intravenous use
BG - Bulgaria	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Magnevist	469 mg/ml	solution for injection	intravenous use
BG - Bulgaria	**GE Healthcare AS** Nycoveien 1-2 P.O.Box 4220 Nydalen N-0401 Oslo Norway	Omniscan	287 mg/ml	solution for injection	intravenous use
BG - Bulgaria	**Insight Agents GmbH** Ringstrasse 19 B D–69115, Heidellberg Germany	Magnegita	500 micromol/ml	Solution for injection	Intravenous use
CY - Cyprus	**PHADISCO LTD** 185 YIANNOU GRANIDIOTI AVE, 2235 LATSIA CYPRUS	OMNISCAN	0.5MMOL/ML	solution for injection	intravenous use
CY - Cyprus	**BAYER HELLAS ABEE** SOROU 18-20 151 25 MAROUSI, ATHENS, GREECE	PRIMOVIST PFS	0.25MMOL/ML	solution for injection in prefilled syringes	intravenous use
CY - Cyprus	**BAYER HELLAS ABEE** SOROU 18-20 151 25 MAROUSI, ATHENS, GREECE	PRIMOVIST	0.25MMOL/ML	solution for injection	intravenous use
CZ - Czech Republic	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding	GADOVIST 1,0 m mol/ml	1 mmol/l	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Germany				
CZ - Czech Republic	**Insight Agents GmbH** Ringstrasse 19 B 69115 Heidelberg Germany	Magnegita 500 mikromol/ml injekční roztok	0,5 mmo/ml	solution for injection	intravenous use
CZ - Czech Republic	**Bracco Imaging Deutschland GmbH** Max-Stromeyer-Strasse 116 D-78467 Konstanz Germany	ProHance	279,3 mg-ml	solution for injection	intravenous use
CZ - Czech Republic	**Bracco Imaging Deutschland GmbH** Max-Stromeyer-Strasse 116 D-78467 Konstanz Germany	MultiHance	529 mg/ml	solution for injection	intravenous use
CZ - Czech Republic	**GE Healthcare AS** Nycoveien 1-2, P.O.Box 4220 Nydalen N-0401 Oslo Norway	Omniscan 0,5mmol/l	287 mg/ml	solution for injection	intravenous use
CZ - Czech Republic	**Guerbet** BP 57400 95943 Roissy CdG cedex France	Dotarem	279.32 mg/ml	solution for injection	intravenous use
CZ - Czech Republic	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Primovist 0,25 mmol/ml	0.25 mmol/ml	solution for injection	intravenous use
DE - Germany	**BRACCO Imaging Deutschland GmbH** Max-Stromeyer-Strasse 116 D - 78467 Konstanz Germany	MultiHance	529 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
DE - Germany	**BRACCO Imaging Deutschland GmbH** Max-Stromeyer-Strasse 116 D - 78467 Konstanz Germany	MultiHance	0,5 mmol/ml	solution for injection, prefilled syringe	intravenous use
DE - Germany	**BRACCO Imaging Deutschland GmbH** Max-Stromeyer-Strasse 116 D - 78467 Konstanz Germany	MultiHance XL	529 mg/ml	solution for injection	intravenous use
DE - Germany	**Bayer Vital GmbH** D-51368 Leverkusen Germany	Gadovist 1,0 mmol/ml Injektioslösung	604.72 mg/ml	solution for injection	intravenous use
DE - Germany	**Bayer Vital GmbH** D-51368 Leverkusen Germany	Gadovist 1.0 mmol/ml Injektioslösung in Fertigspritzen/Patronen	604.72 mg/ml	solution for injection	intravenous use
DE - Germany	**Marotrast GmbH** Otto-Schott-Str. 15 D-07745 Jena Germany	Gadograf 1,0 mmol/ml Injektionslösung in Fertigspritzen	604.72 mg/ml	solution for injection	intravenous use
DE - Germany	**Marotrast GmbH** Otto-Schott-Str. 15 D-07745 Jena Germany	Gadograf 1,0 mmol/ml	604.72 mg/ml	solution for injection	intravenous use
DE - Germany	**GE Healthcare Buchler GmbH & Co.KG** Gieselweg 1 D-38110 Braunschweig Germany	Omniscan 0,5 mmol/ml Injektioslösung	287 mg/ml	solution for injection	intravenous use
DE - Germany	**GE Healthcare Buchler GmbH & Co.KG** Gieselweg 1	Omniscan 0,5 mmol/ml Injektioslösung in Fertigspritzen	287 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	D-38110 Braunschweig Germany				
DE - Germany	**Guerbet** 15 rue des Vanesses Zone Paris Nord II F-83420 VILLEPINTE France	Dotarem 0,5 mmol/ml Injektionslösung in Fertigspritzen	279.32 mg/ml	solution for injection	intravenous use
DE - Germany	**Guerbet** 15 rue des Vanesses Zone Paris Nord II F-83420 VILLEPINTE France	Dotarem 0,5 mmol/ml Injektionslösung in Durchstechflaschen (für Mehrfachentnahme)	279.32 mg/ml	solution for injection	intravenous use
DE - Germany	**Guerbet** 15 rue des Vanesses Zone Paris Nord II F-83420 VILLEPINTE France	Dotarem 0,5 mmol/ml Injektionslösung in Durchstechflaschen	279.32 mg/ml	solution for injection	intravenous use
DE - Germany	**Bayer Vital GmbH** D-51368 Leverkusen Germany	Magnevist 0,5 mmol/ml, Injektionslösung	469.01 mg/ml	solution for injection	intravenous use
DE - Germany	**Bayer Vital GmbH** D-51368 Leverkusen Germany	Gadopentetat-Dimeglumin 0,5 mmol/ml, Injektionslösung	469.01 mg/ml	solution for injection	intravenous use
DE - Germany	**be imaging GmbH** Dr.-Rudolf-Eberle-Str. 8-10 D-76534 Baden-Baden Germany	Magnevision 0,5 mmol/ml Injektionslösung	469 mg/ml	solution for injection	intravenous use
DE - Germany	**Covidien Deutschland GmbH** Gewerbepark 1 D-93333 Neustadt Germany	Marktiv 500 Mikromol/ml Injektionslösung	469 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
DE - Germany	**be imaging GmbH** Dr.-Rudolf-Eberle-Str. 8-10 D-76534 Baden-Baden Germany	Magnevision b.e. 0,5 mmol/ml Injektionslösung	469 mg/ml	solution for injection	intravenous use
DE - Germany	**Helm AG** Nordkanalstr. 28 D-20097 Hamburg Germany	Gadopentetat Dimeglumin Helm AG Injektionslösung	469 mg/ml	solution for injection	intravenous use
DE - Germany	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Magnegita 500 Mikromol/ml Injektionslösung	469.01 mg/ml	solution for injection	intravenous use
DE - Germany	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Gadopentetat Insight 500 Mikromol/ml Injektionslösung	469.01 mg/ml	solution for injection	intravenous use
DE - Germany	**Marotrast GmbH** Otto-Schott-Str. 15 D-07745 Jena Germany	Magnograf 0,5 mmol/ml, Injektionslösung	469.01 mg/ml	solution for injection	intravenous use
DE - Germany	**ratiopharm GmbH** Graf-Arco-Str. 3 D-89079 Ulm Germany	Gadopentetat-MRT-ratiopharm	469 mg/ml	solution for injection	intravenous use
DE - Germany	**Sanochemia Diagnostics Deutschland GmbH** Stresemannallee 4 c D-41460 Neuss Germany	MR-Lux	469 mg/ml	solution for injection	intravenous use
DE - Germany	**Bracco IMAGING Deutschland GmbH** Max-Stromexer-Str. 116	ProHance	279.3 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	D-78467 Konstanz Germany				
DE - Germany	**Bayer Vital GmbH** D-51368 Leverkusen Germany	Primovist 0,25 mml/ml Injektionslösung, Fertigspritze	181.43 mg/ml	solution for injection	intravenous use
DE - Germany	**Bayer Vital GmbH** D-51368 Leverkusen Germany	Primovist 0,25 mml/ml Injektionslösung, Durchstechflasche	181.43 mg/ml	solution for injection	intravenous use
DK - Denmark	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem	279,3 mg/mL	solution for injection	intravenous use
DK - Denmark	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem	279,3 mg/mL	Solution for injection, prefilled syringe	intravenous use
DK - Denmark	**GE Healthcare AS** Nycoveien 1-2, 4220 Nydalen, Oslo N-0401 Norway	Omniscan	0,5 mmol/mL	solution for injection	intravenous use
DK - Denmark	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Magnegita	0,5 mmol/mL	solution for injection	intravenous use
DK - Denmark	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Gadopentetat "Insight"	0,5 mmol/mL	solution for injection	intravenous use
DK - Denmark	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Gadovist	1 mmol/mL	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
DK - Denmark	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Gadovist PFS	1 mmol/mL	solution for injection, prefilled syringe	intravenous use
DK - Denmark	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam Netherlands	Prohance	279,3 mg/mL	solution for injection	intravenous use
DK - Denmark	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Magnevist	469 mg/mL	solution for injection	intravenous use
DK - Denmark	**Bracco S.p.A.** Via Emilio Folli, 50 20134 Milano Italy	Multihance	334 mg/ml	solution for injection	intravenous use
DK - Denmark	**Bracco S.p.A.** Via Emilio Folli, 50 20134 Milano Italy	Multihance	334 mg	Solution for injection, prefilled syringe	intravenous use
EE - Estonia	**Bayer Schering Pharma AG** DE-13342 Berlin- Germany	MAGNEVIST	469 mg/ml	solution for injection	intravenous use
EE - Estonia	**GE Healthcare AS** PO 4220, Nycoveien 1-2 NO-0401 Nydalen Norway	OMNISCAN	0,5 mmol/ml	solution for injection	intravenous use
EE - Estonia	**Bayer Schering Pharma AG** DE-13342 Berlin- Germany	GADOVIST	1 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
EE - Estonia	**Bayer Schering Pharma AG** DE-13342 Berlin- Germany	PRIMOVIST	0.25 mmol/ml	solution for injection	intravenous use
EE - Estonia	**Bayer Schering Pharma AG** DE-13342 Berlin- Germany	PRIMOVIST	0.25 mmol/ml	solution for injection in pre-filled syringe	intravenous use
EE - Estonia	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	MAGNEGITA	469 mg/ml	solution for injection	intravenous use
ES - Spain	**GE HEALTHCARE BIO-SCIENCES** S.A. Avda. de Europa 22 Alcobendas 28108 Madrid Spain	OMNISCAN	0,5 mmol/ml	solution for injection syringe	intravenous use
ES - Spain	**GE HEALTHCARE BIO-SCIENCES** S.A. Avda. de Europa 22 Alcobendas 28108 Madrid Spain	OMNISCAN	0,5 mmol/ml	solution for injection	intravenous use
ES - Spain	**Bracco S.p.A.** Via Egido Folli, 50 20134 Milano Italy	MULTIHANCE	0,5 M	solution for injection	intravenous use
ES - Spain	**QUIMICA FARMACEUTICA BAYER** S.L. Av. Baix Llobregat 3-5 Sant Joan Despi Barcelona 08970 Spain	PRIMOVIST	0,25 mmol/ml	solution for injection	intravenous use
ES - Spain	**QUIMICA FARMACEUTICA BAYER** S.L. Av. Baix Llobregat 3-5 Sant Joan Despi	PRIMOVIST	0,25 mmol/ml	solution for injection (syringe)	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Barcelona 08970 Spain				
ES - Spain	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam Netherlands	PROHANCE	(0.5 M)	solution for injection (syringe)	intravenous use
ES - Spain	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam Netherlands	PROHANCE	(0.5 M)	solution for injection (vial)	intravenous use
ES - Spain	**QUIMICA FARMACEUTICA BAYER S.L.** Av. Baix Llobregat 3-5 Sant Joan Despi Barcelona 08970 Spain	GADOVIST	1,0 mmol/ml	solution for injection (vial)	intravenous use
ES - Spain	**QUIMICA FARMACEUTICA BAYER S.L.** Av. Baix Llobregat 3-5 Sant Joan Despi Barcelona 08970 Spain	GADOVIST	1,0 mmol/ml	solution for injection (syringe and cartridge)	intravenous use
ES - Spain	**QUIMICA FARMACEUTICA BAYER S.L.** Av. Baix Llobregat 3-5 Sant Joan Despi Barcelona 08970 Spain	MAGNEVIST	0,5 mmol/ml	solution for injection	intravenous use
ES - Spain	**QUIMICA FARMACEUTICA BAYER S.L.** Av. Baix Llobregat 3-5 Sant Joan Despi	MAGNEVIST	0,5 mmol/ml	solution for injection (syringe)	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Barcelona 08970 Spain				
ES - Spain	**QUIMICA FARMACEUTICA BAYER S.L.** Av. Baix Llobregat 3-5 Sant Joan Despi Barcelona 08970 Spain	MAGNOGRAF	0,5 mmol/ml	solution for injection	intravenous use
ES - Spain	**QUIMICA FARMACEUTICA BAYER S.L.** Av. Baix Llobregat 3-5 Sant Joan Despi Barcelona 08970 Spain	MAGNOGRAF	0,5 mmol/ml	solution for injection (syringe)	intravenous use
ES - Spain	**Guerbet** BP 57400 95493 Roissy CdG cedex France	Dotarem	0,5 mmol/ml	solution for injection	intravenous use
ES - Spain	**Guerbet** BP 57400 95493 Roissy CdG cedex France	Dotarem	0,5 mmol/ml	solution for injection (syringe)	intravenous use
FI - Finland	**GE Healthcare AS** Nycoveien 1-2 4220 Nydalen, Oslo N-0401 Norway	OMNISCAN	0.5 mmol/ml	Solution for injection	intravenous use
FI - Finland	**Bayer Schering Pharma Oy** Pansiontie 47 20210 Turku Finland	MAGNEVIST	0.5 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
FI - Finland	**Insight Agents GmbH** Ringstr. 19 B, 69115 HEIDELBERG Germany	MAGNEGITA	500 micromol/ml	solution for injection	intravenous use
FI - Finland	**Insight Agents GmbH** Ringstr. 19 B, 69115 HEIDELBERG Germany	GADOPENTETATE INSIGHT	500 micromol/ml	solution for injection	intravenous use
FI - Finland	**Bracco S.p.A.** Via Emilio Folli, 50 20134 Milano Italy	MULTIHANCE	334 mg/ml	solution for injection	intravenous use
FI - Finland	**Bracco S.p.A.** Via Emilio Folli, 50 20134 Milano Italy	MULTIHANCE	334 mg/ml	Solution for injection, pre-filled syringe	intravenous use
FI - Finland	**Bayer Schering Pharma Oy** Pansiontie 47, 20210 Turku Finland	PRIMOVIST	0.25 mmol/ml	solution for injection	intravenous use
FI - Finland	**Bayer Schering Pharma Oy** Pansiontie 47, 20210 Turku Finland	PRIMOVIST	0.25 mmol/ml	Solution for injection, pre-filled syringe	intravenous use
FI - Finland	**Bracco International B.V** Strawinskylaan 3051, NL-1077 ZX Amsterdam Netherlands	PROHANCE	279.3 mg/ml	solution for injection	intravenous use
FI - Finland	**Bayer Schering Pharma Oy** Pansiontie 47, 20210 Turku Finland	GADOVIST	1 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
FI - Finland	**Bayer Schering Pharma Oy** Pansiontie 47, 20210 Turku Finland	GADOVIST	1 mmol/ml	Solution for injection (syringe)	intravenous use
FI - Finland	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM	279,3 mg/ml	solution for injection	intravenous use
FR - France	**GE HEALTHCARE** 11, avenue Morane Saulnier 78140 Vélizy Villacoublay France	OMNISCAN 0,5 mmol/ml, solution injectable	28,7 g / 100 ml	solution for injection	intravenous use
FR - France	**GE HEALTHCARE** 11, avenue Morane Saulnier 78140 Vélizy Villacoublay France	OMNISCAN 0,5 mmol/ml, solution injectable en seringue pré-remplie	287 mg / 1 ml	Solution for injection (pre-filled syringe)	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	MULTIHANCE 0,5 mmol/ml, solution injectable (IV)	529 mg / 1 ml	solution for injection	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	MULTIHANCE 0,5 mmol/ml, solution injectable en seringue pré-remplie	529 mg / 1 ml	solution for injection	intravenous use
FR - France	**BAYER SANTE** 220, avenue de la Recherche 59120 Loos France	MAGNEVIST, solution injectable (IV)	46,901 g / 100 ml	solution for injection	intravenous use
FR - France	**BAYER SANTE** 220, avenue de la Recherche 59120 Loos France	MAGNEVIST, solution injectable en seringue pré-remplie (IV)	46,901 g / 100 ml	Solution for injection (pre-filled syringe)	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 1396,5 mg/5 ml, solution injectable	1396,50 mg / 5 ml	solution for injection	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 1396,5 mg/5 ml, solution injectable en seringue pré-remplie	1396,5 mg / 5ml	Solution for injection (pre-filled syringe)	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 2793 mg/10 ml, solution injectable	2793 mg / 10 ml	solution for injection	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 2793 mg/10 ml, solution injectable en seringue pré-remplie	2793 mg / 10 ml	Solution for injection (pre-filled syringe)	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 4189,5 mg/15 ml, solution injectable	4189,50 mg / 15 ml	solution for injection	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 4189,5 mg/15 ml, solution injectable en seringue pré-remplie	4189,50 mg / 15 ml	Solution for injection (pre-filled syringe)	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 4748,10 mg/17 ml, solution injectable en seringue pré-remplie	4748,1 mg / 17 ml	Solution for injection (pre-filled syringe)	intravenous use
FR - France	**BRACCO IMAGING France** 7, place Copernic 91080 Courcouronnes France	PROHANCE 5586 mg/20 ml, solution injectable	5586 mg / 20 ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
FR - France	**BAYER SANTE** 220, avenue de la Recherche 59120 Loos France	GADOVIST 1,0 mmol/mL, solution injectable	604,72 mg / 1 ml	solution for injection	intravenous use
FR - France	**BAYER SANTE** 220, avenue de la Recherche 59120 Loos France	GADOVIST 1,0 mmol/mL, solution injectable en seringue préremplie	604,72 mg / 1 ml	Solution for injection (pre-filled syringe)	intravenous use
FR - France	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml, solution injectable en flacon	27,932 g / 100 ml	solution for injection	intravenous use
FR - France	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml, solution injectable en seringue pré-remplie	27,932 g / 100 ml	Solution for injection (pre-filled syringe)	intravenous use
GR - Greece	**GE HEALTHCARE** PLAPOUTA 139 & LAMIAS ST NEO IRAKLEIO 14121 GREECE	OMNISCAN	287mg/ml	solution for injection	intravenous use
GR - Greece	**BAYER HELLAS ABEE** SOROU 18-20, 151 25 MAROUSI, ATHENS, GREECE	MAGNEVIST	469.01mg/ml	solution for injection	intravenous use
GR - Greece	**GEROLYMATOS P.G.N. AEBE** ASKLIPIOU ST KRYONERI ATTICA GREECE	MULTIHANCE	529mg/mlm	solution for injection	intravenous use
GR - Greece	**GEROLYMATOS P.G.N. AEBE** ASKLIPIOU ST KRYONERI ATTICA GREECE	MULTIHANCE	529mg/mlm	Solution for injection prefilled syringe	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
GR - Greece	**BAYER HELLAS ABEE** SOROU 18-20, 151 25 MAROUSI, ATHENS, GREECE	PRIMOVIST	0.25 mmol/ml	Solution for injection	intravenous use
GR - Greece	**BAYER HELLAS ABEE** SOROU 18-20, 151 25 MAROUSI, ATHENS, GREECE	PRIMOVIST "PFS"	0.25 mmol/ml	Solution for injection prefilled syringe	intravenous use
GR-Greece	**BAYER HELLAS ABEE** SOROU 18-20, 151 25 MAROUSI, ATHENS, GREECE	GADOVIST	1 mmol/ml	solution for injection	intravenous use
GR-Greece	**BAYER HELLAS ABEE** SOROU 18-20, 151 25 MAROUSI, ATHENS, GREECE	GADOVIST PFS	1 mmol/ml	Solution for injection prefilled syringe	intravenous use
GR-Greece	**Hospital Line SA** K. Palama 36 GR-143 43, N. Chalkidona, Athens Greece	Dotarem	1,4 mg/ml	solution for injection	intravenous use
GR-Greece	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	VASOVIST	0.25mmol/ml	solution for injection	intravenous use
HU - Hungary	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml injection 15ml	0,5 mmol/ml	injection	intravenous use
HU - Hungary	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml injection 20ml	0,5 mmol/ml	injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
HU - Hungary	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml injection 60ml	0,5 mmol/ml	injection	intravenous use
HU - Hungary	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml injection 100ml	0,5 mmol/ml	injection	intravenous use
HU - Hungary	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	GADOVIST 1,0 mmol/ml solution for injection	1 mmol/ml	solution for injection	intravenous use
HU - Hungary	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	GADOVIST	1 mmol/ml	solution for injection, prefilled syringe	intravenous use
HU - Hungary	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	MAGNEVIST	0,5 mmol/ml	solution for injection	intravenous use
HU - Hungary	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	MAGNEVIST	0,5 mmol/ml	injection in a pre-filled syringe	intravenous use
HU - Hungary	**Bracco S.p.A.** Via Emilio Folli, 50 20134 Milano Italy	MULTIHANCE	0,5M	solution for injection	intravenous use
HU - Hungary	**GE Healthcare AS** Nycoveien 1-2 4220 Nydalen, Oslo N-0401	OMNISCAN 0,5 mmol/ml injection	0,5 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Norway				
HU - Hungary	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	PRIMOVIST	0,25 mmol/ml	solution for injection	intravenous use
HU - Hungary	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	PRIMOVIST	0,25 mmol/ml	solution for injection, pre-filled syringe	intravenous use
IE - Ireland	**GE Healthcare AS** Nycoveien 1-2 4220 Nydalen, Oslo N-0401 Norway	Omniscan 0.5mmol/ml solution for injection, glass vial/bottle	0.5 mmol/ml	solution for injection	intravenous use
IE - Ireland	**GE Healthcare AS** Nycoveien 1-2 4220 Nydalen, Oslo N-0401 Norway	Omniscan 0.5mmol/ml solution for injection, polypropylene bottles	0.5 mmol/ml	solution for injection	intravenous use
IE - Ireland	**GE Healthcare AS** Nycoveien 1-2 4220 Nydalen, Oslo N-0401 Norway	Omniscan 0.5mmol/ml solution for injection, prefilled syringe	0.5 mmol/ml	solution for injection, prefilled syringe	intravenous use
IE - Ireland	**Bayer Limited** The Atrium Blackthorn Road Dublin 18 Ireland	Primovist 0.25 mmol/ml Sol for Injection	0.25 mmol/ml	solution for injection	intravenous use
IE - Ireland	**Bayer Limited** The Atrium Blackthorn Road	Primovist 0.25 mmol/ml Sol for Injection, prefilled syringe	0.25 mmol/ml	solution for injection, prefilled syringe	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Dublin 18 Ireland				
IE - Ireland	**Bayer Limited** The Atrium Blackthorn Road Dublin 18 Ireland	Gadovist 1.0 mmol/ml Solution for Injection	1.0 mmol/ml	solution for injection	intravenous use
IE - Ireland	**Bayer Limited** The Atrium Blackthorn Road Dublin 18 Ireland	Gadovist 1.0 mmol/ml Solution for Injection in prefilled syringe	1.0 mmol/ml	solution for injection, in prefilled syringe	intravenous use
IE - Ireland	**Bayer Limited** The Atrium Blackthorn Road Dublin 18 Ireland	Gadovist 1.0 mmol/ml Solution for Injection in prefilled cartridge	1.0 mmol/ml	solution for injection, in prefilled cartridge	intravenous use
IE - Ireland	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam Netherlands	Prohance 279.3 mg/ml Solution for Injection, 5 ml vial	279.3 mg/ml	solution for injection	intravenous use
IE - Ireland	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam Netherlands	Prohance 279.3 mg/ml Solution for Injection, 10 ml vial	279.3 mg/ml	solution for injection	intravenous use
IE - Ireland	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam Netherlands	Prohance 279.3 mg/ml Solution for Injection, 15 ml vial	279.3 mg/ml	solution for injection	intravenous use
IE - Ireland	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam	Prohance 279.3 mg/ml Solution for Injection, 20 ml vial	279.3 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Netherlands				
IE - Ireland	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem 279.32mg/ml Solution for Injection, glass pre-filled syringes	279.32 mg/ml	solution for injection	intravenous use
IE - Ireland	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem 279.32mg/ml Solution for Injection, glass vials	279.32 mg/ml	solution for injection	intravenous use
IE - Ireland	**Bracco SpA** Via Egidio Folli 50 I-20134 Milan Italy	Multihance 0.5 M solution for injection	529 mg/ml	solution for injection	intravenous use
IE - Ireland	**Bracco SpA** Via Egidio Folli 50 I-20134 Milan Italy	Multihance 529 mg/ml solution for injection in prefiled syringe	529 mg/ml	solution for injection in prefilled syringe	intravenous use
IE - Ireland	**Insights Agents GmbH** Ringstrasse 19B D-69115 Heidelberg Germany	Magnegita 500 micromol/ml solution for injection	500 mmol/ml	solution for injection	intravenous use
IE - Ireland	**Bayer Limited** The Atrium Blackthorn Road Dublin 18 Ireland	Magnevist 0.5 mmol/ml Solution for Injection	0.5 mmol/ml	solution for injection	intravenous use
IE - Ireland	**Bayer Limited** The Atrium Blackthorn Road Dublin 18 Ireland	Magnevist 0.5mmol/ml Solution for Injection in pre-filled syringe.	0.5 mmol/ml	solution for Injection in pre-filled syringe	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
IS - Iceland	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Magnevist	469 mg/ml	solution for injection	intravenous use
IS - Iceland	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Magnevist	469 mg/ml	solution for injection, prefilled syringe	intravenous use
IS - Iceland	**GE Healthcare AS** Nycoveien 1-2 4220 Nydalen, Oslo N-0401 Norway	Omniscan	0,5 mmol/ml	solution for injection	intravenous use
IS – Iceland	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Gadovist	1,0 mmol/ml	Solution for injection	Intravenous use
IT - Italy	**Bayer Schering Pharma AG** Müllerstrasse 170-178, DE-13342 Berlin-Wedding Germany	Magnevist	469 mg/ml	solution for injection	intravenous use
IT - Italy	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem	0,5 mmol/ml	solution for injection	intravenous use
IT - Italy	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem	0,0025 mmol/ml	solution for injection	intravenous use
IT - Italy	**GE Healthcare** Via Galeno 36, 20126 Milano	Omniscan	287 mg/ml (0,5 mmol/ml)	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Italy				
IT - Italy	**Bracco Imaging Italia** Via Egidio Folli, 50 20134 Milano Italy	ProHance	279,3 mg/ml (0.5 M)	solution for infusion	intravenous use
IT - Italy	**Bracco Imaging Italia** Via Egidio Folli, 50 20134 Milano Italy	MultiHance	334 mg/ml (0,5 M)	solution for injection	intravenous use
IT - Italy	**Bayer SpA** Viale Certosa, 130 20156 Milano Italy	Gadovist	604.72 mg/ml	solution for injection	intravenous use
IT - Italy	**Bayer SpA** Viale Certosa, 130 20156 Milano Italy	Primovist	0,25 mmol/ml	solution for injection	intravenous use
LT - Lithuania	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13353 Berlin Germany	Gadovist	1 mmol/ml	solution for injection (pre- filled syringe)	intravenous use
LT - Lithuania	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13353 Berlin Germany	Primovist	0,25 mmol/ml	solution for injection	intravenous use
LT - Lithuania	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13353 Berlin Germany	Primovist	0,25 mmol/ml	solution for injection (pre-filled syringe)	intravenous use
LT - Lithuania	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13353 Berlin	Magnevist	0,5 mmol/ml	solution for injection/infusion	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Germany				
LT - Lithuania	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Magnegita	500 micromol/ml	solution for injection	intravenous use
LT - Lithuania	**GE Healthcare AS** Nycoveien 1-2 P.O. Box 4220 Nydalen, Oslo N-0401 Norway	Omniscan	0,5 mmol/ml	solution for injection	intravenous use
LU - Luxembourg	**Codali S.A.** Avenue Henri Dunant 31 1140 Bruxelles Belgium	DOTAREM	37,7G	solution for injection	intravenous use
LU - Luxembourg	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	GADOPENTETATE INSIGHT	469MG/ML	solution for injection	intravenous use
LU - Luxembourg	**Bayer SA-NV** J.E. Mommaertslaan 14 1831 Diegem Belgium	GADOVIST 1	604,72mg	solution for injection	intravenous use
LU - Luxembourg	**Bayer SA-NV** J.E. Mommaertslaan 14 1831 Diegem Belgium	GADOVIST PFS-1	604,72mg /1ml	solution for injection	intravenous use
LU - Luxembourg	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	MAGNEGITA	78,63 MG/1ML	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
LU - Luxembourg	**Bayer SA-NV** J.E. Mommaertslaan 14 1831 Diegem Belgium	MAGNEVIST	4,69G/10 ML	solution for injection	intravenous use
LU - Luxembourg	**Bracco IMAGING Deutschland GmbH** Max-Stromeyer-Str. 116 D-78467 Konstanz Germany	MULTIHANCE	529mg/1 ml	solution for injection	intravenous use
LU - Luxembourg	**GE HEALTHCARE BVBA** Koutervelstraat 20 1831 DIEGEM Belgium	OMNISCAN	287MG/1 ML	solution for injection	intravenous use
LU - Luxembourg	**Bracco IMAGING Deutschland GmbH** Max-Stromeyer-Str. 116 D-78467 Konstanz Germany	PROHANCE	279,3MG/1 ML	solution for injection	intravenous use
LV - Latvia	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Gadovist 1,0 mmol/ml solution for injections	1,0 mmol/ml	solution for injection	intravenous use
LV - Latvia	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Magnegita 500 micromol/ml solution for injection	500 micromol/ml	solution for injection	intravenous use
LV - Latvia	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Magnevist 0,5 mmol/ml solution for injection	0,5 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
LV - Latvia	**GE Healthcare AS** Nycoveien 1-2, 4220 Nydalen, Oslo N-0401 Norway	Omniscan 0,5 mmmol/ml solution for injection	0,5 mmol/ml	solution for injection	intravenous use
LV - Latvia	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Primovist 0,25 mmol/ ml solution for injection	0,25 mmol/ml	solution for injection	intravenous use
LV - Latvia	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Primovist 0,25 mmol/ ml solution for injection pre-filled syringe	0,25 mmol/ml	Solution for injection, pre-filled syringe	intravenous use
MT - Malta	**GE Healthcare AS** Nycoveien 1-2, 4220 Nydalen, Oslo N-0401 Norway	Omniscan	0.5mMol/ml (287 mg equiv. 0.5 mmol)	solution for injection	intravenous use
MT - Malta	**Bayer plc** Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA UK	Magnevist	469.01 mg	Solution for injection	intravenous use
MT - Malta	**Bayer plc** Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA UK	Primovist	PFS 0.25 mmol/ml	Solution for injection, prefilled syringe	intravenous use
NL - Netherlands	**Guerbet Nederland B.V**. Avelingen-West 3A 4202 MS GORINCHEM Netherlands	Dotarem	0,5 mmol/ml	solution for injection	intravenous use
NL - Netherlands	**Bayer B.V**. Energieweg 1 3641 RT MIJDRECHT Netherlands	Gadovisit	1,0 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
NL - Netherlands	**Bayer B.V**. Energieweg 1 3641 RT MIJDRECHT Netherlands	Magnevist	0,5 mmol/ml	solution for injection	intravenous use
NL - Netherlands	**Bracco IMAGING Deutschland GmbH** Max-Stromeyer-Str. 116 D-78467 Konstanz Germany	Multihance	0,5 mmol/ml	solution for injection	intravenous use
NL - Netherlands	**GE Healthcare B.V**. Cygne Centre De Rondom 8 5612 AP EINDHOVEN Netherlands	Omniscan	0,5 mmol/ml	solution for injection	intravenous use
NL - Netherlands	**Bayer B.V**. Energieweg 1 3641 RT MIJDRECHT Netherlands	Primovist	0,25 mmol/ml	solution for injection	intravenous use
NL - Netherlands	**Bracco IMAGING Deutschland GmbH** Max-Stromeyer-Str. 116 D-78467 Konstanz Germany	Prohance	0,5 mmol/ml	solution for injection	intravenous use
NL - Netherlands	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Magnegita	0,5 mmol/ml	solution for injection	intravenous use
NL - Netherlands	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Gadopentetate Insight	0,5 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
NO - Norway	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem	279,3 mg/ml	solution for injection	intravenous use
NO - Norway	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Magnevist	469 mg/ml	solution for injection	intravenous use
NO - Norway	**Bracco S.p.A.** Via Emilio Folli, 50 20134 Milano Italy	MultiHance	334 mg/ml	solution for injection	intravenous use
NO - Norway	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Primovist	0,25 mmol/ml	solution for injection	intravenous use
NO - Norway	**Bracco International B.V** Strawinskylaan 3051 NL-1077 ZX Amsterdam Netherlands	Prohance	279,3 mg/ml	solution for injection	intravenous use
NO - Norway	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Gadovist	1 mmol/ml	solution for injection	intravenous use
NO - Norway	**GE Healthcare AS** Nycoveien 1-2 4220 Nydalen, Oslo N-0401 Norway	Omniscan	0,5 mmol/ml	solution for injection	intravenous use
PL - Poland	**GE Healthcare AS** Nycoveien 1-2 P.O. Box 4220 Nydalen,	Omniscan	0,5 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Oslo NO-0401 Norway				
PL - Poland	**Bracco Imaging Deutschland GmbH** Max-Stromeyer-Str. 116 D-78467 Konstanz Germany	ProHance	279,3 mg/ml	solution for injection	intravenous use
PL - Poland	**Bayer Schering Pharma AG** D-13342 Berlin Germany	Gadovist 1,0	604,72 mg/ml	solution for injection	intravenous use
PL - Poland	**Bayer Schering Pharma AG** D-13342 Berlin Germany	Magnevist	469 mg/ml	solution for injection	intravenous use
PL - Poland	**Bracco ALTANA Pharma GmbH** Max-Stromeyer-Str. 116 78467 Konstanz Germany	Multihance	529 mg/ml	solution for injection	intravenous use
PL - Poland	**Bayer Schering Pharma AG** D-13342 Berlin Germany	Primovist	0,25 mmol/ml	solution for injection	intravenous use
PT - Portugal	**Bayer Portugal S.A.** Rua Quinta do Pinheiro, 5 2794-003 Carnaxide Portugal	Primovist	0.25 mmol/ml	solution for injection	intravenous use
PT - Portugal	**Bayer Portugal S.A.** Rua Quinta Pinheiro, 5, 2794-003 Carnaxide Portugal	Primovist	0.25 mmol/ml	solution for injection (pre-filled syringe)	intravenous use
PT - Portugal	**Lusal - Produção Químico-Farmacêutica Luso-Alemã Lda.** Rua Quinta Pinheiro, 5, Outurela 2794-003 Carnaxide	Gadovist	1 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Portugal				
PT - Portugal	**Lusal - Produção Químico-Farmacêutica Luso-Alemã Lda.** Rua Quinta Pinheiro, 5, Outurela 2794-003 Carnaxide Portugal	Gadovist	1 mmol/ml	solution for injection (pre-filled syringe)	intravenous use
PT - Portugal	**A. Martins & Fernandes S.A.** Rua Raúl Mesnier du Ponsard, 4 B 1750-243 Lisboa Portugal	Dotarem	377 mg/ml	solution for injection	intravenous use
PT - Portugal	**Satis-Radioisótopos e Protecções Contra Sobretensões Eléctricas Unipessoal** Lda. Edifício Ramazzotti, Av. do Forte, n.º 6 - 6A, 2790-502 Carnaxide Portugal	Omniscan	287 mg/ml	solution for injection	intravenous use
RO - Romania	**Bracco S.p.A.** Via Egidio Folli, 50 20134 Milano Italy	MULTIHANCE 0,5M	0.529 g (0.334 g +0.195g)/ml	solution for injection	intravenous use
RO - Romania	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13342 Berlin- Germany	MAGNEVIST	469,01 mg/ml	solution for injection	intravenous use
RO-Romania	**INSIGHT AGENTS GmbH** Ringstrasse. 19B 69115 Heidelberg Germany	MAGNEGITA 500 micromol/ml, soluție injectabilă	500 micromol/ml (469,01 mg/ml)	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
RO - Romania	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml soluție injectabilă în seringă preumplută	27.932 g/ml	solution for injection, pre-filled syringe	intravenous use
RO - Romania	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml soluție injectabilă unidoză	27.932 g/ml	solution for injection	intravenous use
RO - Romania	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	DOTAREM 0,5 mmol/ml soluție injectabilă multidoză	27.932 g/ml	solution for injection	intravenous use
RO - Romania	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13342 Berlin- Germany	PRIMOVIST 0,25 mmol/ml, soluție injectabilă în seringă preumplută	181,430 mg/ml	solution for injection, pre-filled syringe	intravenous use
RO - Romania	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13342 Berlin- Germany	GADOVIST 1,0 mmol/ml,soluție injectabilă	604,720 mg/ml	solution for injection	intravenous use
RO - Romania	**GE Healthcare AS** Nycoveien 1-2 P.O. Box 4220 Nydalen, N-0401 Oslo Norway	OMNISCAN, soluție injectabilă	287,000 mg/ml	solution for injection	intravenous use
SE - Sweden	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13342 Berlin-Wedding Germany	Magnevist	0,5 mmol/m	solution for injection	intravenous use
SE - Sweden	**Bracco SpA** Via Egidio Folli 50 I-20134 Milan	Multihance	334 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Italy				
SE - Sweden	**Bracco SpA** Via Egidio. Folli 50 I-20134 Milan Italy	Multihance	334 mg/ml	solution for injection, pre-filled syringe	intravenous use
SE - Sweden	**Bracco International BV** Stravinskylaan 3051 NL-1077 ZX Amsterdam The Netherlands	Prohance	279,3 mg/ml	solution for injection	intravenous use
SE - Sweden	**GE Healthcare AS** P.O.Box 4220 Nydalen N-0401 Oslo Norway	Omniscan	0,5 mmol/ml	solution for injection	intravenous use
SE - Sweden	**GE Healthcare AS** P.O.Box 4220 Nydalen N-0401 Oslo Norway	Omniscan	0,5 mmol/ml	solution for injection, pre-filled syringe	intravenous use
SE - Sweden	**Bayer Schering Pharma AG,** Müllerstrasse 178 DE-133 42 Berlin Germany	Primovist	0,25 mmol/ml	solution for injection	intravenous use
SE - Sweden	**Bayer Schering Pharma AG,** Müllerstrasse 178 DE-133 42 Berlin Germany	Primovist	0,25 mmol/ml	solution for injection, pre-filled syringe	intravenous use
SE - Sweden	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem	279,3 mg/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
SE - Sweden	**Bayer Schering Pharma AG** Müllerstrasse 178, DE-13342 Berlin-Wedding Germany	Gadovist	1,0 mmol/ml	solution for injection	intravenous use
SE - Sweden	**Bayer Schering Pharma AG** Müllerstrasse 178, DE-13342 Berlin-Wedding Germany	Gadovist	1,0 mmol/ml	solution for injection, pre-filled syringe	intravenous use
SE - Sweden	**Insight Agents GmbH** Ringstr.19 B D-69115 Heidelberg Germany	Magnegita	500 mikromol/ml	solution for injection	intravenous use
SE - Sweden	**Insight Agents GmbH** Ringstr.19 B D-69115 Heidelberg Germany	Gadopentetsyrad imegluminat Insight	500 mikromol/ml	solution for injection	intravenous use
SE - Sweden	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13342 Berlin-Wedding Germany	Magnograf	0,5 mmol/ml	solution for injection	intravenous use
SE - Sweden	**Bayer Schering Pharma AG** Müllerstrasse 178 DE-13342 Berlin-Wedding Germany	Magnograf	0,5 mmol/ml	solution for injection pre-filled syringe	intravenous use
SI - Slovenia	**Higieia d.o.o**. Zastopstva in trgovina, Blatnica 10, 1236 Trzin, Slovenia	Omniscan 0,5 mmol/ml raztopina za injiciranje	0,5 mmol/ml	solution for injection	intravenous use
SI - Slovenia	**Insight Agents GmbH** Ringstr. 19 B D-69115 Heidelberg Germany	Magnetita 500 mikromolov/ml raztopina za injiciranje	500 micromol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
SI - Slovenia	**Bayer Schering Pharma AG** Müllerstrasse 170-178 DE-13342 Berlin-Wedding Germany	Magnevist	0,5 mmol/ml	solution for injection	intravenous use
SI - Slovenia	**Auremiana** izvozno uvozno trgovsko podjetje, d.o.o., Sežana, Partizanska 109, 6210 Sežana	Multihance 0,5 mmol/ml raztopina za injiciranje	334 mg/ml	solution for injection	intravenous use
SI - Slovenia	**Emporio Medical** d.o.o., Prešernova 5, 1000 Ljubljana, Slovenia	Dotarem 0,5mmol/ml raztopina za injiciranje	27,93 g/ml	solution for injection	intravenous use
SI - Slovenia	**Bayer Schering Pharma AG** Müllerstrasse 170-178, DE-13342 Berlin-Wedding Germany	Gadovist 1,0 mmol/ml raztopina za injiciranje	1,0 mmol/ml	solution for injection	intravenous use
SI - Slovenia	**Bayer Schering Pharma AG** Müllerstrasse 170-178, DE-13342 Berlin-Wedding Germany	Primovist 0,25 mmol/ml raztopina za injiciranje v napolnjeni injekcijski brizgi	0,25 mmol/ml	solution for injection	intravenous use
SK - Slovakia	**Bayer Schering Pharma AG** Müllerstrasse 170-178, DE-13342 Berlin-Wedding Germany	Gadovist 1,0 mmol/ ml	604,72 mg/ml	solution for injection	intravenous use
SK - Slovakia	**GE Healthcare AS** Nycoveien 1-2, 4220 Nydalen, Oslo N-0401 Norway	OMNISCAN	0,5 mmol/ml	solution for injection	intravenous use
SK - Slovakia	**Bayer Schering Pharma AG** Müllerstrasse 170-178, DE-13342 Berlin-Wedding Germany	Primovist 0,25 mmol/ ml, injekčný roztok	0,25 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
SK - Slovakia	**Bracco IMAGING Deutschland GmbH** Max-Stromexer-Str. 116 D-78467 Konstanz Germany	PROHANCE	279,3 mg/ml	solution for injection	intravenous use
SK - Slovakia	**Bayer Schering Pharma AG** Müllerstrasse 170-178, DE-13342 Berlin-Wedding Germany	Magnevist	469 mg/ml	solution for injection	intravenous use
UK - United Kingdom	**GE Healthcare AS** Nycoveien 1-2, 4220 Nydalen, Oslo N-0401 Norway	Omniscan injection	0.5 mmol/ml and 0.5 mmol/litre	solution for injection	intravenous use
UK - United Kingdom	**Bayer plc** Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA UK	Magnevist	0.5 mmol/ml	solution for injection	intravenous use
UK - United Kingdom	**Bracco S.p.A.** Via Emilio Folli, 50 20134 Milano Italy	Multihance	0.5 M/ml	solution for injection	intravenous use
UK - United Kingdom	**Bayer plc** Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA UK	Primovist solution for injection	0.25 mmol/ml	solution for injection	intravenous use
UK - United Kingdom	**Bracco International B.V.,** Strawinskylaan 3051 Amsterdam 107 zx Netherlands	Prohance	0.5 M/ml	solution for injection	intravenous use
UK - United Kingdom	**Bayer plc** Bayer House, Strawberry Hill, Newbury,	Gadovist	1.0 mmol/ml	solution for injection	intravenous use

Member State	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical Form	Route of Administration
	Berkshire, RG14 1JA UK				
UK - United Kingdom	**GUERBET** BP 57400 95943 Roissy Charles de Gaulle Cedex France	Dotarem solution for injection	0.5 mmol/ml	solution for injection	intravenous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE EUROPEAN MEDICINES AGENCY

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF GADOLINIUM-CONTAINING CONTRAST AGENTS (see Annex I)

The gadolinium-containing contrast agents (GdCAs) – gadoversetamide, gadodiamide, gadopentetic acid, gadobenic acid, gadofosveset, gadoxetic acid, gadoteridol, gadobutrol and gadoteric acid - are intravenous agents used for contrast enhancement with magnetic resonance imaging (MRI) and with magnetic resonance angiography (MRA). The GdCAs are available for different types of MR scan varying from product to product, including liver, brain and whole body scan.

GdCAs have been associated with nephrogenic systemic fibrosis (NSF), a rare, serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with severe renal impairment. GdCAs were first associated with nephrogenic systemic fibrosis (NSF) in January 2006 when five end-stage renal failure patients undergoing MRA developed signs of NSF two to four weeks after GdCAs administration. This followed a cluster of 25 cases of NSF (20 in Denmark and 5 in Austria) in patients with severe renal impairment, to whom gadodiamide had been administered. Since June 2006 there have been reports of NSF associated with other GdCAs and this issue has been subject to close regulatory reviews leading to risk minimisation measures at the national level.

On 6 November 2008 Denmark asked the CHMP, under Article 31 of Directive 2001/83/EC, to give its opinion on whether the marketing authorisations for GdCAs should be varied in relation to its use in special patient's population more at risk to develop nephrogenic systemic fibrosis (NSF). On 19 November 2008, the European Commission triggered the corresponding procedure under Article 20 of Council Regulation (EC) 726/2004, for GdCAs which are centrally authorised (gadoversetamide and gadofosveset).

The CHMP reviewed all the information made available by the Marketing Authorisation Holders.

The estimated relative risk for NSF calculated based on the number of unconfounded cases and GdCA is higher for gadodiamide (100%), gadoversetamide (94%), and gadopentetic acid (10%) and <1% for gadoteridol and gadoteric acid. No relative risk was estimated for the other GdCAs as their usage is too low.

All GdCAs are chelate complexes containing Gd^{3+}, the highly toxic gadolinium ion, which potentially may be released through transmetallation *in vivo*. The extent of transmetallation differs significantly between the complexes with the linear chelates more likely to release Gd^{3+} than the cyclical chelates where the gadolinium ion is caged in a cavity. Other factors such as renal impairment would likely increase the toxicity of the complexes by slowing the clearance of Gd^{3+}.

Based on the above the CHMP recognised that there are different categories of NSF-risk for GdCAs:

High risk:
a) *Linear non-ionic chelates* including gadoversetamide (OptiMARK) and gadodiamide (Omniscan).
b) *Linear ionic chelate:* gadopentetic acid (Magnevist, Gado-MRT-ratiopharm, Magnegita).

Medium risk:
Linear ionic chelates including gadofosveset (Vasovist), gadoxetic acid (Primovist) and gadobenic acid (MultiHance).

Low risk:
Macrocyclic chelates including gadoteric acid (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist).

The CHMP recognises that within the high risk group the risk of NSF with gadodiamide and gadoversetamide appears higher than with gadopentetic acid based on physicochemical properties, studies in animals and the number of cases of NSF reported. However as the risk with gadopentetic acid remains substantially higher than the NSF risk with the other lower risk contrast agents, the CHMP recommended that gadopentetic acid should be retained in the high risk group and be subject to the same risk minimisation measures.

In order to minimise the recognised risk associated with GdCAs and the development of NSF, the CHMP agreed on the following measures for the following at risk patient groups:

Use during pregnancy and lactation
Use during pregnancy is not recommended for any GdCA due to the possibility of gadolinium accumulation in human tissues. Although only small amounts of gadolinium are excreted into human breast milk, the immaturity of foetal kidneys could delay the excretion of gadolinium leading to the possibility of long-term accumulation of gadolinium in tissues. Discontinuation of breast feeding for at least 24 h is therefore recommended for all patients receiving high NSF-risk GdCAs. For all other GdCAs the continuation or suspension of breast feeding is left to the discretion of the mother in consultation with the doctor.

Renally impaired patients and haemodialysis
The use of high risk GdCAs is contraindicated in patients with severe renal impairment. Strong warnings are included in the GdCAs of medium and low NSF risk as regards use in patients with severe renal impairment but subject to dose restriction to a minimum during a scan and with a minimum 7 day interval between administrations.

For patients with moderate renal impairment, since the risk is unknown for the high risk category of GdCAs it was agreed that use should only be considered after careful consideration of the benefit-risk, subject to dose restriction to not more than one injection of the minimum dose during a scan with a minimum 7 day interval between administrations.

There is no evidence that supports the use of haemodialysis for preventing or treating NSF in patients not already undergoing haemodialysis, but this may be useful at removing GdCAs in patients already on haemodialysis. This information is reflected in all GdCAs' product information.

Liver transplant patients
Patients undergoing liver transplantation are at particular risk of NSF if exposed to GdCAs particularly to the high-risk GdCAs. Therefore the use of high-risk GdCAs is contraindicated in this population. Strong warnings are included for medium and low NSF risk GdCAs as regards use in this particular special population. However, if use is necessary then dose restrictions to a minimum dose during one scan with a minimum 7 day interval between administrations are recommended.

Paediatric patients
The use of the high risk category of GdCAs in neonates up to 4 weeks of age is contra-indicated. The use of medium and low risk GdCAs in neonates should only be considered after careful consideration subject to dose and interval administration restrictions.

Due to the immature renal function of infants below 1 year of age the use of all GdCAs should be subject to careful consideration and to dose and interval administration restrictions to not more than one injection of the minimum dose during a scan with a minimum 7 day interval between dose administrations.

Elderly patients
No dose adjustments are recommended but screening of 65 years and older patients for renal dysfunction is of particular importance prior to the administration of GdCAs.

Other precautionary measures

Screening for renal dysfunction

For all patients to whom high NSF risk GdCAs will be administered, mandatory screening for renal dysfunction by laboratory tests is required. This screening is recommended for all patients who will receive medium and low NSF-risk GdCAs. Laboratory tests are more effective to assess the renal function of all at-risk patients, since changes in renal function are often not reflected symptomatically or clinically.

In addition to the minimisation measures included in the product information, the CHMP having considered the evidence that toxic free gadolinium ions are retained in human tissues concluded that studies evaluating the potential for long-term retention of gadolinium in bone are needed. Therefore, the MAHs are requested to submit to the CHMP protocols and timelines for the studies of gadolinium accumulation in human bone within 3 months of the decision on this referral procedure. The testing of bone samples from patients undergoing hip and knee replacement surgery is recommended. Co-factors that may increase the risk of NSF such as serum calcium and phosphate levels at the time of administration of a GdCA should be studied and biomarkers evaluated.

In addition, the MAHs should submit a cumulative review on NSF cases annually for 3 consecutive years commencing one year after the decision on this referral procedure.

The need to have a harmonised traceability method across Europe for effective monitoring of the use of GdCAs was agreed. The use of "sticky labels" detachable from the vials and syringes are considered an appropriate method to be implemented for all GdCAs.

The MAH for Omniscan (gadodiamide) disagreed with the proposed labelling warnings with respect to screening patients for renal dysfunction and requested a re-examination of the opinion.

The MAH supported the CHMP proposed risk minimisation for all patients to be screened for renal dysfunction irrespectively of the GdCAs. However, screening should only require laboratory testing following evaluation of the patient's medical history and the minimisation measure should be the same for all GdCAs.

Having considered the detailed grounds for re-examination provided by the MAH in writing, the CHMP agrees that medical history could identify some patients with possible renal dysfunction. However, medical history alone could not be relied on, as it will not be sufficient to identify all at-risk patients. Laboratory tests are more effective to assess the renal function of all at-risk patients, since changes in renal function are often not reflected symptomatically or clinically. Encouraging appropriate testing of renal function should ensure identification of patients at risk and ensure use of appropriate diagnostic agents.

This risk minimisation was applied in accordance with the three different categories of NSF-risk for GdCAs recognised by the CHMP based on their thermodynamic and kinetic properties. Therefore and considering the overall benefit/risk, the CHMP agreed that for all patients to be administered with high NSF-risk GdCAs mandatory screening by laboratory tests should be performed.

Based on the above, the CHMP concluded that its Opinion of 19 November 2009 should be maintained with the recommended amendments to relevant sections of the Summary of Product Characteristics and Package Leaflet as set out in Annex III to the opinion.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for gadolinium containing contrast agents (GdCAs) initiated by Denmark.

- The Committee assessed the grounds for re-examination submitted by the MAH of Omniscan (gadodiamide) on 25 January 2010 and the scientific discussion within the Committee;

- The Committee considered all the available data submitted on the safety of the gadolinium containing contrast agents, in relation to the risk of NSF.

- The Committee, concluded that gadolinium contrast agents are associated with NSF and that the risk is increased in renal impaired patients, liver transplant patients, the paediatric population, during pregnancy and lactation and in the elderly.
  The CHMP also recognised that according to their risk for NSF, GdCAs can be classified in 3 risk categories: high, medium and low risk.

- The CHMP concluded that the Product Information of all GdCAs should include safety information to minimise the risk of NSF and therefore recommended the amendments to the relevant sections of the Summaries of Product Characteristics and Package Leaflets in accordance to the risk category.
  Furthermore, Risk Minimisation Measures on the traceability as well as the long-term effects of these products in Europe are recommended.

As a consequence, the CHMP has recommended the maintenance of the Marketing Authorisations for the medicinal products referred to in Annex I for which the amendments to the relevant sections of the Summary of Product Characteristics and Package Leaflet are set out in Annex III and in accordance to the conditions set out in Annex IV.

ANNEX III

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR HIGH RISK GADOLINIUM-CONTAINING CONTRAST AGENTS
(gadodiamide, gadopentetic acid)

4.2 Posology and method of administration

[*Use currently approved text with the addition of guidance for special populations (patients with renal impairment, neonates, infants and the elderly*)]

Special Populations

Renal impairment

{Invented name} is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period (see section 4.3). {Invented name} should only be used after careful risk/benefit evaluation in patients with moderate renal impairment (GFR 30-59 ml/min/1.73m^2) at a dose not exceeding {x} mmol/kg body weight (see section 4.4). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

[*If use is permitted in neonates and infants, add a statement on use in neonates and infants*]

Neonates up to 4 weeks of age and infants up to 1 year of age

{Invented name} is contraindicated in neonates up to 4 weeks of age (see section 4.3).
Due to immature renal function in infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

[*If use is restricted by age for a particular indication add a statement on use in neonates and infants and specify the indication and age at which use is not recommended*]

Neonates up to 4 weeks of age, infants up to 1 year of age and children
{Invented name} is contraindicated in neonates up to 4 weeks of age (see section 4.3).
Due to immature renal function in infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

Use for whole body MRI is not recommended in children less than 6 months of age.

[*If use is restricted for use in children greater than 1 year of age, specify the indication and age at which use is not recommended*]

Neonates up to 4 weeks of age, infants up to 1 year of age and children

{Invented name} is contraindicated in neonates up to 4 weeks of age (see section 4.3).Use of {Invented name} is not recommended in children less than 2 years of age.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

4.3 Contraindications

[*Use currently approved text with addition of contraindication below*]

{Invented name} is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m^2), in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age (see section 4.4).

4.4 Special warnings and precautions for use

[*With the exception of information on impaired renal function, use in neonates and infants and use in the elderly, use currently approved text*]

Impaired renal function

Prior to administration of {Invented name}, all patients should be screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of {Invented name} and some other gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore {Invented name} must not be used in patients with severe renal impairment, in patients in the perioperative liver transplantation period and in neonates (see section 4.3).

The risk for development of NSF in patients with moderate renal impairment (GFR 30–59 ml/min/1.73 m^2) is unknown, therefore, {Invented name} should be only used after careful risk-benefit evaluation in patients with moderate renal impairment.

Haemodialysis shortly after {Invented name} administration may be useful at removing {Invented name} from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

[*If use is not authorised for infants below the age of 1 year a statement in section 4.4 is not necessary. If use is authorised in neonates and infants add the following statement*]

Neonates and infants

{Invented name} is contraindicated in neonates up to 4 weeks of age (see section 4.3). Due to immature renal function in infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration.

[*If use is only authorised in infants above the age of 6 months add the following statement*]

Infants

Due to immature renal function in infants up to 1 year of age, {Invented name} should only be used in patients 6 to 12 months of age after careful consideration.

Elderly

As the renal clearance of {active substance} may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

4.6 Pregnancy and lactation

Pregnancy

[*Amend currently approved text for data in pregnant women and animal studies in line with the CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (24 July 2008)*]

There are no data from the use of {active substance} in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). {Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.
or
There are no data from the use of {active substance} in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3).{Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

Lactation

[*Amend currently approved text for data in lactating women and animal studies in line with the CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (24 July 2008)*]

It is unknown whether {active substance} is excreted in human milk. There is insufficient information on the excretion of {active substance} in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of {Invented name}.
or
It is unknown whether {active substance} is excreted in human milk. Available data in animals have shown excretion of {active substance} in milk (for details see section 5.3). A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of {Invented name}.

4.8 Undesirable effects

Cases of nephrogenic systemic fibrosis (NSF) have been reported with {Invented name} (see section 4.4).

4.9 Overdose

[*Use currently approved text with the addition of haemodialysis wording*]

{Invented name} can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

6.6 Special precautions for disposal and other handling

[*Use currently approved text for information on disposal*]

The peel-off tracking label on the {vials/syringes/bottles} should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be

recorded.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SECTIONS OF THE PACKAGE LEAFLET FOR HIGH RISK GADOLINIUM-CONTAINING CONTRAST AGENTS
(gadodiamide, gadopentetic acid)

2. BEFORE YOU ARE GIVEN {Invented name}

Take special care with {Invented name}:
[*Use currently approved text with addition of the information on the NSF*]

You should not be given {Invented name} if you suffer from severe kidney problems, or if you are a patient who is about to have or has recently had a liver transplant, as use of {Invented name} in patients with these conditions has been associated with a disease called nephrogenic systemic fibrosis (NSF). NSF is a disease involving thickening of the skin and connective tissues. NSF may result in severe joint immobility, muscle weakness or may affect the normal working of internal organs which may potentially be life threatening.
{Invented name} should also not be given to newborn babies up to age of 4 weeks.

Tell your doctor if:
[*Use currently approved text*]

- your kidneys do not work properly
- you have recently had, or soon expect to have, a liver transplant

[*Use currently approved text with the addition of information on impaired renal function*]

Before you receive {Invented name}, you will need to have a blood test to check how well your kidneys are working.

[*Use currently approved text with the addition of information on use in neonates and infants]*

[*If use is authorised in infants add the following statement*]

{Invented name} should not be used in newborn babies up to the age of 4 weeks. As kidney function is immature in infants up to 1 year of age, {Invented name} will only be used in infants after careful consideration by the doctor.

[*If use is only authorised in infants above the age of 6 months add the following statement*]

{Invented name} should not be used in newborn babies up to the age of 4 weeks. As kidney function is immature in infants up to 1 year of age, {Invented name} will only be used in patients 6 to 12 months of age after careful consideration by the doctor.

[*If use is not authorised in children under 2 years add the following statement*]

{Invented name} should not be used in newborn babies up to the age of 4 weeks and is not recommended in children under 2 years.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

Pregnancy
You must tell your doctor if you think you are or might become pregnant as {Invented name} should not be used during pregnancy unless strictly necessary.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Breast-feeding should be discontinued for at least 24 hours after you receive {Invented name}.

3. HOW TO USE {Invented name}

Dosage in special patient groups
[*Use currently approved text with the addition of information on impaired renal function, use in neonates and infants and use in the elderly*

than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

Due to immature renal function in infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days. {Invented name} should not be given to newborn babies up to age of 4 weeks.

As the renal clearance of {active substance} may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Haemodialysis shortly after {Invented name} administration may be useful at removing {Invented name} from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

{Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

Breast-feeding should be discontinued for at least 24 hours after the administration of {Invented name}.

The peel-off tracking label on the {vials/syringes/bottles} should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR MEDIUM RISK GADOLINIUM-CONTAINING CONTRAST AGENTS
(gadoxetic acid, gadobenic acid)

4.2 Posology and method of administration

[*Use currently approved text with the addition of guidance for special populations (patients with renal impairment, neonates, infants and the elderly)]*

Special Populations

Impaired renal function

Use of {Invented name} should be avoided in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If use of {Invented name} cannot be avoided, the dose should not exceed {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

[*If use is permitted in neonates and infants add a statement on use in neonates and infants*]

Neonates up to 4 weeks of age and infants up to 1 year of age

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

[*If use is restricted by age for a particular indication, add a statement on use in neonates and infants and specify the indication and age at which use is not recommended*]

Neonates up to 4 weeks of age, infants up to 1 year of age and children

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

Use for whole body MRI is not recommended in children less than 6 months of age.

[*If use is restricted for use in children greater than 1 year of age, specify the indication and age for which use is not recommended*]

Neonates up to 4 weeks of age, infants up to 1 year of age and children

Use of {Invented name} is not recommended in children less than 2 years of age.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

4.4 Special warnings and precautions for use

[*With the exception of information on impaired renal function, use in neonates and infants and use in the elderly, use currently approved text*]

Impaired renal function

Prior to administration of {Invented name}, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with {Invented name}, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after {Invented name} administration may be useful at removing {Invented name} from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

[*If use is not authorised for infants below the age of 1 year a statement in section 4.4 is not necessary. If use is authorised in neonates and infants add the following statement*]

Neonates and infants

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration.

[*If use is only authorised in infants above the age of 6 months add the following statement*]

Infants

Due to immature renal function in infants up to 1 year of age, {Invented name} should only be used in patients 6 to 12 months of age after careful consideration.

Elderly

As the renal clearance of {active substance} may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

4.6 Pregnancy and lactation

Pregnancy

[*Amend currently approved text for data in pregnant women and animal studies in line with the CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (24 July 2008)]*

There are no data from the use of {active substance} in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). {Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

or

There are no data from the use of {active substance} in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3). {Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

Lactation

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of {Invented name}, should be at the discretion of the doctor and lactating mother.

4.8 Undesirable effects

[*Use currently approved text with the addition of information on NSF*]

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with {Invented name} (see section 4.4).

or

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with {Invented name}, most of which were in patients co-administered other gadolinium-containing contrast agents (see section 4.4).

or

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with {Invented name} in patients co-administered other gadolinium-containing contrast agents (see section 4.4).

or

Cases of nephrogenic systemic fibrosis (NSF) have been reported with other gadolinium-containing contrast agents (see section 4.4).

4.9 Overdose

[*Use currently approved text with the addition of haemodialysis wording*]

{Invented name} can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

6.6 Special precautions for disposal and other handling

[*Use currently approved text for information on disposal*]

The peel-off tracking label on the {vials/syringes/bottles} should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SECTIONS OF THE PACKAGE LEAFLET FOR MEDIUM RISK GADOLINIUM-CONTAINING CONTRAST AGENTS
(gadoxetic acid, gadobenic acid)

2. BEFORE YOU ARE GIVEN {Invented name}

Take special care with {Invented name}:
[*Use currently approved text with the addition of information on impaired renal function, use in neonates and infants and use in the elderly*]

Tell your doctor if:
- your kidneys do not work properly
- you have recently had, or soon expect to have, a liver transplant

[*The following statement should be added*]

Your doctor may decide to take a blood test to check how well your kidneys are working before making the decision to use {Invented name}, especially if you are 65 years of age or older.

[*If use is not authorised in neonates and infants add the following statement*]

The safety of {Invented name} in persons under 18 years has not yet been tested.

[*If use is authorised in neonates and infants add the following statement*]

Neonates and infants
As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, {Invented name} will only be used in these patients after careful consideration by the doctor.

[*If use is only authorised in infants above the age of 6 months add the following statement*]

Infants
As kidney function is immature in infants up to 1 year of age, {Invented name} will only be used in patients 6 to 12 months of age after careful consideration by the doctor.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine.

Pregnancy
You must tell your doctor if you think you are or might become pregnant as {Invented name} should not be used during pregnancy unless strictly necessary.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Your doctor will discuss whether you should continue breast-feeding or interrupt breast-feeding for a period of 24 hours after you receive {Invented name}.

3. HOW TO USE {Invented name}

Dosage in special patient groups
[*Use currently approved text with the addition of information on impaired renal function, use in neonates and infants and use in the elderly*]

The use of {Invented name} is not recommended in patients with severe kidney problems and patients who have recently had, or soon expect to have, a liver transplant. However if use is required you should only receive one dose of {Invented name} during a scan and you should not receive a second injection for at least 7 days.

Neonates, infants, children and adolescents
[*If use is permitted in neonates and infants add a statement on use in neonates and infants*]

As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, {Invented name} will only be used in these patients after careful consideration by the doctor. Neonates and infants should only receive one dose of {Invented name} during a scan and should not receive a second injection for at least 7 days.

[*If use is restricted for use in children greater than 1 year of age, specify the indication and age for which use is not recommended*]

Use of {Invented name} is not recommended in children less than 2 years of age.

[*If use is restricted by age for a particular indication, add a statement on use in neonates and infants and specify the indication and age at which use is not recommended*]

Use for whole body MRI is not recommended in children less than 6 months of age.

Elderly
It is not necessary to adjust your dose if you are 65 years of age or older but you may have a blood test to check how well your kidneys are working.

4. POSSIBLE SIDE EFFECTS
[*Use currently approved text with the addition of information on NSF*]

There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs).
or
There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs) most of which were in patients who received {Invented name} together with other gadolinium-containing contrast agents.
or
There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs) in patients who received {Invented name} together with other gadolinium-containing contrast agents.
or
There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs) associated with use of other gadolinium-containing contrast agents.

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The following information is intended for medical or healthcare professionals only:

[*Use currently approved text with the addition of information on NSF*]

Prior to administration of {Invented name}, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR< 30ml/min /1.73 m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with {Invented name}, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI. If use of {Invented name} cannot be avoided, the dose should not exceed {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

As the renal clearance of {active substance} may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Haemodialysis shortly after {Invented name} administration may be useful at removing {Invented name} from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

{Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

Continuing breast feeding or discontinuing {Invented name} for a period of 24 hours after administration, should be at the discretion of the doctor and lactating mother.

The peel-off tracking label on the {vials/syringes/bottles} should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR LOW RISK GADOLINIUM-CONTAINING CONTRAST AGENTS
(gadoteric acid, gadoteridol, gadobutrol)

4.2 Posology and method of administration

[*Use currently approved text with the addition of guidance for special populations (patients with renal impairment, neonates, infants and the elderly)*]

Special Populations

Impaired renal function

{Invented name} should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use {Invented name}, the dose should not exceed {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

[*If use is permitted in neonates and infants add a statement on use in neonates and infants*]

Neonates up to 4 weeks of age and infants up to 1 year of age

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

[*If use is restricted by age for a particular indication add a statement on use in neonates and infants and specify the indication and age at which use is not recommended*]

Neonates up to 4 weeks of age, infants up to 1 year of age and children

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {X} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

Use for whole body MRI is not recommended in children less than 6 months of age.

[*If use is restricted for use in children greater than 1 year of age specify the indication and age at which use is not recommended*]

Neonates up to 4 weeks of age, infants up to 1 year of age and children

Use of {Invented name} is not recommended in children less than 2 years of age.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

4.4 Special warnings and precautions for use

[*With the exception of information on impaired renal function, use in neonates and infants and use in the elderly, use currently approved text*]

Impaired renal function

Prior to administration of {Invented name}, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with {Invented name}, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after {Invented name} administration may be useful at removing {Invented name} from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

[*If use is not authorised for infants below the age of 1 year a statement in section 4.4 is not necessary. If use is authorised in neonates and infants add the following statement*]

Neonates and infants

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration.

[*If use is only authorised in infants above the age of 6 months add the following statement*]

Infants

Due to immature renal function in infants up to 1 year of age, {Invented name} should only be used in patients 6 to 12 months of age after careful consideration.

Elderly

As the renal clearance of {active substance} may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

4.6 Pregnancy and lactation

Pregnancy

[*Amend currently approved text for data in pregnant women and animal studies in line with the CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (24 July 2008)*]

There are no data from the use of {active substance} in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). {Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

or

There are no data from the use of {active substance} in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3). {Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

Lactation

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of {Invented name}, should be at the discretion of the doctor and lactating mother.

4.8 Undesirable effects

[*Use currently approved text with the addition of information on NSF*]

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with {Invented name} (see section 4.4).
or
Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with {Invented name}, most of which were in patients co-administered other gadolinium-containing contrast agents (see section 4.4).
or
Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with {Invented name} in patients co-administered other gadolinium-containing contrast agents (see section 4.4).
or
Cases of nephrogenic systemic fibrosis (NSF) have been reported with other gadolinium-containing contrast agents (see section 4.4).

4.9 Overdose

[*Use currently approved text with the addition of haemodialysis wording*]

{Invented name} can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

6.6 Special precautions for disposal and other handling

[*Use currently approved text for information on disposal*]

The peel-off tracking label on the {vials/syringes/bottles} should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SECTIONS OF THE PACKAGE LEAFLET FOR LOW RISK GADOLINIUM-CONTAINING CONTRAST AGENTS
(gadoteric acid, gadoteridol, gadobutrol)

2. BEFORE YOU ARE GIVEN {Invented name}

Take special care with {Invented name}:
[*Use currently approved text with the addition of information on impaired renal function, use in neonates and infants and use in the elderly*]

Tell your doctor if:
- your kidneys do not work properly
-

The use of {Invented name} is not recommended in patients with severe kidney problems and patients who have recently had, or soon expect to have, a liver transplant. However if use is required you should only receive one dose of {Invented name} during a scan and you should not receive a second injection for at least 7 days.

Neonates, infants, children and adolescents
[*If use is permitted in neonates and infants add a statement on use in neonates and infants*]

As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, {Invented name} will only be used in these patients after careful consideration by the doctor. Neonates and infants should only receive one dose of {Invented name} during a scan and should not receive a second injection for at least 7 days.

[*If use is restricted for use in children greater than 1 year of age, specify the indication and age for which use is not recommended*]

Use of {Invented name} is not recommended in children less than 2 years of age.

[*If use is restricted by age for a particular indication, add a statement on use in neonates and infants and specify the indication and age at which use is not recommended*]

Use for whole body MRI is not recommended in children less than 6 months of age.

Elderly
It is not necessary to adjust your dose if you are 65 years of age or older but you may have a blood test to check how well your kidneys are working.

4. POSSIBLE SIDE EFFECTS
[*Use currently approved text with the addition of information on NSF*]

There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs).
or
There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs) most of which were in patients who received {Invented name} together with other gadolinium-containing contrast agents.
or
There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs) in patients who received {Invented name} together with other gadolinium-containing contrast agents.
or
There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs) associated with use of other gadolinium-containing contrast agents.

<----------

The following information is intended for medical or healthcare professionals only:

[*Use currently approved text with the addition of information on NSF*]

Prior to administration of {Invented name}, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR< 30ml/min /1.73 m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with {Invented name}, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI. If it is necessary to use {Invented name}, the dose should not exceed {x} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, {Invented name} should only be used in these patients after careful consideration at a dose not exceeding {X} mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {Invented name} injections should not be repeated unless the interval between injections is at least 7 days.

As the renal clearance of {active substance} may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Haemodialysis shortly after {Invented name} administration may be useful at removing {Invented name} from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

{Invented name} should not be used during pregnancy unless the clinical condition of the woman requires use of {active substance}.

Continuing breast feeding or discontinuing {Invented name} for a period of 24 hours after administration, should be at the discretion of the doctor and lactating mother.

The peel-off tracking label on the {vials/syringes/bottles} should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

CONDITIONS OF THE MARKETING AUTHORISATIONS

Annual cumulative safety review

The MAHs should provide to the CHMP an annual cumulative review on nephrogenic systemic fibrosis (NSF) cases commencing one year after Commission Decision and for 3 consecutive years.

Long-term effects study

The MAHs should submit to the CHMP protocols and timelines for studies evaluating the potential for long-term accumulation of gadolinium in human bone. Co-factors that may increase the risk of NSF such as serum calcium and phosphate levels at the time of administration of GdCA should be studies and biomarkers evaluated. The testing of bone samples from patients undergoing hip and knee replacement surgery is recommended. This should be submitted to the CHMP within 3 months of the Commission Decision on this Referral procedure.

Communication

National Competent Authorities should ensure that prescribers will be informed of the measures agreed by CHMP to minimise the risk of NSF. The communication should be based on the "key message document" agreed by CHMP.

Other Minimisation Measures

In order to have a harmonised traceability method across Europe for the effective monitoring of the use of GdCAs the National Competent Authorities, coordinated by the Reference Member State (where applicable) should ensure the implementation by the MAHs of detachable ("sticky") labels on the vials and syringes of the GdCAs.