The European Agency for the Evaluation of Medicinal Products

London, 07 October 2002
EMEA/CPMP/24844/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

OPINION FOLLOWING AN ARTICLE 31 REFERRAL

CISAPRIDE

International Non-Proprietary Name (INN): **Cisapride**

BACKGROUND INFORMATION

Cisapride is a prokinetic active substance belonging to the pharmacotherapeutic group of propulsives.

It has been authorised nationally in the EU Member States for the treatment of a variety of motility-related gastrointestinal disorders since 1988.

On 29 June 2000, Germany presented a referral to the EMEA under Article 31 of Directive 2001/83/EC (previously Article 12 of Council Directive 75/319/EEC). Germany considered that the use of cisapride containing medicinal products raised concerns as it might exert a substantial QT-prolonging action leading to potentially life-threatening cardiac arrythmia.

The Marketing Authorisation Holders provided written explanations by 4 September 2000, and supplementary information by 5 March 2001, 02 July 2001, 24 September 2001 and 23 November 2001. Oral explanations were given by the Marketing Authorisation Holders on 25 April 2001 and 13 November 2001.

Upon consideration of all available data, the CPMP adopted an opinion on 13 December 2001. This opinion recommended the maintenance of the Marketing Authorisations for cisapride containing medicinal products listed in Annex I but restricting the use of these medicinal products, with subsequent amendments to the Summary of Product Characteristics (SPC) set out in Annex III. It should be noted however, that Marketing Authorisations for Cisapride containing medicinal products could only be maintained, if their SPCs were in line with the amended SPCs, presented in Annex III to the CPMP Opinion on Cisapride. As a consequence, the Cisapride Marketing Authorisations for 30 mg suppositories and 20 mg tablets, dispersible tablets, oral lyophilisate and lozenges, listed in Annex I to the Opinion, which are not in line with the CPMP recommendation on the use of Cisapride as reflected in the amended SPCs cannot be maintained, as they concern a different pharmaceutical form or a different strength.
In addition, the opinion contains certain conditions set out in Annex IV such as inclusion of treated patients in either a clinical trial, a safety study or a registry program, to be applied to Marketing Authorisations for cisapride containing medicinal products.

The list of product names concerned is given in the Annex I. The scientific conclusions are provided in the Annex II, together with the amended Summary of Product Characteristics in the Annex III and the conditions of the marketing authorisations in the Annex IV.

On the basis of the CPMP Opinion, the European Commission issued a Decision on 30 May 2002.

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ANNEX I

LIST OF THE NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDERS, STRENGTHS, PHARMACEUTICAL FORMS, ROUTE OF ADMINISTRATION, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

CISAPRIDE CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN THE EUROPEAN UNION

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
AUSTRIA	Janssen-Cilag Pharma GmbH Pfarrg. 75 A-1232 Wien Austria	Prepulsid 1 mg/ml - orale suspension	1 mg/ml	oral suspension	oral use	bottle	100 ml
AUSTRIA	Janssen-Cilag Pharma GmbH Pfarrg. 75 A-1232 Wien Austria	Prepulsid 1 mg/ml - orale suspension	1 mg/ml	oral suspension	oral use	sachet	20 sachets of 5 ml 50 sachets of 5 ml 20 sachets of 10 ml 50 sachets of 10 ml
AUSTRIA	Janssen-Cilag Pharma GmbH Pfarrg. 75 A-1232 Wien Austria	Prepulsid 5 mg Tabletten	5 mg	tablet	oral use	blister	10 20 30 50
AUSTRIA	Janssen-Cilag Pharma GmbH Pfarrg. 75 A-1232 Wien Austria	Prepulsid 10 mg Tabletten	10 mg	tablet	oral use	blister	10 20 30 50
AUSTRIA	Janssen-Cilag Pharma GmbH Pfarrg. 75 A-1232 Wien Austria	Prepulsid 20 mg Tabletten	20 mg	tablet	oral use	blister	20
BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	5 mg	tablet	oral use	strip	30 UD
BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	1 mg/ml	oral suspension (Adults)	oral use	bottle	100 ml

BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	1 mg/ml	oral suspension	oral use	sachet	20 sachets of 5 ml
BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	10 mg	tablet	oral use	strip	100
BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	20 mg	tablet	oral use	strip	50 100 U.D.
BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	10 mg	effervescent tablet	oral use		20 100
BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	1 mg/ml	oral suspension (paediatric)	oral use	bottle	100 ml
BELGIUM	Janssen-Cilag n.v. Roderveldlaan B-2600 Berchem Belgium	Prepulsid	1 mg/ml	oral suspension	oral use	sachet	50 sachets of 10 ml
DENMARK	Janssen-Cilag A/S Postboks 149 Hammerbakken 19 3460 Birkerød Denmark	Prepulsid	1 mg/ml	oral solution	oral use	Bottle (glass)	200 ml
DENMARK	Janssen-Cilag A/S Postboks 149 Hammerbakken 19 3460 Birkerød Denmark	Prepulsid	10 mg	tablet	oral use	blister PVC-PE-PVDC/ ALU	50 100

DENMARK	Janssen-Cilag A/S Postboks 149 Hammerbakken 19 3460 Birkerød Denmark	Prepulsid	20 mg	tablet	oral use	blister PVC-PE-PVDC/ ALU	50 100
DENMARK	Janssen-Cilag A/S Postboks 149 Hammerbakken 19 3460 Birkerød Denmark	Prepulsid	10 mg	oral lyophilisate	oral use	blister PVC-PE / ALU	Not applicable since it is not marketed
DENMARK	Janssen-Cilag A/S Postboks 149 Hammerbakken 19 3460 Birkerød Denmark	Prepulsid	20 mg	oral lyophilisate	oral use	blister PVC-PE / ALU	Not applicable since it is not marketed
FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid	5 mg	tablet	oral use	blister ALU/PVC/PVDC	30
FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid	10 mg	tablet	oral use	blister ALU/PVC/PVDC	50 100
FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid	20 mg	tablet	oral use	blister ALU/PVC/PVDC	60
FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid	1 mg/ml	oral suspension	oral use	Bottle (glass)	100 ml 200 ml
FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid	30 mg	suppository	rectal use	PVC/HDPE blister	6

FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid Quicklet	5 mg	oral lyophilisate	oral use	blister aclar/alu	28 56
FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid Quicklet	10 mg	oral lyophilisate	oral use	blister aclar/alu	28 56
FINLAND	Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo Finland	Prepulsid Quicklet	20 mg	oral lyophilisate	oral use	blister aclar/alu	28 56
FRANCE	Janssen -Cilag 1, rue Camille Desmoulins TSA 91003 92787 Issy les Moulineaux Cedex 9 France	Prepulsid 10 mg, comprimé	10 mg	tablet	oral use	PVC/PVDC/ Aluminium/ Polythylene blister	40
FRANCE	Janssen -Cilag 1, rue Camille Desmoulins TSA 91003 92787 Issy les Moulineaux Cedex 9 France	Prepulsid adultes 1 mg/ml suspension buvable en flacon	1 mg/ml	oral suspension	oral use	glass vial	200 ml
FRANCE	Janssen -Cilag 1, rue Camille Desmoulins TSA 91003 92787 Issy les Moulineaux Cedex 9 France	Prepulsid enfants et nourrissons 1 mg/ml suspension buvable en flacon	1 mg/ml	oral suspension	oral use	glass vial	100 ml
FRANCE	Janssen -Cilag 1, rue Camille Desmoulins TSA 91003 92787 Issy les Moulineaux Cedex 9 France	Prepulsid 5 mg/5 ml suspension buvable en sachet	5 mg/5 ml	oral suspension	oral use	sachet paper/alu/ polyethelen/ surlyn	20 40 sachets of 5 ml
FRANCE	Janssen -Cilag 1, rue Camille Desmoulins TSA 91003 92787 Issy les Moulineaux Cedex 9 France	Prepulsid 10 mg/10 ml suspension buvable en sachet	10 mg/10 ml	oral suspension	oral use	sachets paper/alu/ polyethelen/ surlyn	20 40 sachets of 10 ml

GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Alimix	1 mg/ml	oral suspension	oral use	Bottle (amber glass)	100ml, 200ml, 5x100ml (hospital pack), 5x200ml (hospital pack), 100ml (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Alimix 5mg, Tabletten	5 mg	tablet	oral use	PVC-PE-PVDC/Alu blister Alu/Alu blister	100 20 50 200(10x20) (hospital pack) 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Alimix 10mg, Tabletten	10 mg	tablet	oral use	PVC-PE-PVDC/Alu blister Alu/Alu blister	100 20 50 200(10x20) (hospital pack) 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Alimix 20mg, Tabletten	20 mg	tablet	oral use	PVC-PE-PVDC/Alu blister Alu/Alu blister	100 20 50 200(10x20) (hospital pack) 20 (sample pack not for sale)

GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Cisaprid-Janssen 5 mg, Tabletten	5 mg	tablet	oral use	PVC-PE-PVDC/Alu blister Alu/Alu blister	100 20 50 200(10x20) (hospital pack) 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin	1 mg/ml	oral suspension	oral use	Bottle (amber glass)	100ml, 200ml, 5x100ml (hospital pack), 5x200ml (hospital pack), 100ml (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin 5mg, Tabletten	5 mg	tablet	oral use	PVC-PE-PVDC/Alu blister Alu/Alu blister	100 20 50 200(10x20) (hospital pack) 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin 10mg, Tabletten	10 mg	tablet	oral use	PVC-PE-PVDC/Alu blister Alu/Alu blister	100 20 50 200(10x20) (hospital pack) 20 (sample pack not for sale)

GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin 20mg, Tabletten	20 mg	tablet	oral use	PVC-PE-PVDC/Alu blister Alu/Alu blister	100 20 50 200(10x20) (hospital pack) 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin Beutel 5ml	5 mg/5ml	oral suspension	oral use		20X5ml, 50X5ml, 20X5ml (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin Beutel 10ml	10 mg/10ml	oral suspension	oral use		20X10ml 50X10ml, 20X10ml (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin lingual 5 mg, Lutschtabletten	5 mg	lozenge	oral use	Aclar/Alu blister Alu/Alu blister	20 48 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin lingual 10 mg, Lutschtabletten	10 mg	lozenge	oral use	Aclar/Alu blister Alu/Alu blister	20 48 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin lingual 20 mg, Lutschtabletten	20 mg	lozenge	oral use	Aclar/Alu blister Alu/Alu blister	20 48 20 (sample pack not for sale)
GERMANY	Janssen-Cilag Raiffeisenstr. 8 41470 Neuss Germany	Propulsin Lösungstabletten 10mg	10 mg	effervescent tablet	oral use		20

GREECE	Cosmopharm Ltd P.O.Box 42 Korinthos 20100 Greece	Evifix	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Help Ltd 14 Valaoritou Str. 14452 Metamorhosi - Athens Greece	Lirebin	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Help Ltd 14 Valaoritou Str. 14452 Metamorhosi - Athens Greece	Lirebin	5 mg	tablet	oral use	blister	30 500 (10 x 50)
GREECE	Help Ltd 14 Valaoritou Str. 14452 Metamorhosi - Athens Greece	Lirebin	10 mg	tablet	oral use	blister	50 (2x25)
GREECE	Biomedica - Chemica S.A. 25 G. Lyra str. 14564 Kiphisia Greece	Systilan	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Biomedica - Chemica S.A. 25 G. Lyra str. 14564 Kiphisia Greece	Systilan	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Biomedica - Chemica S.A. 25 G. Lyra str. 14564 Kiphisia Greece	Circocric	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Biomedica - Chemica S.A. 25 G. Lyra str. 14564 Kiphisia Greece	Circocric	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Uni-Pharma 14th Km Athens-Lamia 14564 Kifisia – Athens Greece	Oferin	5 mg/5 ml	oral suspension	oral use	bottle	200 ml

GREECE	Uni-Pharma 14th Km Athens-Lamia 14564 Kifisia – Athens Greece	Oferin	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Chrispa 16th Km Marathona 15344 Palini Athens Greece	Bozaxtral	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Janssen-Cilag 56 Irinis Ave. 15121 Perxi - Athens Grece	Alimix	5 mg	tablet	oral use	blister	30
GREECE	Janssen-Cilag 56 Irinis Ave. 15121 Perxi - Athens Greece	Alimix	10 mg	tablet	oral use	blister	50 (2 x 25)
GREECE	Janssen-Cilag 56 Irinis Ave. 15121 Perxi - Athens Greece	Alimix	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Janssen-Cilag 56 Irinis Ave. 15121 Perxi - Athens Greece	Alimix	5 mg/5 ml	oral suspension	oral use	sachet	20 sachets of 5 ml 50 sachets of 5 ml 20 sachets of 10 ml 50 sachets of 10 ml
GREECE	Janssen-Cilag 56 Irinis Ave. 15121 Perxi - Athens Greece	Alimix	30 mg	suppository	rectal use	blister	6
GREECE	Janssen-Cilag 56 Irinis Ave. 15121 Perxi - Athens Greece	Alimix	20 mg	tablet	oral use	blister	60 (3 x 20)

GREECE	Janssen-Cilag 56 Irinis Ave. 15121 Perxi - Athens Greece	Alimix	10 mg	tablet	oral use	blister	20 56
GREECE	Rafarm A.E.B.E. Kapodistriov and 12 Kopinthou Str. GR-15451 N. Psychiko - Athens Greece	Ruvetine	10 mg	tablet	oral use	blister	50 (2 x 25)
GREECE	Rafarm A.E.B.E. Kapodistriov and 12 Kopinthou Str. GR-15451 N. Psychiko - Athens Greece	Ruvetine	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Rafarm A.E.B.E. Kapodistriov and 12 Kopinthou Str. GR-15451 N. Psychiko - Athens Greece	Ruvetine	20 mg	tablet	oral use	blister	60 (3 x 20)
GREECE	Genepharm S.A. 18th Km Athens Marathona Ave. GR-15344 Palini - Attikis Greece	Dolyzinax	5 mg/5 ml	oral suspension	oral use	bottle	150 ml
GREECE	Genepharm S.A. 18th Km Athens Marathona Ave. GR-15344 Palini - Attikis Greece	Dolyzinax	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	BROS Ltd Galinis and 15 Argis Str. 15464 N. Kiphisia Greece	Lamafer	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	BROS Ltd Galinis and 15 Argis Str. 15464 N. Kiphisia Greece	Lamafer	5 mg	tablet	oral use	blister	30 (3 x 10)
GREECE	BROS Ltd Galinis and 15 Argis Str. 15464 N. Kiphisia Greece	Lamafer	10 mg	tablet	oral use	blister	50 (5 x 10)

GREECE	Kleva Ltd 189 Parnithos Ave. GR-13671 Acharnai - Attiki Greece	Kinussen	5 mg	tablet	oral use	blister	30 (3 x 10)
GREECE	Kleva Ltd 189 Parnithos Ave. GR-13671 Acharnai - Attiki GREECE	Kinussen	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Kleva Ltd 189 Parnithos Ave. GR-13671 Acharnai - Attiki Greece	Kinussen	5 mg/5 ml	oral suspension	oral use	bottle	200 ml
GREECE	Kleva Ltd 189 Parnithos Ave. GR-13671 Acharnai - Attiki Greece	Kinussen	20 mg	tablet	oral use	blister	60 (3 x 20)
GREECE	Faran ABEE Achaias and Trizinias 14564 N. Kiphisia - Athens Greece	Cefanyl	5 mg	tablet	oral use	blister	30 (3 x 10)
GREECE	Faran ABEE Achaias and Trizinias 14564 N. Kiphisia - Athens Greece	Cefanyl	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Faran ABEE Achaias and Trizinias 14564 N. Kiphisia - Athens Greece	Cefanyl	5 mg/5 ml	oral suspension	oral use	bottle	200 ml
GREECE	Farmaten Ltd 68 Menanorou Str. 10432 Athens Greece	Nastilox	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Farmaten Ltd 68 Menanorou Str. 10432 Athens Greece	Nastilox	5 mg	tablet	oral use	blister bottle	30 (3 x 10) 250 500 1000

GREECE	Farmaten Ltd 68 Menanorou Str. 10432 Athens Greece	Nastilox	10 mg	tablet	oral use	blister bottle	50 (5 x 10) 250 500 1000
GREECE	Finifarm Ltd 5 Anavritis Str. 11143 Athens Greece	Spabucol	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Finifarm Ltd 5 Anavritis Str. 11143 Athens Greece	Spabucol	5 mg/5 ml	oral suspension	oral use	bottle	200 ml
GREECE	Anfarm Hellas S.A. 442 Acharnon Str. 11143 Athens Greece	Minsk	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Anfarm Hellas S.A. 442 Acharnon Str. 11143 Athens Greece	Minsk	5 mg/5 ml	oral suspension	oral use	bottle	200 ml
GREECE	Elpen S.A. Pharmaceutical Industry 21st Km Marathona Ave. GR-19009 Pikermi - Attiki Greece	Elpegon	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Elpen S.A. Pharmaceutical Industry 21st Km Marathona Ave. GR-19009 Pikermi - Attiki Greece	Elpegon	5 mg	tablet	oral use	blister	30 (3 x 10)
GREECE	Elpen S.A. Pharmaceutical Industry 21st Km Marathona Ave. GR-19009 Pikermi - Attiki Greece	Elpegon	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Remedina ABEE 25 Gounari 13451 Kamatero - Attiki Greece	Zenopar	5 mg	tablet	oral use	blister	30 (3 x 10)

GREECE	Remedina ABEE 25 Gounari 13451 Kamatero - Attiki Greece	Zenopar	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Remedina ABEE 25 Gounari 13451 Kamatero - Attiki Greece	Zenopar	5 mg/5 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Antor Ltd 4 Omirou 15126 Marousi Greece	Cevilor	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Zikides N.G. 45 Victoros Ougo 104 37 Athens Greece	Epasan	5 mg/5 ml	oral suspension	oral use	bottle	200 ml
GREECE	Zikides N.G. 45 Victoros Ougo 104 37 Athens Greece	Epasan	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Hexal Hellas 189 Parnithos Ave. 13671 Athens Greece	Cisapride/ Hexal	5 mg	tablet	oral use	blister	30 (3 x 10)
GREECE	Hexal Hellas 189 Parnithos Ave. 13671 Athens Greece	Cisapride/ Hexal	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Hexal Hellas 189 Parnithos Ave. 13671 Athens Greece	Cisapride/ Hexal	5 mg/5 ml	oral suspension	oral use	bottle	200 ml
GREECE	Medichrom S.A. 26th Km Markopoulou Ave. 19003 Koropi - Attiki Greece	Gastridol	1 mg/1 ml	oral suspension	oral use	bottle	200 ml

GREECE	Medichrom S.A. 26th Km Markopoulou Ave. 19003 Koropi - Attiki Greece	Gastridol	10 mg	tablet	oral use	blister	50 (5 x 10)
GREECE	Komep S.A. Pireos and 64 Aristovoulou Str. 11853 Athens Greece	Saprimix	1 mg/1 ml	oral suspension	oral use	bottle	100 ml 200 ml
GREECE	Komep S.A. Pireos and 64 Aristovoulou Str. 11853 Athens Greece	Saprimix	10 mg	tablet	oral use	blister	50 (5 x 10)
IRELAND	Janssen-Cilag Ltd Saunderton, High Wycombe, Buckinghamshire, HP 14 4HJ, United Kingdom	Prepulsid Suspension	1 mg/ml	oral suspension	oral use	amber glass bottle	200 ml 500 ml
IRELAND	Janssen-Cilag Ltd Saunderton, High Wycombe, Buckinghamshire, HP 14 4HJ, United Kingdom	Prepulsid Paediatric Suspension	1 mg/ml	oral suspension	oral use	amber glass bottle	100 ml
IRELAND	Janssen-Cilag Ltd Saunderton, High Wycombe, Buckinghamshire, HP 14 4HJ, United Kingdom	Prepulsid Tablets 5mg	5 mg	tablet	oral use	ALU/PVC/PE/ PVDC blister	6 10 60 84
IRELAND	Janssen-Cilag Ltd Saunderton, High Wycombe, Buckinghamshire, HP 14 4HJ, United Kingdom	Prepulsid tablets 10mg	10 mg	tablet	oral use	ALU/PVC/PE/ PVDC blister	10 30 60 84 90 100 112 120

ITALY	J.C. Healthcare S.R.L. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Alimix	5mg/5 ml	oral suspension	oral use	sachet	30 sachets of 5 ml
ITALY	J.C. Healthcare S.R.L. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Alimix	10mg/10 ml	oral suspension	oral use	sachet	30 sachets of 10 ml
ITALY	Italchimici SPA Via G. Winckelmann, 2 20146 Milano MI Italy	Cipril	10 mg	tablet	oral use	blister	30
ITALY	Italchimici SPA Via G. Winckelmann, 2 20146 Milano MI Italy	Cipril	1 mg/1 ml	oral suspension	oral use	bottle	100 ml 200 ml
ITALY	Italchimici SPA Via G. Winckelmann, 2 20146 Milano MI Italy	Cipril	10 mg	effervescent granules	oral use	sachet	30
ITALY	Italchimici SPA Via G. Winckelmann, 2 20146 Milano MI Italy	Cipril	5 mg	chewable tablet	oral use		28
ITALY	Italchimici SPA Via G. Winckelmann, 2 20146 Milano MI Italy	Cipril	10 mg	chewable tablet	oral use		28
ITALY	Italchimici SPA Via G. Winckelmann, 2 20146 Milano MI Italy	Cipril	5 mg/5 ml	oral suspension	oral use	sachet	30 sachets of 5 ml
ITALY	Janssen Cilag S.P.A. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Prepulsid	1 mg/1 ml	oral suspension	oral use	bottle	100 ml 200 ml

ITALY	Janssen Cilag S.P.A. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Prepulsid	10 mg	effervescent granules	oral use	sachet	30
ITALY	Janssen Cilag S.P.A. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Prepulsid	5 mg	chewable tablet	oral use	blister	28
ITALY	Janssen Cilag S.P.A. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Prepulsid	10 mg	chewable tablet	oral use	blister	28
ITALY	Janssen Cilag S.P.A. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Prepulsid	5 mg/5 ml	oral suspension	oral use	sachet	30 sachets of 5 ml
ITALY	Janssen Cilag S.P.A. Via Michelangelo Buonarroti, 23 20093 Cologno Monzese MI Italy	Prepulsid	10 mg/10 ml	oral suspension	oral use	sachet	30 sachets of 10 ml
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Cyprid	5 mg	tablet	oral use	strip	20 30
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Cyprid	1 mg/ml	oral solution	oral use	bottle	100 ml
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Cyprid	5 mg/5 ml	oral solution	oral use	sachet	20 sachets of 5 ml
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Cyprid Quicklet	5 mg	tablet	oral use	blister	20

LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid	10 mg	tablet	oral use	strip	40 100
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid	20 mg	tablet	oral use	strip	50 100
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid	1 mg/ml	oral solution	oral use	bottle	100 ml
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid	30 mg	suppository	rectal use	strip	6
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid	10 mg	effervescent tablet	oral use		20 100
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid	10 mg/10 ml	oral solution	oral use	sachet	50 sachets of 10 ml
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid Quicklet	10 mg	tablet	oral use	blister	20 56 100
LUXEMBOURG	Janssen-Cilag n.v. Uitbreidingstraat 2 B-2600 Berchem Belgium	Prepulsid Quicklet	20 mg	tablet	oral use	blister	20 56 100
NETHERLANDS	Janssen-Cilag B.V. Dr. Paul Janssenweg 150 5026 RH Tilburg Netherlands	Prepulsid suspensie voor oraal gebruik 1 mg/ml	1 mg/ml	oral suspension	oral use	bottle	

NETHERLANDS	Janssen-Cilag B.V. Dr. Paul Janssenweg 150 5026 RH Tilburg Netherlands	Prepulsid Tabletten 5 mg	5 mg	tablet	oral use	strip	
NETHERLANDS	Janssen-Cilag B.V. Dr. Paul Janssenweg 150 5026 RH Tilburg Netherlands	Prepulsid Tabletten 10 mg	10 mg	tablet	oral use	strip	
NETHERLANDS	Janssen-Cilag B.V. Dr. Paul Janssenweg 150 5026 RH Tilburg Netherlands	Prepulsid Tabletten 20 mg	20 mg	tablet	oral use	strip	
NETHERLANDS	Janssen-Cilag B.V. Dr. Paul Janssenweg 150 5026 RH Tilburg Netherlands	Prepulsid Zetpillen 30 mg	30 mg	Suppository	rectal use	strip	
PORTUGAL	Laboratório B A Farma, Lda Rua Prof. Sousa da Câmara, nº 207 a 211 Apartado 15087 1074-803 Lisboa Portugal	Ciside	10 mg	tablet	oral use	PVC/aluminium blister	10 60
PORTUGAL	Laboratório B A Farma, Lda Rua Prof. Sousa da Câmara, nº 207 a 211 Apartado 15087 1074-803 Lisboa Portugal	Ciside	1 mg/ml	oral suspension	oral use	amber-coloured glass bottle	200 ml
PORTUGAL	Laboratórios Azevedos - Indústria Farmacêutica, S.A Estrada Nacional 117 2 Alfragide 2724-503 Amadora Portugal	Clotioride	5 mg	tablet	oral use	PVC/aluminium blister	10 60

PORTUGAL	Laboratórios Azevedos - Indústria Farmacêutica, S.A Estrada Nacional 117 2 Alfragide 2724-503 Amadora Portugal	Clotioride	10 mg	tablet	oral use	PVC/aluminium blister	60
PORTUGAL	Laboratórios Azevedos - Indústria Farmacêutica, S.A Estrada Nacional 117 2 Alfragide 2724-503 Amadora Portugal	Clotioride	30 mg	suppository	rectal use	PVC polyethylene alveole	10
PORTUGAL	Laboratórios Azevedos - Indústria Farmacêutica, S.A Estrada Nacional 117 2 Alfragide 2724-503 Amadora Portugal	Clotioride	1 mg/ml	oral suspension	oral use	Amber-coloured glass bottle, PVC/alum. cap	200 ml
PORTUGAL	Labesfal - Laboratórios Almiro, S.A Campo de Besteiros Apartado 7 3465-051 Tondela Portugal	Hagasical	10 mg	tablet	oral use	PVC/aluminium bilster	60
PORTUGAL	Labesfal - Laboratórios Almiro, S.A Campo de Besteiros Apartado 7 3465-051 Tondela Portugal	Hagasical	1 mg/ml	oral suspension	oral use	Amber-coloured glass bottle	200 ml
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	5 mg	tablet	oral use	PVC/PVDC/PE/ Aluminium Blister	10 20 60

PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	10 mg	tablet	oral use	PVC/PVDC/PE/ Aluminium Blister	10 60
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	10 mg	effervescent tablet	oral use	Sachet Aluminium/ Aluminium	20 56
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	10 mg	effervescent granules	oral use	Polyethylene, aluminium and paper sachet	20
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	20 mg	tablet	oral use	PVC/PVDC/PE/ Aluminium Blister	60
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	30 mg	suppository	rectal use	PVC and polyethylene	6
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	1 mg/ml	oral suspension	oral use	Amber-coloured glass bottles	100 ml 200 ml
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	5 mg/5 ml	oral suspension	oral use	Polyethylene/ aluminium/paper/ ionomer sachet	20 and 50 sachets of 5 ml

PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid	10 mg/10 ml	oral suspension	oral use	Polyethylene/ aluminium/paper/ ionomer sachet	20 and 50 sachets of 10 ml
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid Quicklet	5 mg	dispersible tablet	oral use	blister Aclar/Aluminium	16 28 56
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid Quicklet	10 mg	dispersible tablet	oral use	blister Aclar/Aluminium	16 28 56
PORTUGAL	Janssen Farmacêutica Portugal, Lda Estrada Consiglieri Pedroso, 69-a, Queluz de Baixo 2749-503 Barcarena Portugal	Prepulsid Quicklet	20 mg	dispersible tablet	oral use	blister Aclar/Aluminium	16 28 56
SPAIN	Lab. Dr. Esteve S.A. Avda. Mare de Deu de Monserrat, 221 0841 Barcelona Spain	Arcasín	10 mg	tablet	oral use	blister	50
SPAIN	Lab. Dr. Esteve S.A. Avda. Mare de Deu de Monserrat, 221 0841 Barcelona Spain	Arcasín	10 mg/10 ml	oral suspension	oral use	sachet (paper)	50
SPAIN	Lab. Dr. Esteve S.A. Avda. Mare de Deu de Monserrat, 221 0841 Barcelona Spain	Arcasín	20 mg	tablet	oral use	blister	30

SPAIN	Lab. Dr. Esteve S.A. Avda. Mare de Deu de Monserrat, 221 0841 Barcelona Spain	Arcasín	1 mg/1 ml	oral suspension	oral use	bottle	100 ml 200 ml
SPAIN	Lab. Dr. Esteve S.A. Avda. Mare de Deu de Monserrat, 221 0841 Barcelona Spain	Arcasín	5 mg	tablet	oral use	blister	30 60
SPAIN	S.A.L.V.A.T., S.A. Gall, 30-36 08950 Esplugues de Llobregat Barcelona Spain	Fisiogastrol	10 mg	tablet	oral use	PVC/AL blister	50 500
SPAIN	S.A.L.V.A.T., S.A. Gall, 30-36 08950 Esplugues de llobregat Barcelona Spain	Fisiogastrol	10 mg/10 ml	oral suspension	oral use	sachet	50 500
SPAIN	S.A.L.V.A.T., S.A. Gall, 30-36 08950 Esplugues de Llobregat Barcelona Spain	Fisiogastrol	1 mg/1 ml	oral suspension	oral use	bottle	100 ml 200 ml
SPAIN	S.A.L.V.A.T., S.A. Gall, 30-36 08950 Esplugues de Llobregat Barcelona Spain	Fisiogastrol	5 mg	tablet	oral use	PVC/AL blister	30 60 500
SPAIN	Quimifar, S.A. Comandran, 37 08210 Barcelona Spain	Kelosal	10 mg	tablet	oral use	PVC/PVDC/AL blister	50
SPAIN	Quimifar, S.A. Comandran, 37 08210 Barcelona Spain	Kelosal	5 mg	tablet	oral use	PVC/PVDC/AL blister	30 60

SPAIN	Quimifar, S.A. Comandran, 37 08210 Barcelona Spain	Kelosal	1 mg/1 ml	oral suspension	oral use	bottle (glass)	100 ml 200 ml
SPAIN	Janssen Cilag, S.A. Paseo de las doce estrellas, 5-7 28042 Madrid Spain	Prepulsid	10 mg	tablet	oral use	blister	50
SPAIN	Janssen Cilag, S.A. Paseo de las doce estrellas, 5-7 28042 Madrid Spain	Prepulsid	10 mg/10 ml	oral suspension	oral use	sachet	50
SPAIN	Janssen Cilag, S.A. Paseo de las doce estrellas, 5-7 28042 Madrid Spain	Prepulsid	20 mg	tablet	oral use	blister	30
SPAIN	Janssen Cilag, S.A. Paseo de las doce estrellas, 5-7 28042 Madrid Spain	Prepulsid	1 mg/1 ml	oral suspension	oral use	bottle (plastic)	100 ml 200 ml
SPAIN	Janssen Cilag, S.A. Paseo de las doce estrellas, 5-7 28042 Madrid Spain	Prepulsid	5 mg	tablet	oral use	blister	30 60
SWEDEN	Janssen Cilag AB Rotebergsvägen 1 Box 7073 SE-19207 Sollentuna Sweden	Prepulsid	10 mg	tablet	oral use	PVC/ALU blister	50 100 250 100 (single dose package)
SWEDEN	Janssen Cilag AB Rotebergsvägen 1 Box 7073 SE-19207 Sollentuna Sweden	Prepulsid	20 mg	tablet	oral use	PVC/ALU blister	100

SWEDEN	Janssen Cilag AB Rotebergsvägen 1 Box 7073 SE-19207 Sollentuna Sweden	Prepulsid	1 mg/ml	oral suspension	oral use	bottle (glass)	200 ml
UNITED KINGDOM	Janssen-Cilag Limited Saunderton High Wycombe Bucks HP14 4HJ	Prepulsid Tablets	5mg	tablet	oral use	ALU/PE/PVC/ PVDC blister	6 10 60 84
UNITED KINGDOM	Janssen-Cilag Limited Saunderton High Wycombe Bucks HP14 4HJ	Prepulsid Tablets	10 mg	tablet	oral use	ALU/PE/PVC/ PVDC blister	10 30 60 84 90 100 112 120
UNITED KINGDOM	Janssen-Cilag Limited Saunderton High Wycombe Bucks HP14 4HJ	Prepulsid Suspension 1 mg/ml	1mg/ml	oral suspension	oral use	bottle (glass)	200ml 500ml
UNITED KINGDOM	Janssen-Cilag Limited Saunderton High Wycombe Bucks HP14 4HJ	Prepulsid Quicklet Tablets	5 mg	quicklet tablet	oral use	ALU/aclar foil blister	8 16 28 56 120
UNITED KINGDOM	Janssen-Cilag Limited Saunderton High Wycombe Bucks HP14 4HJ	Prepulsid Quicklet Tablets	10 mg	quicklet tablet	oral use	ALU/aclar foil blister	8 16 28 56 120
UNITED KINGDOM	Janssen-Cilag Limited Saunderton High Wycombe Bucks HP14 4HJ	Prepulsid Quicklet Tablets	20 mg	quicklet tablet	oral use	ALU/aclar foil blister	8 16 28 56 120

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE MARKETING AUTHORISATIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CISAPRIDE CONTAINING MEDICINAL PRODUCTS

Cisapride is a prokinetic drug that has been authorised in the EU Member States (MS) for use in the treatment of motility-related gastrointestinal disorders since 1988. The indications for which cisapride has been approved vary within the MS and include gastro-esophageal reflux disease (GERD) in adults and children, gastroparesis, functional dyspepsia, intestinal pseudo-obstruction and constipation.

In the last five years, concerns have been raised upon reports of serious QT prolongation, ventricular arrhythmias, including *Torsade de Pointes (TdP),* with fatalities and sudden death, in patients taking cisapride. Taking this into account, the cardiac risk associated with cisapride, including the risk factors for such cardiac adverse reactions, was discussed by the CPMP Pharmacovigilance Working Party (PhVWP) since 1997. As a consequence, the Summary of Product Characteristics (SPC) of cisapride containing medicinal products has been nationally amended in several EU Member States. Other measures, such as Dear Doctor Letters and educational programmes, have also been taken by MS.

On 3 May 2000, a CPMP Ad Hoc Expert Group on cisapride took place with the aim to review the risks and the benefits of cisapride in the light of increasing concern about safety in relation to prolongation of the QT interval and reports of serious and fatal cardiac arrhythmias, and regulatory actions taken by non-EU countries. In view of the above and of the availability of other effective alternatives, the CPMP Ad Hoc Expert Group recommended the restriction of the therapeutic indications for cisapride. Further to this, different decisions were taken by the MS with regard to cisapride containing medicinal products: indications were restricted in Austria, Belgium, Finland, France, Greece, Italy, The Netherlands, Portugal, Spain and Sweden and Marketing Authorisations (MA) have been temporarily suspended by Germany, Luxembourg and the UK.

On 29 June 2000, Germany triggered a referral for cisapride containing medicinal products under Article 12 of Council Directive 75/319/EEC, as amended, requesting the CPMP to give an opinion on which therapeutic indications cisapride containing medicinal products were still justified. Germany considered that the use of cisapride containing medicinal products raised concerns as it might exert a substantial QT-prolonging action leading to potentially life-threatening cardiac arrythmia.

OVERVIEW OF EFFICACY

A discussion on the efficacy of cisapride containing medicinal products took place in CPMP based on the Rapporteur's and Co-Rapporteurs' Assessment Reports and the data presented by the MAHs. Considerations made on this issue are summarised below.

EFFICACY OF CISAPRIDE IN ADULT INDICATIONS

GASTRO-OESOPHAGEAL REFLUX DISEASE (GERD)

<u>HEALING OF REFLUX ESOPHAGITIS AND SYMPTOMATIC RELIEF OF GERD</u>

Several published and unpublished studies regarding the use of cisapride in this indication, including placebo controlled studies (in low, high and standard doses) and active comparator controlled studies, were assessed by the CPMP.

The active comparator studies assessed by CPMP included studies comparing cisapride with H2-antagonists, studies comparing cisapride with proton-pump inhibitors (PPIs) and studies comparing cisapride with other prokinetics. Further to the assessment of these studies the following conclusions were drawn by the CPMP:

- Regarding the studies comparing cisapride with H2-antagonists, none of the small to medium size study showed a statistically significant difference between cisapride and cimetidine or ranitidine, respectively.

- Regarding the studies comparing cisapride with PPIs, the studies considered showed that cisapride is undoubtedly less effective concerning the improvement of GERD symptoms in comparison to PPIs.
- Regarding the studies comparing cisapride with other prokinetics, no conclusion could be drawn from the assessed studies as neither of the comparators used (domperidone or metoclopramide) can be considered as reliable therapeutic agents in the treatment of GERD

In addition, a meta-analysis of cisapride, omeprazole and ranitidine in the treatment of GERD, published in 1998 by Iskedijan was also analysed. This meta-analysis provides some evidence in favour of cisapride in the treatment of GERD. However, the CPMP considered that the meaningfulness of this meta-analysis is restricted as there are inconsistencies on the results, a response in the studies was not evaluated to placebo and there were more studies of cisapride that were not included.

Other studies including studies of cisapride in patients poorly responsive to other therapies were also presented by the MAHs. It was concluded that these studies were very heterogeneous in their inclusion criteria, comparator drugs and sample sizes. No study was submitted including patients with treatment failure after therapy with the therapeutic standard - PPIs. Therefore, no conclusion can be drawn from these studies.

Studies of cisapride as add-on therapy to PPIs and H2-blockers were also considered. From the available data studies where cisapride was used in a dose of 40 mg daily as add-on therapy to H2-blockers in patients with GERD, positive results were presented. However, H2-blocker/cisapride combination therapy is still inferior to other therapeutic alternatives such as PPI-therapy. From the available studies involving cisapride as add-on therapy to PPIs no statistically significant difference could be found for the add-on therapy group in comparison to monotherapy.

In conclusion, considering the above-mentioned data, cisapride as monotherapy in the treatment of GERD lacks therapeutic efficacy: a substantial number of negative trials are documented and the number of patients corresponding to trials with a positive response in comparison to placebo is similar the one corresponding to trials which failed to show statistically significant differences. Equivalence to H2-blockers has not been shown. Treatment of GERD with cisapride is clearly inferior to therapy with PPIs and the superior efficacy of an add-on therapy to PPIs has not been proven.
Therefore, according to the available data, the indication gastro-esophageal reflux disease is not justified due to a lack of a demonstrated efficacy. Furthermore cisapride presents a sufficiently documented risk that needs to be taken into account and other equivalent or superior therapeutic alternatives are available.

PREVENTION OF RELAPSE OF REFLUX ESOPHAGITIS

From the available placebo controlled studies, efficacy of cisapride in comparison to placebo to prevent relapse of reflux esophagitis or symptomatic relapse of GERD has not been proven. In addition, active comparator studies were assessed but their value is not clear and did not support the efficacy of cisapride in this indication.
The meta-analysis by Iskedijan (1998) concerning the prevention of relapse was also assessed. The results seem in favour of cisapride (being superior to ranitidine). However, the CPMP noted that only the studies with positive results and the smallest of the negative trials were included. Therefore, the CPMP considered this meta-analysis unreliable.

Considering the above, cisapride lacks efficacy in the prevention of relapse of reflux esophagitis.

GASTROPARESIS

Regarding gastroparesis, the available data on the use of cisapride has been reviewed by the CPMP.

Concerning the treatment of diabetic gastroparesis, several placebo-controlled and comparator-controlled (vs metoclopramide, domperidone or erythromycine) studies were assessed. In short-term comparative studies in diabetic gastroparesis the results of cisapride are comparable to domperidone, erythromycin and metoclopramide on gastric emptying and symptom scores. The CPMP concluded that, even though the available data were limited (small populations), cisapride has a place in the treatment of acute diabetic gastroparesis.

The effects of cisapride on patients with idiopathic gastroparesis were also assessed on the basis of a small number of studies. Even though no significant improvement of symptoms with cisapride in comparison to placebo has been clearly demonstrated, there is some evidence that cisapride may result in accelerated gastric emptying. Corinaldesi et al (1987) evaluated patients with chronic idiopathic dyspepsia and gastroparesis. Cisapride produced an acceleration of gastric emptying in some patients and the authors calculated a statistical significance. Other unpublished studies showed similar results (gastric emptying shorter with cisapride than placebo).

With regard to the effects of cisapride on patients with 'other causes of gastroparesis', the available data were obtained from small numbers of patients and did not reveal any superiority over placebo or included heterogenous populations. Therefore, these data cannot demonstrate the efficacy of cisapride in such conditions. Some meta-analysis involving patients with gastroparesis of different causes were also evaluated by the CPMP but their meaningfulness was considered very restricted.

In conclusion, despite the fact that the available data give some arguments in favour of the efficacy of cisapride in the treatment of diabetic and idiopathic gastroparesis, the CPMP considered that there were still concerns regarding the efficacy of cisapride in such conditions and therefore agreed to further restrict the indications (Section 4.1 of the SPC) as follows:

"Treatment of acute and severe exacerbation of demonstrated chronic idiopathic or diabetic gastroparesis after failure of other treatment options."

This indication was accepted by the MAHs which provided oral explanations in November 2001 CPMP.

In addition, the CPMP considered that there is a need to perform clinical trials to better define the efficacy of cisapride in the above-mentioned restricted indications. The protocols for such clinical trials in adults suffering from gastroparesis should be in accordance to the following recommendations:

- Population defined by the SPC therapeutic indication;
- Placebo controlled randomised design. The study should not include an enrichment design;
- Symptomatic evaluation as primary endpoint and supportive physiopathological secondary endpoints.

Proposals for such trials were received from some MAHs and are further addressed under the section "Overall Conclusion on benefit/risk".

FUNCTIONAL DYSPEPSIA (FD)

The CPMP assessed a significant number of clinical trials in the use of cisapride in FD. However, most studies were of small sample size or insufficient duration of treatment and had an inappropriate methodology. This is especially relevant for the use of low-dose cisapride. The efficacy of cisapride in a dose of 10 mg tid over placebo in the treatment of FD has not been proven in studies complying with accepted standards.

As there is no established comparator substance in the treatment of functional dyspepsia, no conclusions can be drawn from controlled studies comparing cisapride with alternative treatments. For this reason also meta-analyses in functional dyspepsia are not relevant. Reliable alternative drug treatments for this indication do not exist. However, considering the lack of evidence for efficacy, the nature of the disease, and taking into consideration the documented risk, the indication functional dyspepsia is not justified for cisapride containing medicinal products.

INTESTINAL PSEUDO-OBSTRUCTION (IPO)

ACUTE INTESTINAL PSEUDO-OBSTRUCTION (AIPO)

Several placebo-controlled studies were revised for AIPO. These studies do not show that cisapride is effective in this condition for the following reasons:

- None of the studies had a "lege artis" confirmatory approach and thus had very small sample sizes.
- All the studies investigated endpoints of unknown clinical relevance and were definitely not validated (gastrointestinal motility, effect on nasogastric intubation).
- Higher oral dosages of cisapride (i.e. 20 mg q.i.d.) could not show superiority over placebo (Loick et al. 1995).
- The "largest" most recent study (Brown et al. 1999) which indicated that cisapride could have an advantage over placebo regarding time of hospitalisation, used a high dose of oral cisapride (20 mg q.i.d.) which is not approved. Furthermore, the results of the study were not adjusted for multiple statistical testing and thus, the finding of a statistically significant difference is of hypothetical value only.

Therefore, from the available data cisapride containing medicinal products lack efficacy in the treatment of patients with acute intestinal pseudo-obstruction.

CHRONIC INTESTINAL PSEUDO-OBSTRUCTION (CIPO)

The placebo-controlled studies evaluated for CIPO do not show that cisapride is superior to placebo in patients with chronic intestinal pseudo-obstruction. Therefore, the CPMP concluded that cisapride is not effective in this therapeutic indication.

CONSTIPATION

Several randomised controlled studies for chronic functional constipation were presented by the MAHs and considered by CPMP, but only three of these comprised at least 15 patients per treatment group. These studies included 140 patients who received cisapride in doses of 10 mg to 40 mg per day. These studies showed that cisapride has an activity in patients with functional constipation, but a proof according to current accepted diagnostic criteria has not been established.

In addition, there were two clinical studies for constipation predominant IBS comprising at least 15 patients per treatment group taken into account by the CPMP. These two studies evaluated 51 patients who administered cisapride in doses of 7,5 mg to 30 mg per day. The results of the other available studies were not consistent and therefore cannot contribute to show the efficacy of cisapride. In conclusion, in the two above-mentioned studies cisapride showed an activity in patients with constipation predominant IBS, but a proof according to current accepted diagnostic criteria has not been established.

A few randomised controlled studies in neurologically induced chronic constipation each only comprising less than 11 patients per treatment group were analysed by the CPMP. These studies provide a tendency to effectiveness of cisapride in patients with chronic constipation caused by neurologic disorders but a clear proof of efficacy needs to be established.

In conclusion, the efficacy of cisapride in the treatment of chronic constipation has not been demonstrated in accordance to current scientific standards.

EFFICACY OF CISAPRIDE IN CHILDREN INDICATIONS

GASTRO-OESOPHAGEAL REFLUX DISEASE (GERD)

The epidemiology and pathophysiology of paediatric GERD are different from that of adult GERD and even differ across paediatric age groups. Data confirm that GERD in premature neonates, infants and children up to approximately 36 months of age is primarily a motor disorder. The pathophysiology of GERD in older children mirrors that in adults.

PREMATURE NEONATES (GESTATIONAL AGE UP TO 36 WEEKS)

The following published controlled clinical studies – Enriquez, 1998; McClure, 1999; Reddy, 1999; Craig, 1998 and other unpublished studies were assessed by the CPMP.

The pathophysiological mechanism of GERD in premature neonates is the immature motility of the oesophagus which means that the ad hoc treatment is a prokinetic agent. The objective of a prokinetic treatment as cisapride in premature neonates is to increase rapidly the tolerance of oral milk feeding. From the available studies the efficacy of cisapride in the treatment of GERD in this population is not established. However, according to the current medical guidelines such as the guidelines from ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition) and NASPGAN (North America Society for paediatric Gastroenterology and Nutrition), cisapride is considered the only medicinal option in prematurely born babies with gastrointestinal motility disorders. The CPMP noted that there are no controlled studies of alternative treatments in premature neonates and that there is no medicinal product authorised in the EU for this indication in this category of age.

As data from safety studies suggest that this subpopulation is at higher risk for arrhythmia, the CPMP considered that cisapride is not recommended for use in premature neonates and therefore agreed on the following wording to be included in section 4.4 – Special Warnings and Special Precautions for Use – of the SPC:

"***Premature neonates***
It is generally inadvisable to use cisapride in premature neonates. If absolutely necessary, the treatment in premature neonates should be restricted to specialised critical care units and cisapride should be administered only under constant cardiac monitoring.
The maximum daily dose should not exceed 0.8 mg/kg/day (the oral suspension should be used in infants and children). The daily dose should be divided in several administrations, each of them < 0.2 mg/kg."

NEONATES, INFANTS AND CHILDREN UP TO 36 MONTHS OF AGE

GERD in infants and young children is a motility disorder, which differs in pathophysiology and clinical course from GERD in adults, and warrants the use of prokinetic agents under certain circumstances. Gastroesophageal reflux in infants must be treated effectively because of its association with complications and its potential long-term effects.

Published (Van Eygen, 1989; Vandenplas, 1991; Cucchiara, 1990; Cohen, 1999; Scott, 1997) and unpublished placebo controlled studies, and comparator controlled studies with metoclopramide (Bravo Matus, 1995; Rode, 1987; Gonzalez, 1992; Mundo, 1990), feed thickeners (Greally, 1992; Moya, 1999; Rode, 1992) and cimetidine (Evans, 1990; Orenstein, 2000) have been assessed by CPMP.

From the reviewed placebo controlled studies, a few studies reached positive results on the primary endpoint in children, and showed a benefit in children not responding to positional and dietary measures, with a cisapride average dose of 0.6 mg/kg/day.

However, the CPMP noted that in most published trials, the randomisation was performed in first line intention, prior to parental reassurance and dietary manipulation, contravening published therapeutic recommendations. In addition, the CPMP also noted a recent paper reviewing all available data in children conducted for the Cochrane Collaboration (Gilbert RE et al., Cisapride treatment for gastro-oesophageal reflux in children: A systematic review of randomized controlled trials. J. Paediatr. Child Health (2000) 36, 524-529). In this analysis, it is concluded that there was no clear evidence that cisapride reduced symptoms of gastro-oesophageal reflux.

Regarding comparator-controlled studies conclusions have to take into account that cisapride was not compared with the effects of comparators alone. In comparison with metoclopramide, the efficacy of cisapride seems similar.

In addition to the clinical studies, the CPMP took into consideration the recommendations of the international and national guidelines regarding the treatment of paediatric GERD. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN), and other national paediatric societies consider that cisapride has a place in the treatment of gastro-oesophageal reflux in children up to 3 years of age.

Despite the fact that published data give some arguments in favour of the efficacy of cisapride in pediatric GERD and that there are several clinical recommendations for the use of cisapride in this indication for this category of age, the CPMP considered that there were still concerns regarding the efficacy of cisapride and therefore proposed to restrict the indications of cisapride as follows (Section 4.1 of the SPC):

"Treatment of demonstrated pathological gastro-oesophageal reflux disease (GERD) after failure of other treatment options in neonates, infants and children up to 36 months of age."

This indication was accepted by the MAHs who provided oral explanations in November 2001 CPMP.

In addition, the CPMP considered that there is a need to perform clinical trials to better define the efficacy of cisapride in the above-mentioned restricted indication. The protocol for a clinical trial in neonates with GERD should be in accordance to the following recommendations:
- Population defined by the SPC therapeutic indication;
- Placebo controlled randomised design;
- Time to total enteral feeding as primary endpoint.

The clinical trial in children with GERD up to 36 month of age should be in accordance to the following recommendations:
- Population defined by the SPC therapeutic indication;
- Placebo controlled randomised design;
- Symptomatic evaluation as primary endpoint;

Proposals for such trials were received from some MAHs and are further addressed under the section "Overall Conclusion on benefit/risk".

<u>CHILDREN OVER 36 MONTHS</u>
A few placebo-controlled trials were analysed in this category of age. In the majority of them cisapride was not superior to placebo. Furthermore it should be noted that with regard to children over 36 months of age, GERD is no longer a motility disorder. In this population the persistence of GERD induces erosive oesophagitis. Other therapeutic alternatives such as postural and dietary measures with H2-antagonists, proton-pump inhibitors are indicated. A prokinetic agent is not indicated in this category of age. Therefore the CPMP taking into consideration the lack of demonstrated efficacy in this category of age and the availability of other therapeutic alternatives considers that cisapride should not be used in the treatment of GERD in children over 36 months.

FUNCTIONAL DYSPEPSIA (FD)

On the basis of the available data, the CPMP concluded that there is no support to the use of cisapride on functional dyspepsia in children.

INTESTINAL PSEUDO-OBSTRUCTION (IPO)

On the basis of the available data the CPMP concluded that there is no support to use of cisapride on intestinal pseudo-obstruction in children.

CONSTIPATION

On the basis of the available data the CPMP concluded that there is no support to use of cisapride on constipation in children.

OVERVIEW OF SAFETY

The overall safety profile of cisapride containing medicinal products was reviewed by the CPMP. The main safety issue identified is the cardiovascular effect and its assessment is based on the available information concerning electrophysiological data, clinical studies, spontaneous reports of adverse drug reactions (ADRs) and pharmacoepidemiological studies. The conclusions from the CPMP are hereafter presented.

Electrophysiological data
Available data from in-vitro electrophysiological studies were assessed by the CPMP. From these studies, it is clear that cisapride is a highly potent blocker of HERG channels with potency similar to that of the class III antiarrhythmic agent dofetilide. Therefore, cisapride possesses class III antiarrhythmic properties, and the arrhythmogenic properties of cisapride are markedly enhanced under conditions of metabolic inhibition (concomitant inhibition of CYP3A4, e.g. by imidazole antimycotics, macrolide antibiotics, HIV protease inhibitors) leading to an increase in cisapride plasma concentrations (up to 1.6 μM). In the absence of metabolic inhibition, therapeutically free plasma concentrations of cisapride are in the nanomolar range (about 2.4-3.4 nM) and are therefore, slightly lower compared to the half-maximally inhibitory concentrations of cisapride for blocking of I_{Kr} and HERG channels (6.5-44.5 nM). Then, cisapride seems to have arrhythmogenic properties even in the absence of metabolic inhibition, especially under conditions favouring the occurrence of torsade de pointe (TdP), arrhythmias (e.g. hypokalaemia, bradycardia, congenital long QT syndrome, concomitant administration of other drugs known to prolong the QT interval).

Clinical studies
In most studies in humans, cisapride containing medicinal products caused a mean increase in QTc. The effect is most pronounced when cisapride is given concomitantly with drugs that inhibit the metabolism or prolong the QTc. Several drugs are known to interact with cisapride, most of them being of great use and importance in daily practice.

Regarding children, the arrhythmogenic potential of cisapride is highly substantiated through specific clinical studies and suggest that young infants may be at higher risk of QT prolongation. Overdose and association with the use of concomitant contraindicated medication were clearly identified as risk factors in the studies. Even if the number of contraindicated drugs used more frequently in children is probably shorter (macrolides, antifungals) than in adults, in clinical practice the need for the prescription of antibiotics in a child who had a previous prescription of cisapride is probably usual. Prematurity was also identified as a risk factor. Furthermore, it should be taken into consideration that the pharmacokinetic profile is variable in this paediatric population, this being an additional reason of concern.

Spontaneous reports on cardiac adverse drug reactions
The main spontaneous reports reviewed by CPMP were related to the cardiac safety, mainly with regard to QT prolongation, cardiac arrythmias and sudden cardiac death. The cases of serious ventricular arrhythmia, sudden death and serious QT prolongation were reviewed (reports since launch

up to 30 June 2000). In addition further safety data provided by some MAHs and covering a reporting period till 31 March 2001 was also reviewed.
Cisapride has been marketed in the EU since 1988 and in the USA since 1993; there are significant differences in the reporting incidences between the USA and the EU with a tenfold higher reporting incidence in the USA. Till June 2000 a total of 386 spontaneous reports of serious ventricular arrhythmias (VA) were reported with the use of cisapride (US: 267; EU: 63). In 125 cases, the outcome was fatal. Sudden death was reported in 50 cases, and a confirmed QT-prolongation was reported in 221 cases. With regard to reports on serious VA and sudden death, high doses of cisapride (> 40 mg per day) were much more often used by the patients in the US than in the EU (28.7 % vs. 14.2 %). Nearly a quarter of patients with serious VA (n=89) from the US had a co-medication with a substance inhibiting CYP 3A4 activity. In the reported cases co-medication with QT-prolonging substances was more frequent in the EU (25%) than in the US (14%). Reports, in which QT-prolongation has been documented, have been analysed separately. 126 reports originate from the US and 61 from the EU. In five cases from the US, the outcome of the reaction was fatal; no fatal case was reported from the EU.
An analysis focusing in children showed that worldwide, since launch and up to 30 June 2000, a total of 120 cases of serious VA (n=25), sudden deaths (n=15) and QT prolongation (n =80) have been reported. Among the 25 cases of serious VA, the outcome was favourable in 8/25 cases, not yet recovered in 4/25 cases and fatal in 13/25 cases. Among the 80 cases of QT prolongation, a fatal outcome due to sepsis was reported in 1 premature neonate. 98/120 (82%) of these reports describe children with labelled risk factors for these events. However, QT prolongation and arrhythmia have also been reported in children without any identified risk factors. In the EU, 41% of the cases of QT prolongation, serious VA and sudden deaths reported since the launch up to 30 June 2000 occurred in children < 16 years. Most of these cases were QT prolongation (n=42/56).

In addition to the above latest data provided by the MAHs (covering the period from 1 April 2000 to 31 March 2001) suggested a four-fold increase in spontaneous reporting rate of ventricular arrhythmias and sudden death. In this period, the total of deaths confirmed due to cardiac arrest or serious cardiac arrhythmia was 25 cases. The total of other deaths in which arrhythmic death was considered possible was 13 cases. A total of 64 cases of serious ventricular arrhythmia were reported (torsade de pointes, ventricular tachycardia, ventricular fibrillation, cardiac arrest, asystolia); all these cases are medically confirmed cases and the outcome was not fatal.

The CPMP recognised that true incidences for cardiac ADRs, VA, QT prolongation or death in patients exposed to cisapride cannot be expressed from numbers of spontaneous reports or from reporting incidences.

In conclusion, analysis of spontaneous reports on cardiac ADRs confirms information coming from formal clinical and electrophysiological studies, that cisapride has a marked potential for prolonging the QT interval. Cisapride itself may cause serious ventricular arrhythmias, which may be life threatening or fatal. This effect is dose dependent, and various risk factors, i.e. co-medication or the individual condition of the patient, increase the risk considerably. The CPMP noted that many of these contraindicated situations (ex. diabetes; acute treatment with insulin; electrolytic imbalance like – hypomagnesaemia, hypokalemia, hypocalcaemia; vomiting; history of ischaemic heart disease, etc) are frequent, not immediately diagnosed, and most relevant, are co-morbid entities in the indications for which cisapride is used (ex. GERD, gastroparesis, intestinal pseudo-obstruction).

Pharmacoepidemiological studies

Prescription Event Monitoring (PEM) Study

Cisapride has been studied by Prescription Event Monitoring (PEM) in 13 234 patients who had received prescriptions from general practitioners in England between October 1990 and April 1991. The events were compared with pooled data from a population of 332 402 patients in 33 PEM studies including those of omeprazole, nizatidine and famotidine which were used to provide estimates of background rates. This PEM study (Inman, 1993) was not specifically designed to assess the risk of serious ventricular arrhythmia (VA) for cisapride but to provide more data on the drug's safety overall after market introduction in England. Disorders of cardiac rhythm were reported in 2.8/1000 patients with cisapride exposure and 3.3/1000 patients who had used the other drugs, which had been surveyed by the PEM system in the past. Cardiac arrest occurred in 3.8/10,000 patients with cisapride exposure. This study used the PEM system, which is not designed to detect rare events. Accordingly, the power to detect an increased risk for an outcome as rare as serious ventricular arrhythmia is very limited. The outcome definition 'cardiac dysrhythmia' is too broad to provide meaningful results, since it includes a lot of non-ventricular rhythm disorders as e.g. atrial fibrillation and supraventricular tachycardias. The resulting misclassification masks any increased risk. In conclusion, due to its limitations, the CPMP considered that this study does not provide meaningful information as to the level of excess risk of serious ventricular arrhythmias associated with cisapride.

General Practice Research Database (GPRD) and Saskatchewan Health Database Studies

The results of 2 cohort studies with nested case-control analysis on the association between cisapride and ventricular arrhythmias (VA) were presented together as pooled results in one published paper. One of the cohort studies was conducted in Great Britain with the GPRD database and the other in Saskatchewan with the Saskatchewan Health database. In each study, patients who have had at least one prescription (GPRD) or dispensation (Saskatchewan) of cisapride between 1990 and 1995 (study period) were included. The GPRD cohort included 18,571 patients and the respective Saskatchewan cohort 18,172 patients. Both studies appear to have been well designed. They have been conducted with databases that have been shown to provide good quality data in a number of validation studies. However, only a pooled meta-analysis of both study results is published. This is unacceptable since in a meta-analysis the single study results are an important part to judge whether the studies are combinable or not. This is of particular concern in this meta-analysis, since the effects were significantly different for both countries ($p=0.03$, as is stated in the last paragraph of the results section). The study has limited power to rule out an increased risk. It was impossible to interpret this data with respect to a possible increase in risk under cisapride and potentially interacting drugs.
Other unpublished pharmacoepidemiologic studies were also considered by CPMP. However, as an overall conclusion the pharmacoepidemiological studies performed to assess risk were in general underpowered, and firm conclusions could not be established.

Overall conclusion on safety

Considering the overall available data on the cardiac safety of cisapride the CPMP concluded that cisapride is associated with a risk of cardiotoxicity:

- Cisapride is associated with a risk of QTc prolongation, serious ventricular arrhythmia and sudden cardiac death in normal clinical practice.
- Cisapride has a plausible mechanism of action in producing abnormal cardiac repolarisation and inducing QTc prolongation. This is likely to involve potassium rectifier currents and the potency of this effect may be similar to a recognised anti-arrhythmic agent.
- The risk of QTc prolongation and serious ventricular arrhythmia is shown, not only by spontaneous data but by clinical studies as well.
- The risk of cardiotoxicity is increased by administration of concomitant medication known to interact with cisapride and by administration in patients with other known risk factors
- Cisapride can also induce serious cardiac arrhythmias in patients without known risk factors and ECG screening or monitoring is unlikely to be a successful preventative option.

As a consequence, the CPMP agreed on several amendments to be introduced mainly in section 4.2, in order to restrict the prescription to initiation in hospital setting; the treatment with Cisapride should be closely monitored through therapy by specialist experienced in the treatment of the indicated conditions and in section 4.4 of the SPC of cisapride containing medicinal products.

Furthermore, in view of the above safety profile, the CPMP considered that all patients treated with cisapride should be closely monitored and therefore should be enrolled either in a Clinical Safety Study (CSS) targeting cardiovascular safety on patients, or in a register of treated or in the efficacy clinical trials requested by the CPMP.

OVERALL CONCLUSION ON BENEFIT/RISK

Regarding efficacy, cisapride lacks therapeutic efficacy in the indications of GERD, functional dyspepsia, intestinal pseudo-obstruction and constipation in adults. With regard to the efficacy of cisapride in the treatment of gastroparesis, the CPMP considered that, according to the available data, cisapride has a place in the treatment of acute and severe exacerbation of demonstrated chronic idiopathic or diabetic gastroparesis after failure of other treatment options.
With regard to the efficacy of cisapride in the treatment of children the CPMP considered that according to the available data (clinical studies and consensus guidelines) cisapride can be effective in the treatment of demonstrated pathological gastro-esophageal reflux disease (GERD) after failure of other treatment options in neonates, infants and children up to 36 months of age. However, as the CPMP still have some concerns on the efficacy of cisapride, the MAHs should perform further clinical trials in adult and pediatric patients in the recommended restricted indication.

Regarding safety, data from electrophysiological studies, clinical studies, spontaneous reporting and epidemiological studies show that cisapride is associated with a risk of QTc prolongation, serious ventricular arrhythmia and sudden cardiac death. The QTc prolongation is dose-dependent. The risk of cardiotoxicity is also increased by administration of concomitant medication known to interact with cisapride and by administration in patients with other known risk factors. Due to these safety concerns, the CPMP concluded that all patients treated with cisapride containing medicinal products should be enrolled either in a Clinical Safety Study (CSS) targeting cardiovascular safety on patients, in a register of treated patients or in the efficacy clinical trials requested by CPMP.

Therefore the CPMP considered that the benefit/risk balance of cisapride containing medicinal products in the agreed restricted indications for adults and children is favourable and the Marketing Authorisations should be maintained according to:

1. The Summaries of Product Characteristics as set out in Annex III of the CPMP Opinion with emphasis to the following:

- Therapeutic Indications
    - in adult patients, in the treatment of acute and severe exacerbation of demonstrated chronic idiopathic or diabetic gastroparesis after failure of other treatment options.
    - in paediatric patients, in the treatment of demonstrated pathological gastro-esophageal reflux disease (GERD) after failure of other treatment options in neonates, infants and children up to 36 months of age

- Posology and method of administration
  Treatment with cisapride should only be initiated in hospital setting and closely monitored throught therapy by specialist experienced in the treatment of the indicated conditions.

- Special Warnings
  Reinforce of warnings with regard to the monitoring of the cardiac risk.

2. The CPMP requirements set out in Annex IV of the CPMP Opinion with regard to:

- Clinical studies

The MAHs should perform clinical trials in the restricted adult and paediatric indications. These trials should be designed in accordance to the CPMP recommendations. Some MAHs submitted outline of protocols for such studies. The CPMP considered that such outlines comply with the CPMP requirements. The final study protocols should be submitted to the CPMP within 6 months, with an interim update presented within 3 months of the CPMP Opinion.

- Clinical Safety Study (CSS)
  The MAHs should perform a CSS targeting cardiovascular safety. An outline of the protocol for such study was submitted by some MAHs. The CPMP considered the proposed outline acceptable. The final study protocol should be submitted to the CPMP within 6 months, with an interim update presented within 3 months of the CPMP Opinion.

- Register of treated patients
  The MAHs should set up a register of patients treated with cisapride. Proposals for such register were submitted by some MAHs. The CPMP considered such proposals acceptable.

The CPMP concluded that all patients treated with cisapride containing medicinal products should be enrolled either in the Clinical Safety Study (CSS), in the register of treated patients or in the efficacy clinical trials.

6-monthly updates on the progress of all clinical studies and register should be provided to CPMP.

- Post-marketing data
  6-monthly Periodic Safety Update Reports should be provided to the CPMP. The following data with regard to the Clinical Safety Study and the register of treated patients should be included: number of patients enrolled and patients followed-up, baseline demographic data, indication for use, estimation of the overall exposure in cumulated patient months of cisapride use and number of patients treated, outcomes information, response rate as assessed by the physician, safety information, frequency table of all cumulated serious adverse events, number and nature of serious cardiac arrhythmias, QT prolongations and sudden deaths, number and causes of hospitalizations, number and causes of death, and table on the reasons for stopping cisapride during the study.

GROUNDS FOR AMENDMENT OF THE MARKETING AUTHORISATIONS

Whereas

- The Committee considered the referral made under article 12 of Council Directive 75/319/EEC as amended, for Cisapride containing medicinal products;

- The Committe agreed that cisapride containing medicinal products lack therapeutic efficacy in the treatment of GERD, functional dyspepsia, intestinal pseudo-obstruction and constipation in adults;

- The Committe agreed that cisapride containing medicinal products have a place in the treatment of acute and severe exacerbation of demonstrated chronic idiopathic or diabetic gastroparesis after failure of other treatment options, in adults and in the treatment of demonstrated pathological gastro-esophageal reflux disease (GERD) after failure of other treatment options in neonates, infants and children up to 36 months of age.

- The Committee agreed that there were serious concerns related to the cardiovascular safety of cisapride containing medicinal products. Cisapride is associated with a risk of dose-dependent QTc prolongation, serious ventricular arrhythmia and sudden cardiac death.

- The Committee, as a consequence, considered the benefit/risk balance of cisapride containing medicinal products to be favourable in adult patients, in the treatment of acute and severe exacerbation of demonstrated chronic idiopathic or diabetic gastroparesis after failure of other

treatment options and in paediatric patients, in the treatment of demonstrated pathological gastro-esophageal reflux disease (GERD) after failure of other treatment options in neonates, infants and children up to 36 months of age. Therefore, the Committee concluded that the Marketing Authorisations for these medicinal products should be maintained as amended in accordance with the Summary of Product Characteristics set out in Annex III and under the conditions set out in Annex IV.

As a result, the CPMP has recommended the maintenance of the Marketing Authorisations for cisapride containing medicinal products (see Annex I) as amended in accordance with the Summary of Product Characteristics set out in Annex III and under the conditions set out in Annex IV.

ANNEX III

SUMMARIES OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

ORAL SUSPENSION FOR USE IN CHILDREN

1. NAME OF THE MEDICINAL PRODUCT

<Tradename>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cisapride 1 mg / ml.

For 100 / 200 / 500 ml:
Cisapride ... mg (as cisapride monohydrate: ... to be completed as appropriate)

The suspension contain ... mg of sacarose per ml. (to be completed as appropriate)

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

To be completed as appropriate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral suspension for infants and children:

FOR USE IN CHILDREN ONLY.

Treatment of demonstrated pathological gastro-oesophageal reflux disease (GERD) after failure of other treatment options in neonates, infants and children up to 36 months of age.

4.2 Posology and method of administration

This presentation is for use in children only.

Treatment with Cisapride should only be initiated in hospital setting and closely monitored throught therapy by specialist experienced in the treatment of the indicated conditions.

Cisapride should be administered 15 minutes before meals and before going to bed when a fourth dose is necessary.

Cisapride is administered using a dosing pipette.
The dose per intake is 0.2 mg/kg (i.e. 1 ml/5 kg), 3 to 4 times a day, not exceeding a total daily dose of 0.8 mg/kg/day.
(Each graduation of the dosing pipette corresponds to the dose per kilogram and per intake; for example the graduation 4 corresponds to the dose, per intake, for a child of 4 kilograms)(as example; to be completed as apropriate)

Cisapride should not be administered with grapefruit juice (see section 4.5 “Interaction with other medicinal products and other forms of interaction”).
Hepatic and renal impairment

In hepatic and renal insufficiency, it is recommended to halve the daily dose.

4.3 Contraindications

<*Tradename*> is contraindicated in the following situations:

- Known hypersensitivity to cisapride or any of the excipients
- Association with oral and parental potent cyctochrome P 450 3A4 (CYP3A4) inhibiting drugs (see section 4.5 "Interaction with other medicinal products and other forms of interaction"), including:
  - azole antifungals
  - macrolide antibiotics
  - HIV protease inhibitors
  - nefazodone
- Association with drugs known to induce torsade de pointes and/or to prolong the QT interval (see section 4.5 "Interaction with other medicinal products or other forms of interaction")
- Hypokalaemia or hypomagnesaemia
- Clinically significant bradycardia
- Other clinically significant heart rhythm disorders
- Decompensated heart failure
- Known congenital long QT interval or family history of congenital long QT syndrome
- In case of fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency

This drug should not be used when stimulation of the gastro-intestinal motility could be harmful: organic occlusions.

The use of this drug is generally inadvisable in premature new-borns (see section 4.4 "Special warnings and special precautions for use").

4.4 Special warnings and special precautions for use

WARNING:

Before prescribing <Tradename>, it is necessary to consider and to assess the potential risk of arrhythmias that may be serious or fatal.

Cisapride should not be used as an "anti-regurgitation treatment".

Premature neonates

It is generally inadvisable to use cisapride in premature neonates. If absolutely necessary, the treatment in premature neonates should be restricted to specialised critical care units and cisapride should be administered only under constant cardiac monitoring.
The maximum daily dose should not exceed 0.8 mg/kg/day (the oral suspension should be used in infants and children). The daily dose should be divided in several administrations, each of them < 0.2 mg/kg.

Neonates, infants and children up to 36 months

The benefit-risk ratio of a treatment with cisapride should be reassessed in patients presenting, or likely to present the following predisposing factors of cardiac arrhythmias:

At risk patients for heart rhythm disturbances are defined as patients with a history of heart disease (ventricular arrhythmia, second or third degree atrioventricular block, sinus node dysfunction, ischaemic heart disease, heart failure), family history of sudden death, renal insufficiency, serious pulmonary disease, respiratory insufficiency, predisposing factors for electrolyte imbalance

(particularly patients receiving diuretics causing hypokalaemia and patients being treated with insulin on an emergency basis), patients with vomiting and/or prolonged diarrhoea.

In all treated patients an ECG and laboratory profile should be performed before and during treatment.

During treatment, all patients should be closely monitored to identify the occurrence of at risk situations such as vomiting or prolonged diarrhoea.

Cisapride should not be prescribed in-patients with a QTc interval > 450 msec or with uncorrected electrolyte disturbances (see section 4.3 "Contraindications").

In case of fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency, <Tradename> oral suspension should not be used because of the presence of sucrose (see section 4.3 "Contraindications")(to be included as appropriate)

Precautions for use:

In case of renal failure or hepatic insufficiency, it is recommended to halve the daily dose.

In case of diabetes or a low sugar diet, the sucrose content should be taken into account: ... ml of the oral suspension contains ... g of sucrose (to be completed as appropriate).

This medicinal product contains ... mg/ml of sodium, to be considered in-patients on a strict low sodium diet (to be completed as appropriate).

Caution is recommended in case of administration to patients treated with oral anticoagulants (see section 4.5 "Interaction with other medicinal products and other forms of interaction").

4.5 Interaction with other medicinal products and other forms of interaction

Cisapride has no influence on the pharmacokinetics of digoxin and propranolol.

Contraindicated associations:
Cisapride is mainly metabolised through CYP3A4. The concomitant oral or parenteral use of potent inhibitors of this cytochrome may result in an increase of plasma levels of cisapride and could increase the risk of QT prolongation and of severe cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsade de pointes. Therefore, the concomitant use of the following drugs is contraindicated with cisapride (see section 4.3 "Contraindications"):

- Oral or parenteral azole antifungals: ketoconazole, itraconazole, miconazole, fluconazole
- Oral or parenteral macrolide antibiotics: in particular azithromycin, erythromycin, clarithromycin, troleandomycin
- HIV protease inhibitors: by analogy with ritonavir and indinavir for which *in vitro* studies evidenced a potent inhibitor effect of CYP3A4, whereas saquinavir seems to be a weak inhibitor
- Nefazodone
- Drugs known to prolong the QT interval and/or to induce torsade de pointes: Class IA antiarrhythmics (quinidine, hydroquinidine, disopyramide, procainamide) and Class III antiarrhythmics (amiodarone, sotalol); bepridil, halofantrine, certain quinolone antibiotics (in particular sparfloxacin, grepafloxacin, gatifloxacin, moxifloxacin), tri- and tetracyclic antidepressants (amytriptiline, maprotiline); vincamine; neuroleptics (such as phenothiazines, pimozide, sertindole, haloperidol, droperidol, sultopride); ziprasidone; diphemanil; certain antihistamines (such as astemizole and terfenadine)

Inadvisable associations:

When using cisapride, repeated intake of grapefruit juice is inadvisable due to a possible increase of cisapride bioavailability (see section 4.2 “Posology and method of administration”).

Associations needing precaution:

Oral anticoagulant agents (described for acenocoumarol): Concurrent treatment may cause an increase in the anticoagulant effect and in the risk of haemorrhage. More frequent checking of the prothrombin rate and INR investigation are needed. Possible adaptation of the oral dose of anticoagulant agent during cisapride treatment and within 8 days after stopping it should be considered.

Associations to take into account:

A transient increase in the sedative effect of diazepam due to an increase in its absorption rate may occur.
Cimetidine: There is a slight increase in cisapride bioavailability, which is not considered to be clinically significant.

4.6 Pregnancy and lactation

This product is indicated for children only.

It should be reminded that in animals, there is no effect on primary fertility, no primary embryotoxic and no teratogenic effect. In a large population study in humans, cisapride has shown no increase in foetal anomalies. However, the anticipated therapeutic benefits should be weighed against the potential hazards before <*Tradename*> is given during pregnancy, especially during the first trimester.

Although the excretion in breast milk is minimal, nursing mothers are advised not to breast-feed while taking <*Tradename*>.

4.7 Effects on ability to drive and use machines

This product is indicated for children only.

It should be reminded that <*Tradename*> does not affect psychomotor function and does not induce sedation or drowsiness. <*Tradename*> may, however, accelerate the absorption of central nervous system depressants, such as barbiturates and alcohol. Caution should, therefore, be exercised when <*Tradename*> is administered with these drugs.

4.8 Undesirable effects

Some cases of QT prolongation have been reported in premature new-borns, for doses generally exceeding 0.8 mg/kg/day.

Cases of QT prolongation and/or severe and sometimes fatal ventricular arrhythmias, such as torsade de pointes, ventricular tachycardia and ventricular fibrillation have been reported. In most cases, patients were receiving multiple other medication, including CYP3A4 inhibitors and/or had pre-existing cardiac disease or risk factors for arrhythmias (see section 4.5 “Interaction with other medicinal products and other forms of interaction”, section 4.3 “Contraindications” and section 4.4 “Special warnings and special precautions for use”).

The following adverse reactions have also been reported:

Common (>1/100 <1/10)
Due to the pharmacological action of the product, transient abdominal cramping, borborygmi and diarrhoea may occur. When diarrhoea occurs in children, the dose should be reduced.

Uncommon (>1/1000 <1/100)
Cases of hypersensitivity including rash, urticaria and pruritus, mild and transient headache or light-headedness have been occasionally reported. Dose-related increase in urinary frequency has also been reported.

Very rare (<1 in 10 000)
There are isolated case reports of convulsive seizures and extrapyramidal effects.
Rare reversible cases of gynaecomastia and galactorrhoea, sometimes associated with hyperprolactinaemia have also been reported.
Reversible liver function abnormalities with or without cholestasis have been reported.
Bronchospasm.

4.9 Overdose

Symptoms: The symptoms that occur after overdosing are abdominal cramping and increased stool frequency. QT interval prolongation may occur as well as severe ventricular arrhythmias including torsades de pointes. In infants (< 1 year of age), also mild sedation, apathy and atony were observed.

Treatment: In case of overdose, hospital care is necessary. Clinical and electrocardiographic monitoring is recommended. Predisposing factors to QT prolongation such as electrolyte imbalance (especially hypokalaemia or hypomagnesaemia) and bradycardia should be investigated and corrected

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives

ATC code: A03F A02

In vitro studies have shown that cisapride is a serotonin (5-HT4) receptor agonist.

Cisapride increases the gastro-intestinal motility.

The mechanism of action of cisapride is mainly linked to an enhancement of the physiological release of acetylcholine at the myenteric plexus.
Cisapride does not stimulate muscarinic or nicotinic receptors nor does it inhibit acetylcholinesterase activity.

Cisapride has no blocking action on dopaminergic receptors at therapeutic doses.

Effects on gastro-intestinal motility
- Oesophagus: Cisapride increases oesophageal peristaltic activity; cisapride increases lower oesophageal sphincter tone in volunteers as in patients with gastro-oesophageal reflux and improves oesophageal clearance.
- Stomach: Cisapride increases gastric and duodenal contractility; cisapride improves gastric and duodenal emptying.
- Bowel: Cisapride enhances intestinal propulsive activity and accelerates small and large bowel transit.

The onset of pharmacological action of cisapride is approximately 30 to 60 minutes after oral administration.

Other effects
- On the basis of its lack of direct cholinomimetic effects, cisapride does not increase basal or pentagastrin-induced gastric acid secretion.
- On the basis of its low affinity for dopaminergic receptors, cisapride rarely enhances prolactin levels.

5.2 Pharmacokinetic properties

After oral administration in man, cisapride is rapidly and completely absorbed but its absolute bioavailability is 40 to 50%, due to an extensive intestinal metabolism and to a hepatic first pass effect.
Peak plasma levels are reached within 1 to 2 hours.

The better bioavailability is reached when the intake takes place 15 minutes before meals. Cisapride is mainly metabolised through cytochrome P 450 3A4; it is mainly metabolised by oxidative N-dealkylation and aromatic hydroxylation. Norcisapride is one of the main metabolites. The elimination half-life of cisapride is about 10 hours.

The excretion of cisapride is nearly equal in urine and faeces, almost exclusively as metabolites. Its excretion in maternal milk is very limited.
The pharmacokinetic behaviour of cisapride is linear for doses between 5 and 20 mg.
At steady-state, morning pre-dose plasma levels and evening peak levels fluctuate between 10-20 ng/ml and 30-60 ng/ml for 5 mg cisapride t.i.d., and between 20-40 ng/ml and 50-100 ng/ml for 10 mg cisapride t.i.d.
There is no accumulation nor metabolism change of the compound during administration of repeated doses.

Kinetic parameters of the compound are not affected by renal failure, except for norcisapride accumulation.

In-patients with hepatic dysfunction, the plasma elimination half-life can be increased, without change in the bioavailability.

In elderly, steady-state plasma levels are generally higher (moderate increase of the bioavailability). However, therapeutic doses are similar to the ones used in younger patient.

Cisapride is extensively bound to plasma proteins (97.5%).

5.3 Preclinical safety data

Cardiac electrophysiological studies in vitro and in vivo have shown that cisapride, under certain conditions, may prolong cardiac depolarisation. Under these conditions, this may lead to prolongation of the QT interval.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

To be completed as appropriate.

6.2 Incompatibilities

To be completed as appropriate.

6.3 Shelf-life

To be completed as appropriate.

6.4 Special precautions for storage

To be completed as appropriate.

6.5 Nature and contents of container

To be completed as appropriate.

6.6 Instructions for use and handling

To be completed as appropriate.

7. MARKETING AUTHORISATION HOLDER

To be completed as appropriate.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed as appropriate.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed as appropriate.

10. DATE OF REVISION OF THE TEXT

To be completed as appropriate.

SUMMARY OF PRODUCT CHARACTERISTICS

FORMULATIONS FOR USE IN ADULTS

1. NAME OF THE MEDICINAL PRODUCT

<Tradename>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet / coated tablet / dispersible tablet / soluble tablet / effervescent tablet/ chewable tablet / oral lyophilisate / lozenge / sachet *(as appropriate)* contains:

Cisapride 5 mg *(as cisapride monohydrate: …to be completed as appropriate)*

Cisapride 10 mg *(as cisapride monohydrate: …to be completed as appropriate)*

Oral suspension:
Cisapride 1 mg / ml.

Cisapride … mg (as cisapride monohydrate: … to be completed as appropriate)
The suspension contain … mg of sacarose per ml. (to be completed as appropriate)

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet / coated tablet / dispersible tablet / soluble tablet / effervescent tablet/ chewable tablet / oral lyophilisate / lozenge / effervescent granules / oral suspension *(as appropriate)*

To be completed as appropriate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADULTS:
Treatment of acute and severe exacerbation of demonstrated chronic idiopathic or diabetic gastroparesis after failure of other treatment options.

4.2 Posology and method of administration

This presentation is for adult use only.

Treatment with Cisapride should only be initiated in hospital setting and closely monitored throught therapy by specialist experienced in the treatment of the indicated conditions.

Cisapride should be administered 15 minutes before meals and when appropriate before retiring (if a fourth dose is necessary), together with some beverage.

The following dose is recommended: 10 mg t.i.d. to 10 mg q.i.d. The total daily dose of 40 mg should not be exceeded.

Cisapride should not be administered with grapefruit juice (see section 4.5 “Interaction with other medicinal products and other forms of interaction”).

Cisapride should only be used in short-term treatment.

Elderly
In the elderly, steady-state plasma levels are generally higher, due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger patients.

Hepatic and renal impairment
In hepatic and renal insufficiency, it is recommended to halve the daily dose.

4.3 Contraindications

<*Tradename*> is contraindicated in the following situations:

- Known hypersensitivity to cisapride or any of the excipients
- Association with oral and parenteral potent cytochrome P 450 3A4 (CYP 3A4) inhibiting drugs (see section 4.5 "Interaction with other medicinal products and other forms of interaction"), including:
  - azole antifungals
  - macrolide antibiotics
  - HIV protease inhibitors
  - nefazodone
- Association with drugs known to induce torsade de pointes and/or to prolong the QT interval (see section 4.5 "Interactions with other medicinal products and other forms of interaction")
- Hypokaliaemia or hypomagnesaemia
- Clinically significant bradycardia
- Other clinically significant heart rhythm disorders
- Decompensated heart failure
- Known congenital long QT interval or family history of congenital long QT syndrome
- *In case of fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency.(to be included as appropriate)*

This drug should not be used when stimulation of the gastro-intestinal motility could be harmful: organic occlusions.

4.4 Special warnings and special precautions for use

WARNING:

Before prescribing <Tradename>, it is necessary to consider and to assess the potential risk of arrhythmias that may be serious or fatal.

The benefit-risk ratio of a treatment with cisapride should be reassessed in patients presenting, or likely to present the following predisposing factors of cardiac arrhythmias:

At risk patients for heart rhythm disturbances defined as patients with a history of heart disease (ventricular arrhythmia, second or third degree atrioventricular block, sinus node dysfunction, ischaemic heart disease, heart failure), family history of sudden death, renal insufficiency, serious pulmonary disease; respiratory insufficiency; predisposing factors for electrolyte imbalance (particularly patients receiving diuretics causing hypokalaemia and patients being treated with insulin on an emergency basis), patients with vomiting and/or prolonged diarrhoea.

In all treated patients an ECG and laboratory profile should be performed before and during treatment.

During treatment, all patients should be closely monitored to identify the occurrence of at risk situations such as vomiting or prolonged diarrhoea.

Cisapride should not be prescribed in patients with a QTc interval > 450 msec or with uncorrected electrolyte disturbances (see section 4.3 " Contraindications").

In case of fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency, <Tradename> oral suspension should not be used because of the presence of sucrose (see section 4.3 "Contraindications")(to be included as appropriate)

Precautions for use:

In case of renal failure or hepatic insufficiency, it is recommended to halve the daily dose.

In case of diabetes or a low sugar diet, the sucrose content should be taken into account: .... ml contain ... g of sucrose. (to be completed as appropriate)

This medicinal product contains ....mg/ml of sodium, to be considered in patients on a strict low sodium diet.(to be completed as appropriate)

Caution is recommended in case of administration to patients treated with oral anticoagulants (see section 4.5 "Interaction with other medicinal products and other forms of interaction").

Patients prescribed cisapride should be clearly instructed to discuss any changes to their medication, including self-medication with their physician or pharmacist with respect to the potential for interaction (see section 4.5 "Interaction with other medicinal products and other forms of interaction").

4.5 Interaction with other medicinal products and other forms of interaction

Cisapride has no influence on the pharmacokinetics of digoxin and propranolol.

Contraindicated associations:
Cisapride is mainly metabolised by the CYP3A4. The concomitant oral or parenteral use of potent inhibitors of this cytochrome may result in an increase of plasma levels of cisapride and could increase the risk of QT prolongation and of severe cardiac arrhythmias**,** including ventricular tachycardia, ventricular fibrillation, torsade de pointes. Therefore, the concomitant use of the following drugs is contraindicated with cisapride (see section 4.3 "Contraindications"):

- Oral or parenteral azole antifungals: ketoconazole, itraconazole, miconazole, fluconazole
- Oral or parenteral macrolide antibiotics: in particular azithromycin, erythromycin, clarithromycin, troleandomycin
- HIV protease inhibitors: by analogy with ritonavir and indinavir for which in vitro studies evidenced a potent inhibitor effect of CYP 3A4 , whereas saquinavir seems to be a weak inhibitor.
- Nefazodone
- Drugs known to prolong QT interval and/or to induce torsade de pointes: Class IA antiarrhythmics (quinidine, hydroquinidine, disopyramide, procainamide) and Class III (amiodarone, sotalol) ; bepridil, halofantrine, certain quinolone antibiotics (in particular sparfloxacin, grepafloxacin, gatifloxacin, moxifloxacin), tri- and tetracyclic antidepressants (amytriptiline, maprotiline,); vincamine ; neuroleptics (such as phenothiazines, pimozide, sertindole, haloperidol, droperidol, sultopride) ; Zyprasidone ; diphemanil ; certain antihistamines (such as astemizole and terfenadine).

Inadvisable associations:
When using cisapride, repeated intake of grapefruit juice is inadvisable due to a possible increase of cisapride bioavailability (see section 4.2 "Posology and method of administration").

Associations needing precaution:
Oral anticoagulant agents (described for acenocoumarol): concurrent treatment may cause an increase in the anticoagulant effect and in the risk of haemorrhage. More frequent checking of the prothrombin rate and INR investigation are needed. Possible adaptation of the oral dose of anticoagulant agent during cisapride treatment and 8 days after stopping it should be considered.

Associations to take into account:
A transient increase in the sedative effect of diazepam due to an increase in its absorption rate may occur.
Cimetidine: there is a small increase in cisapride bioavailability considered as not clinically significant.
The sedative effect of alcohol may be accelerated.

4.6 Pregnancy and lactation

In animals, there is no effect on primary fertility, no primary embryotoxic and no teratogenic effect. In a large population study in humans, cisapride has shown no increase in foetal anomalies. However, the anticipated therapeutic benefits should be weighed against the potential hazards before <*Tradename*> is given during pregnancy, especially during the first trimester.

Although the excretion in breast milk is minimal, nursing mothers are advised not to breast-feed while taking <*Tradename*>.

4.7 Effects on ability to drive and use machines

<*Tradename*> does not affect psychomotor function and does not induce sedation or drowsiness. <*Tradename*> may, however, accelerate the absorption of central nervous system depressants, such as barbiturates and alcohol. Caution should, therefore, be exercised when <*Tradename*> is administered with these drugs.

4.8 Undesirable effects

Cases of QT prolongation and/or severe and sometimes fatal ventricular arrhythmias, such as torsade de pointes, ventricular tachycardia and ventricular fibrillation have been reported. In most cases patients were receiving multiple other medication, including CYP3A4 inhibitors and/or had pre-existing cardiac disease or risk factors for arrhythmias (see section 4.5 “Interaction with other medicinal products and other forms of interaction”, section 4.3 “Contraindications” and section 4.4 “Special warnings and special precautions for use”).

The following adverse reactions have also been reported:

Common (>1/100<1/10)
Due to the pharmacological action of the product, transient abdominal cramping, borborygmi and diarrhoea may occur.

Uncommon (>1/1000<1/100)
Cases of hypersensitivity including rash, urticaria and pruritus, mild and transient headache or lightheadedness have been occasionally reported. Dose-related increase in urinary frequency has also been reported.

Very rare (<1/10 000)
There are isolated cases reports of convulsive seizures and extrapyramidal effects.
Reversible cases of gynaecomastia and galactorrhoea, sometimes associated with hyperprolactinemia have been also reported.
Reversible liver function abnormalities with or without cholestasis have been reported.
Bronchospasm.

4.9 Overdose

Symptoms: the symptoms that occur after overdosing are abdominal cramping and increased stool frequency. QT interval prolongation may occur as well as severe ventricular arrhythmias, including torsades de pointes.

Treatment: in case of overdose, hospital care is necessary. The administration of activated charcoal and clinical and electrocardiographic monitoring is recommended. Predisposing factors to QT prolongation such as electrolyte imbalance (especially hypokalaemia or hypomagnesaemia) and bradycardia should be investigated and corrected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: propulsives, ATC code A03F A02.

In vitro studies have shown that cisapride is a serotonin (5-HT4) receptor agonist.

Cisapride increases the gastro-intestinal motility.

The mechanism of action of cisapride is mainly linked to an enhancement of the physiological release of acetylcholine at the myenteric plexus.

Cisapride does not stimulate muscarinic or nicotinic receptors nor does it inhibit acetylcholinesterase activity.

Cisapride has no blocking action on dopaminergic receptors at therapeutic doses.

Effects on gastro-intestinal motility
- Oesophagus: cisapride increases oesophageal peristaltic activity; cisapride increases lower oesophageal sphincter tone in volunteers as in patients with gastro-oesophageal reflux and improves oesophageal clearance.
- Stomach: cisapride increases gastric and duodenal contractility; cisapride improves gastric and duodenal emptying.
- Bowel: cisapride enhances intestinal propulsive activity and accelerates small and large bowel transit.

The onset of the pharmacological action of cisapride is approximately 30 to 60 minutes after oral administration.

Other effects
- On the basis of its lack of direct cholinomimetic effects, cisapride does not increase basal or pentagastrin-induced gastric acid secretion.
- On the basis of its low affinity for dopaminergic receptors, cisapride rarely enhances prolactin levels.

5.2 Pharmacokinetic properties

After oral administration in man, cisapride is rapidly and completely absorbed, but its absolute bioavailability is 40 to 50 %, due to an extensive intestinal metabolism and to an hepatic first pass effect.
Peak plasma levels are reached within 1 to 2 hours.

The better bioavailability is reached when the intake takes place 15 minutes before meals. Cisapride is mainly metabolized through cytochrome P450 3A4; it is mainly metabolized by oxydative N-

dealkylation and aromatic hydroxylation. Norcisapride is one of the main metabolites. The cisapride elimination half-life is about 10 hours.

The excretion is nearly equal in urine and faeces, almost exclusively as metabolites. The excretion in maternal milk is very limited.

Cisapride kinetic is linear for doses between 5 and 20 mg.
At steady-state, morning pre-dose plasma levels and evening peak levels fluctuate between 10-20 ng/ml and 30-60 ng/ml for 5 mg cisapride t.i.d. and between 20-40 ng/ml and 50-100 ng/ml for 10 mg cisapride t.i.d..
There is no accumulation nor metabolism change during administration of repeated doses.

Kinetic parameters are not affected by renal failure, except for norcisapride accumulation.

In patients with hepatic dysfunction, the plasma elimination half-life can be increased, without change in the bioavailability.

In elderly, steady-state plasma levels are generally higher (moderate increase of the bioavailability). However, therapeutic doses are similar to the ones used in younger patients.

Cisapride is extensively bound to plasma proteins (97.5%).

5.3 Preclinical safety data

Cardiac electrophysiological *in vitro* and *in vivo* studies have shown that cisapride, under certain conditions, may prolong cardiac repolarization. Under these conditions, this may lead to prolongation of the QT interval.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

To be completed as appropriate.

6.2 Incompatibilities

To be completed as appropriate.

6.3 Shelf-life

To be completed as appropriate.

6.4 Special precautions for storage

To be completed as appropriate.

6.5 Nature and contents of container

To be completed as appropriate.

6.6 Instructions for use / handling

To be completed as appropriate.

7. MARKETING AUTHORISATION HOLDER

To be completed as appropriate.

8. MARKETING AUTHORISATION NUMBER

To be completed as appropriate.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed as appropriate.

10. DATE OF REVISION OF THE TEXT

To be completed as appropriate.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

Conditions of the Marketing Authorisations

CPMP requirements in relation to clinical studies and register of patients

Clinical studies
The MAHs should perform clinical trials in the restricted adult and paediatric indications. These trials should be designed in accordance to the CPMP recommendations. The final study protocols should be submitted to the CPMP within 6 months, with an interim update presented within 3 months of the CPMP Opinion.

Clinical Safety Study (CSS)
The MAHs should perform a CSS targeting cardiovascular safety. The final study protocol should be submitted to the CPMP within 6 months, with an interim update presented within 3 months of the CPMP Opinion.

Register of treated patients
The MAHs should set up a register of patients treated with cisapride.

All patients treated with cisapride containing medicinal products should be enrolled either in the Clinical Safety Study (CSS), in the register of treated patients or in the efficacy clinical trials.

6-monthly updates on the progress of all the clinical studies and the register should be provided to CPMP.

Post-marketing data
6-monthly Periodic Safety Update Reports should be provided to the CPMP. The following data with regard to the Clinical Safety Study and the register of treated patients should be included: number of patients enrolled and patients followed-up, baseline demographic data, indication for use, estimation of the overall exposure in cumulated patient months of cisapride use and number of patients treated, outcomes information, response rate as assessed by the physician, safety information, frequency table of all cumulated serious adverse events, number and nature of serious cardiac arrhythmias, QT prolongations and sudden deaths, number and causes of hospitalizations, number and causes of death, and table on the reasons for stopping cisapride during the study.