

**ANNEX I**

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

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Austria	Stada Arzneimittel GmbH Heiligenstädter Straße 52/2/8 A-1190 Wien Austria	Floxacin 400 mg - Filmtabletten	400 mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau - City - Straße 6 A-1220 Wien Austria	Norfloxacin "MSD" - Filmtabletten	400 mg	Film-coated tablet	Oral use
Austria	Ratiopharm Arzneimittel Vertriebs-GmbH Albert-Schweitzer Gasse 3 A-1140 Wien Austria	Norfloxacin "ratiopharm" – 400 mg Filmtabletten	400 mg	Film-coated tablet	Oral use
Austria	Sandoz GmbH Biochemiestraße 10 A-6250 Kundl Austria	Norfloxacin Sandoz - 400 mg Filmtabletten	400 mg	Film-coated tablet	Oral use
Austria	Merck, Sharp & Dohme GmbH Donau - City - Straße 6 A-1220 Wien Austria	Zoroxin - Filmtabletten	400 mg	Film-coated tablet	Oral use
Belgium	Merck, Sharp et Dohme Chaussée de Waterloo 1135, 1180 Bruxelles Belgium	Zoroxin	400 mg	Tablet	Oral use
Belgium	Docpharma N.V Ambachtenlaan 13H 3001 Heverlee Belgium	Docnorfloxa (ex: Floxolone)	400 mg	Film-coated tablet	Oral use
Belgium	Socobom N.V Louizalaan 149 B24 1050 Brussel Belgium	Floxolone 400mg	400 mg	Film-coated tablet	Oral use

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Belgium	Ratiopharm Belgium S.A Rue St-Lambert 141 1200 Bruxelles Belgium	Norfloxacin – Ratiopharm 400	400 mg	Tablet	Oral use
Belgium	Eurogenerics Heizel Esplanade B22 1020 Brussel Belgium	Norfloxacin EG	400 mg	Film-coated tablet	Oral use
Belgium	Teva Generics Belgium NV Laarstraat 16 2610 Wilrijk Belgium	Norfloxacin Teva 400mg	400 mg	Coated tablets	Oral use
Bulgaria	Krka, d.d.Novo Mesto Smarjeka cesta 6 8501 Novo mesto Slovenia	Nolicin	400 mg	Film-coated tablet	Oral use
Bulgaria	Hexal AG Industriestrasse 25, D-83607 Holzkirchen, Germany	NorfloHexal	400 mg	Film-coated tablet	Oral use
Cyprus	Merck Sharp & Dohme BV, Waarderweg 39, NL-2031 BN Haarlem, The Netherlands	Noroxin	400mg	Tablet	Oral use
Cyprus	Medochemie Ltd, P.O Box 51409 Lemesos Cyprus	Gyrablock	400mg	Tablet	Oral use
Cyprus	Remedica Ltd, P.O Box 51706 Lemesos Cyprus	Trizolin	400mg	Tablet	Oral use

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Czech Republic	Medochemie Ltd, Limassol Constantinoupoleos St. 1-10, P.O.Box 51409, CY-3505 Limassol Cyprus	Gyrablock 400	400 mg	Film-coated tablet	Oral use
Czech Republic	Krka, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia	Nolicin	400mg	Coated tablet	Oral use
Czech Republic	Ratiopharm GmbH Graf-Arco-Strasse 3 D-89070 Ulm Germany	Norfloxacin- Ratiopharm 400 mg	400mg	Film-coated tablet	Oral use
Denmark	Tad Pharma GmbH Heinz-Lohmann Strasse 5, DE-27472, Cuxhaven Germany	Norflocux	400 mg	Film-coated tablet	Oral
Estonia	Krka, d.d. Šmarješka cesta 6 8501 Novo mesto Slovenia	Nolicin	400mg	Tablet	Oral use
Finland	Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria	Norfloxacin Sandoz	200 mg	Film-coated tablet	Oral use
Finland	Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria	Norfloxacin Sandoz	400 mg	Film-coated tablet	Oral use
Finland	Ratiopharm Oy, Vitikka 1 F, P.O Box 67, 02630 Espoo, Finland	Norfloxacin- Ratiopharm	400 mg	Film-coated tablet	Oral use

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France	Arrow Generiques 26 av Tony Garnier 69007 Lyon France	Norfloxacin Arrow	400 mg	Tablet	Oral use
France	Biogaran 15 Bd Charles de Gaulle 92700 Colombes France	Norfloxacin Biogaran	400 mg	Tablet	Oral use
France	EG Labo "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex France	Norfloxacin EG	400 mg	Tablet	Oral use
France	Ivax Pharmaceuticals SAS 1 cours du triangle, Immeuble palatin 1 92936 Paris la Défense cedex France	Norfloxacin Ivax	400 mg	Tablet	Oral use
France	Merck Generiques 34, rue Saint-Romain 69359 Lyon Cedex 08 France	Norfloxacin Merck	400 mg	Tablet	Oral use
France	Laboratoire Qualimed 34, rue Saint-Romain 69008 Lyon France	Norfloxacin Qualimed	400 mg	Tablet	Oral use
France	Laboratoire RPG 4 place Louis Armand 75012 Paris France	Norfloxacin Ranbaxy	400 mg	Tablet	Oral use

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France	Ratiopharm GmbH Graf Arco Strasse 3 89079 Ulm Germany	Norfloxacin Ratiopharm	400 mg	Tablet	Oral use
France	Sandoz 49, avenue Georges Pompidou 92300 Levallois-Perret France	Norfloxacin Sandoz	400 mg	Tablet	Oral use
France	Socit�te Teva Classics Le Palatin 1 1, cours du Triangle 92936 Paris la D�fense Cedex France	Norfloxacin Teva	400 mg	Tablet	Oral use
France	Sanofi Aventis France 1/13, Bd Romain Rolland 75014 Paris France	Norfloxacin Winthrop	400 mg	Tablet	Oral use
France	Merck Sharp – Dohme Chibret 3 avenue Hoche 75114 Paris Cedex 08 France	Noroxine	400 mg	Tablet	Oral use
Germany	1 A Pharma GmbH Keltenring 1 + 3 D-82041 Oberhaching Germany	Norflox-1A Pharma	400 mg	Film-coated tablet	Oral use
Germany	AbZ-Pharma GmbH Dr. Georg-Spohn-Str. 7 D-89143 Blaubeuren Germany	Norfloxacin AbZ 400mg Filmtabletten	400 mg	Film-coated tablet	Oral use
Germany	Aliud Pharma GmbH & Co.KG Gottlieb-Daimler-Str. 19 D-89150 Laichingen	Norfloxacin AL 400 mg	400 mg	Film-coated tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Germany	Germany Apogepha Arzneimittel GmbH Kyffhäuserstr. 27 D-01309 Dresden	Bactracid	400 mg	Film-coated tablet	Oral use
Germany	Germany CT Arzneimittel GmbH Lengeder Str. 42 a D-13407 Berlin	Norflox-CT 400 mg Filmtabletten	400 mg	Film-coated tablet	Oral use
Germany	Germany Heumann Pharma GmbH & Co.Generica.KG Südwestpark 50 D-90449 Nürnberg	Norfloxacin Heumann 400 mg Filmtabletten	400 mg	Film-coated tablet	Oral use
Germany	Germany Hexal AG Industriestr. 25 D-83607 Holzkirchen	Norflohexal 400mg	400 mg	Film-coated tablet	Oral use
Germany	Germany Ratiopharm GmbH Graf-Arco-Str. 3 D-89079 Ulm	Norfloxacin- ratiopharm 400 mg	400 mg	Film-coated tablet	Oral use
Germany	Germany Ruhrpharm AG Heidsieker Heide 114 D-33739 Bielefeld	Norfluxx	400 mg	Film-coated tablet	Oral use
Germany	Germany Sandoz Pharmaceuticals GmbH Raiffeisenstr. 11 D-83607 Holzkirchen	Norflox-Sandoz 400 mg Filmtabletten	400 mg	Film-coated tablet	Oral use
Germany	Germany Sandoz Pharmaceuticals GmbH Raiffeisenstr. 11 D-83607 Holzkirchen	Norflox-Sandoz 400mg	400 mg	Film-coated tablet	Oral use

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Germany	Germany Schwarz Pharma Deutschland GmbH Alfred-Nobel-Str. 10 D-40789 Monheim	Firin	400 mg	Film-coated tablet	Oral use
Germany	Germany Stada Arzneimittel AG Stadastr. 2-18 D-61118 Bad Vilbel	Norfloxa Stadapharm 400 mg	400 mg	Film-coated tablet	Oral use
Germany	Germany Stadapharm GmbH Stadastr. 2-18 D-61118 Bad Vilbel	Norfloxacin Stada 400 mg	400 mg	Film-coated tablet	Oral use
Germany	Germany TAD Pharma GmbH Heinz-Lohmann-Str. 5 D-27472 Cuxhaven	Norflosal	400 mg	Film-coated tablet	Oral use
Germany	Germany Teofarma S.R.L. Via F.lli Cervi 8 I-27010 Valle Salimbene (PV)	Barazan	400 mg	Film-coated tablet	Oral use
Germany	Germany Uropharm AG Erfurtstr. 64 D-53125 Bonn	Norflox-Uropharm 400mg	400 mg	Film-coated tablet	Oral use
Greece	Germany Anfarm Hellas A.E K. Paleologou & Perikleous 27, Halandri, 15232	Fluseminal	400 mg	Film-coated tablet	Oral use
Greece	Greece Rafarm Aebe Korinthou 12, N. Psychiko, 15451 Greece	Pistofil	400 mg	Coated tablet	Oral use



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Greece	Vianex S.A Tatoiou Street Nea Erythrea 14671 Greece	Norocin	400 mg	Film-coated tablet	Oral use
Greece	Bros Epe Avgis & Gallinis 15, N. Kifissia Greece	Constilax	400 mg	coated tablet	Oral use
Greece	Faran Abee Production and Trading Medicines Averof 19A, Athens, 10433 Greece	Sofasin	400 mg	Film-coated tablet	Oral use
Greece	Xrispa Alpha Farmaceuticals S.A 16 <sup>th</sup> Km Marathonos Avenue Pallini 15344 Greece	Alenbit	400 mg	Coated tablet	Oral use
Greece	Vilco S.A Pefkon Street 121 N. Irakleion 14122 Greece	Setanol	400 mg	Coated tablet	Oral use
Greece	Medicrom S.A 6 Km Markopoulo-Koropi Avenue Markopoulo Mesogeion 19003 Greece	Steinaclox- Medichrom	400 mg	Capsule	Oral use
Greece	Genepharm A.E 18th Km Marathonos Avenue, Pallini Attikis, 15351 Greece	Grenis	400 mg	Coated tablet	Oral use
Greece	Biospray Abee 18th Km Marathonos Avenue, Pallini, 15344 Greece	Sinobid	400 mg	Film-coated tablet	Oral use

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Greece	Specifar Abee 28th October Street No 1 Agia Barbara 12351 Greece	Urospes-N	400 mg	Film-coated tablet	Oral use
Greece	Coup Abee Agias Varvaras 53-55, Dafni, Athens, 17235 Greece	Lorcamin	400 mg	Coated tablet	Oral use
Greece	Viofar Epe Ethnikis Antistaseos & Trifyllias, Aharnai, 13671 Greece	Vetamol	400 mg	Film-coated tablet	Oral use
Greece	Sandoz GmbH, Kundl, Austria Biochemiestrasse 10, A-6520, Kundl Austria	Urobacid	400 mg	Film-coated tablet	Oral use
Hungary	Krka Magyarország Kereskedelmi Kft 1036 Budapest, Pacsirtamező u. 5 Hungary	Nolicin	400mg	Tablet	Oral use
Hungary	Krka Magyarország Kereskedelmi Kft 1036 Budapest, Pacsirtamező u. 5 Hungary	Nolicin-S	400mg	Film-coated tablet	Oral use
Hungary	AC Helcor Hungary Kft 1131 Budapest, Madarász Viktor u.27 Hungary	Norfloxacin-Helcor	400mg	Film-coated tablet	Oral use

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Hungary	Ratiopharm Hungária Kft. 1145 Budapest Uzsoki u. 36/a Hungary	Norfloxacin- Ratiopharm	400mg	Film-coated tablet	Oral use
Ireland	Tad Pharma GmbH, Heinz-Lohmann-Strasse 5 27472 Cuxhaven Germany	Norflocux 400	400mg	Tablet	Oral use
Italy	Sede legale: ABC Farmaceutici S.p.A. Corso Vittorio Emanuele II, 72 Torino Italy	Norfloxacina	400mg	Capsule	Oral use
Italy	Actavis Italy SpA V.Jose'Escrivia De Balaguer, 6 21047 Saronno (VA) Italy	Norfloxacina	400mg	Film-coated tablet	Oral use
Italy	Boniscontro & Gazzone s.r.l. Via Pavia, 6 20136 Milano Italy	Renoxacin	400mg	Film-coated tablet	Oral use
Italy	EG S.p.A. Via Pavia 6, 20131 Milano Italy	Norfloxacina EG	400mg	Film-coated tablet	Oral use
Italy	Farmaceutici Caber S.p.A. Viale Città d'Europa 681 - 00144 Roma Italy	Flossac	400mg	Capsule	Oral use
Italy	GlaxoSmithKline S.p.A. Via A. Fleming 2 - 37135 Verona Italy	Sebercim	400mg	Tablet	Oral use

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Italy	Jet Generici s.r.l. Via Mario Lalli, 8 - 56127 Pisa Italy	Norfloxacin	400mg	Capsule	Oral use
Italy	Sede legale: Laboratori Alter s.r.l. Via Egadi, 7 - 20144 Milano Italy	Norfloxacin	400mg	Film-coated tablet	Oral use
Italy	Merck Sharp & Dohme S.p.A. Via G. Fabbroni, 6 - 00191 Roma Italy	Noroxin	400mg	Film-coated tablet	Oral use
Italy	Neopharmed S.p.A Via G. Fabbroni, 6 - 00191 Roma Italy	Utinor	400mg	Film-coated tablet	Oral use
Italy	Pliva Pharma S.p.A. via Tranquillo Cremona, 10 – 20092 Cinisello Balsamo (MI) Italy	Norfloxacin	400mg	Film-coated tablet	Oral use
Italy	Sandoz S.p.A. Largo Umberto Boccioni, 1 21040 – Origgio (VA) Italy	Norfloxacin Sandoz	400mg	Film-coated tablet	Oral use
Italy	So. Se. Pharm S.r.l. Via dei Castelli Romani 22 - 00040 Pomezia (RM) Italy	Uticina	400mg	Film-coated tablet	Oral use
Italy	Tad Pharma Italia S.r.l. via Felice Casati, 16 – 20124 Milano Italy	Norfloxacin	400mg	Film-coated tablet	Oral use

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Italy	Francia Farmaceutici Industria Farmaco Biologica Srl - Via dei Pestagalli 7 Milano Italy	Diperflox	540mg of Norfloxacin pivaloil-oxy- methyl-ester as 400mg of Norfloxacin	Tablet	Oral use
Italy	Francia Farmaceutici Industria Farmaco Biologica Srl Via dei Pestagalli 7 Milano Italy	Diperflox	100ml contains 5,4g of Norfloxacin pivaloil-oxy- methyl-ester as 4,0g of Norfloxacin	Oral suspension	Oral use
Italy	Pliva Pharma S.p.A via Tranquillo Cremona, 10 – 20092 Cinisello Balsamo (MI) Italy	Norflox	540mg of Norfloxacin pivaloil-oxy- methyl-ester as 400mg of Norfloxacin	Tablet	Oral use
Italy	Pliva Pharma S.p.A. via Tranquillo Cremona, 10 – 20092 Cinisello Balsamo (MI) Italy	Norflox	100ml contains 5,4g of Norfloxacin pivaloil-oxy- methyl-ester as 4,0g of Norfloxacin	Oral suspension	Oral use
Latvia	Cipla (UK) Ltd Old Post House, Hithrow Road, Webbger Bridge, Surrey KT 138TS United Kingdom	Norflox	400 mg	Film-coated tablet	Oral use

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Latvia	Krka d.d. Smarješka cesta 6, SI-8501 Novo mesto Slovenia	Nolicin	400 mg	Film-coated tablet	Oral use
Latvia	Laboratorios Inkeya S.A. Juran XXIII, 15-19, 3a planta ES-08950, Esplugas de Llobregat, Barcelona Spain	Norflok	400 mg	Tablet	Oral use
Latvia	Ranbaxy (UK) Ltd., 20 Balderton Street, London W1K6TL United Kingdom	Norbactin	400 mg	Film-coated tablet	Oral use
Lithuania	Krka d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia	Nolicin	400 mg	Film-coated tablet	Oral use
Lithuania	Ranbaxy (UK) Ltd. C.P. House, 97/107 Uxbridge Road, Ealing London W5 5TL, United Kingdom	Norbactin	400 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp & Dohme Chaussée de Waterloo 1135 B-1180 Bruxelles Belgium	Zoroxin	400mg	Tablet	Oral use
Luxembourg	Eurogenerics Esplanade Heysel, B.22 B-1020 Bruxelles Belgium	Norfloxacin - Eurogenerics	400mg	Tablet	Oral use

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Luxembourg	TAD Pharm. Werk Heinz-Lohmann Str. 5 D-27472 Cuxhaven Germany	Norflosal	400mg	Tablet	Oral use
Malta	Merck, Sharp & Dohme Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Utinor 400mg tablets	400mg	Tablet	Oral use
Malta	Anfarm Hellas S.A. K Paleologou & Perikleous 153 32 Halandri Athens Greece	Fluseminal 400mg tablets	400mg	Tablet	Oral use
The Netherlands	Ratiopharm Nederland BV, Ronde Tocht 11, 1507 CC Zaandam, The Netherlands	Norfloxacin ratiopharm 400 mg,	400 mg	Tablet	Oral use
The Netherlands	Centrafarm Services B.V. Nieuwe Donk 9, 4879 AC Etten-Leur, The Netherlands	Norfloxacin CF 400 mg	400 mg	Film-coated tablet	Oral use
The Netherlands	Sandoz B.V., Veluwezoom 22, 1327 AH Almere, The Netherlands	Norfloxacin Sandoz tablet 400	400 mg	Film-coated tablet	Oral use
The Netherlands	Merck Generics BV, Dieselweg 25, 3752 LB Bunschoten, The Netherlands	Norfloxacin Merck 400 mg	400 mg	Film-coated tablet	Oral use

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Poland	Krka d.d., Novo mesto, Slowenia, 8501, Novo Mesto, Smarjeska Cesta 6 Slovenia	Nolicin	400 mg	Tablet	Oral use
Poland	Pabianickie Zakłady Farmaceutyczne Polfa S.A., ul.Marszałka J. Piłsudskiego 5 95-200 Pabianice Poland	Norsept	400 mg	Film-coated tablet	Oral use
Portugal	Labesfal - Laboratórios Almiro, S.A. 3465-051 Campo de Besteiros, Portugal	Besflox	400 mg	Coated tablet	Oral use
Portugal	Cinfa Portugal, Lda. Av. Tomás Ribeiro, 43 - Bloco 2, 3º F – Edifício Neopark 2790-221 Carnaxide, Portugal	Norfloxacina Cinfa 400 mg Comprimidos	400 mg	Coated tablet	Oral use
Portugal	Ratiopharm - Comércio e Indústria de Produtos Farmacêuticos, Lda., Rua Quinta do Pinheiro – Edifício Tejo - 6º Piso, 2790-143 Carnaxide Portugal	Norfloxacina Ratiopharm 400 mg Comprimidos Revestidos	400 mg	Coated tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda., Quinta da Fonte Edifício Vasco da Gama, 19 - Porto Salvo, 2770-192 Paço d' Arcos Portugal	Noroxin	400 mg	Film-coated tablet	Oral use
Portugal	Bialfar - Produtos Farmacêuticos, S.A., Av. da Siderurgia Nacional, P.O. Box 56 4745-457 S. Mamede do Coronado, Portugal	Uroflox	400 mg	Coated tablet	Oral use



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Romania	S.C AC Helcor S.R.L Str. Victor Babes nr.50, Baia Mare, Jud Maramures, zip code; 430092 Romania	H-NORFLOXACIN 400mg	400mg	Film-coated tablets	Oral use
Romania	S.C Labormed-Pharma S.A Splaiul Independentei nr. 319E, sector 6, Bucharest, zip code: 060044 Romania	Norfloxacin LPH 400mg	400mg	Film-coated tablet	Oral use
Romania	Krka d.d Novo Mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia	Nolicin 400mg	400mg	Film-coated tablet	Oral use
Romania	Ozone Laboratories Ltd, 38 Princes Court 88 Brompton Road, Knightsbridge, SW3 1ES London United Kingdom	Norfloxacin 400mg	400mg	Film-coated tablet	Oral use
Romania	Ozone Laboratories Ltd, 38 Princes Court, 88 Brompton Road, Knightsbridge, SW3 1ES London United Kingdom	Norfloxacin Ozone 400 mg	400mg	Film-coated tablet	Oral use
Romania	S.C Terapia S.A Str. Fabricii nr. 124, Zip code : 400640 Cluj Napoca, România	Norfloxacin Terapia 400 mg	400mg	Film-coated tablet	Oral use

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Romania	S.C Laropharm S.R.L Șoseaua Alexandriei nr. 145 A, Comuna Bragadiru, Zip code; 077025 Jud. Ilfov, România	Norfloxacin 400 mg	400mg	Film-coated tablet	Oral use
Slovak Republic	Krka, d.d. Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia	Nolicin	400 mg	Film-coated tablet	Oral use
Slovak Republic	Medochemie Ltd. P.O.Box 51409, Limassol, CY – 3505 Cyprus	Gyrablock 400 mg	400 mg	Film-coated tablet	Oral use
Slovenia	Krka, d.d. Novo mesto, Šmarješka cesta 6 8501 Novo mesto Slovenia	Nolicin filmsko obložene tablete 400 mg	400 mg	Film-coated tablet	Oral use
Spain	Sharp & Dohme, S.A Josefa Valcárcel, 38 28027 Madrid Spain	Noroxin 400 mg comprimidos recubiertos con película	400 mg	Film-coated tablet	Oral use
Spain	VP Pharma Baru, S.L. C/ Valle de Tobalina, 16 Nave 3, 28021 Madrid Spain	Xasmun 400 mg comprimidos	400 mg	Film-coated tablet	Oral use
Spain	Abbott Laboratories, S.A Avda. de Burgos, 91 28050 Madrid Spain	Baccidal	400 mg	Capsule	Oral use

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Spain	Sandoz Farmaceutica, S.A Avenida de Osa Mayor 4. 28023 Aravaca Madrid Spain	Nalion comprimidos	400 mg	Film-coated tablet	Oral use
Spain	Inkeysa, S.A, Juan XXIII, 15 - 19, 3ª planta, Esplugas de Llobregat, 08950 Spain	Norflok Comprimidos	400 mg	Film-coated tablet	Oral use
Spain	Biosarto, S.A Foc, 68-82, 08038 Barcelona, Spain	Senro cápsulas	400 mg	Capsule	Oral use
Spain	Almirall Prodesfarma S.A Ronda General Mitre, 151, 08022 Barcelona, Spain	Uroctal Comprimidos	400 mg	Film-coated tablet	Oral use
Spain	Alacan S.A Capricornio, 5, 03006 Alicante, Spain	Esclebin 400mg comprimidos recubiertos con película	400 mg	Film-coated tablet	Oral use
Spain	Quimifar, S.A Comadran, 37, 08210 Barbera del Valles, Spain	Amicrobin Capsulas	400 mg	Capsule	Oral use
Spain	Qualigen Avda, Barcelona, 69 08970 Sant Joan Despi Barcelona Spain	Norfloxacino Qualigen 400 mg comprimidos recubiertos con película	400mg	Film-coated tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Sweden	AstraZeneca AB 151 85 Södertälje Sweden	Lexinor	200 mg 400 mg	Film-coated tablet	Oral use
Sweden	Stada Arzneimittel Stadastrasse 2-18 DE-61118 Bad Vilbel Germany	Norfloxacin Stada	400 mg	Film-coated tablet	Oral use
Sweden	Sandoz GmbH Biochemiestrasse 10 AT-6250 Kundl Austria	Norfloxacin Sandoz	400 mg	Film-coated tablet	Oral use
Sweden	Recip AB Box 906 170 09 Solna Sweden	Norfloxacin AstraZeneca	200 mg 400 mg	Film-coated tablet	Oral use
Sweden	Alternova AB Vallgatan 11 170 67 Solna Sweden	Norfloxacin Alternova	200 mg 400 mg	Film-coated tablet	Oral use
Sweden	Krka Sverige AB Göta Ark 175 Medborgarplatsen 25 118 72 Stockholm Sweden	Norfloxacin Krka	200 mg 400 mg	Film-coated tablet	Oral use
United Kingdom	Merck Sharpe & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU. United Kingdom	Utinor Tablets 400mg	400mg	Coated tablet	Oral Use
United Kingdom	TAD Pharma GmbH, Heinz-Lohmann-Strasse 5, Cuxhaven, D-27472 Germany	Norfloxacin 400mg Tablets	400mg	Coated tablet	Oral Use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
United Kingdom	TAD Pharma GmbH, Heinz-Lohmann-Strasse 5, Cuxhaven, D-27472 Germany	Norflocux	400mg	Coated tablet	Oral Use
United Kingdom	Ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm, Germany	Norfloxacin- Ratiopharm 400	400mg	Coated tablet	Oral Use
United Kingdom	Ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm, Germany	Norquin 400	400mg	Coated tablet	Oral Use
United Kingdom	Ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm, Germany	Norflocin 400	400mg	Coated tablet	Oral Use

**ANNEX II**

**SCIENTIFIC CONCLUSIONS AND GROUNDS  
FOR THE REMOVAL OF THE THERAPEUTIC INDICATION  
“ACUTE AND CHRONIC COMPLICATED PYELONEPHRITIS”  
PRESENTED BY THE EMEA**

## **SCIENTIFIC CONCLUSIONS**

### **OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF NORFLOXACIN CONTAINING MEDICINAL PRODUCTS (see Annex I)**

Norfloxacin is a broad-spectrum, quinolone bactericidal agent indicated for the treatment of acute or chronic complicated or uncomplicated pyelonephritis due to susceptible organisms.

It is currently authorised in the EU under the different names referred in Annex I.

Belgium triggered a referral procedure on 14 September 2007 and requested the CHMP to give its opinion on whether the marketing authorisations for oral formulations of products containing norfloxacin in the treatment of acute or chronic complicated or uncomplicated pyelonephritis should be maintained, varied, suspended or withdrawn across the European Union following the re-assessment of norfloxacin benefit/risk balance. This request was based on the following reasons:

- Pyelonephritis is often associated with bacteraemia. Norfloxacin containing medicinal products, which are only available as an oral formulation, do not provide adequate serum levels for the treatment of concomitant bacteraemia.
- There are other alternative treatments available for the above-mentioned indication. Second generation fluoroquinolones such as ciprofloxacin, ofloxacin and levofloxacin show higher serum concentrations and a much better tissue distribution than norfloxacin.
- Complicated pyelonephritis can be treated orally or intravenously (according to local treatment policy and diagnostic criteria used for defining complicated infection). In case of oral treatment, second generation fluoroquinolones are superior to norfloxacin because they present higher serum and tissue levels. The same objections are obviously valid for the oral treatment of uncomplicated pyelonephritis.

The referral procedure was then started on 20 September 2007.

#### **Efficacy**

Most of the Marketing Authorisation Holders (MAHs) involved in the referral did not provide any answer to the list of questions adopted by the CHMP in September 2007, when the procedure was initiated. The MAHs that answered to the questions were unable to provide unpublished scientific data, and some proposed to withdraw this indication, at the exception of 2 MAHs.

As a response to CHMP, most of the MAHs proposed to withdraw the indication in question, while some MAHs chose to submit bibliographic data, because no unpublished data from clinical trials were available to them.

The data submitted did not demonstrate that serum levels after oral treatment with norfloxacin are adequate for eradicating pathogens involved in bacteraemia associated with complicated pyelonephritis.

Additionally, the relationship between the Pharmacokinetic and the Pharmacodynamic of orally administered norfloxacin in the treatment of complicated pyelonephritis was been established.

The MAHs did not provide any relevant information showing comparison of tissue concentrations after oral treatment with norfloxacin, ciprofloxacin, ofloxacin and levofloxacin.

It is though known that the second generation fluoroquinolones (ciprofloxacin, ofloxacin and levofloxacin) show higher serum concentrations and a more favourable tissue distribution than norfloxacin.

Further to the discussion held in May 2008, the CHMP agreed that the second generation of fluoroquinolones result in higher serum concentrations than norfloxacin. However the CHMP requested a more detailed review of all relevant data specifically on resistance to common urinary

pathogens and the possible consequences on the section 5.1 of the SPC before the final conclusion could be made, which lead to the adoption of a List of Outstanding Issues.

Only 3 MAHs answered to this List of outstanding issues adopted in May 2008. Overall, the responses provided included bibliographical data and a proposal to update the section 5.1 of the SPC. None of the answer submitted in June 2008 could demonstrate the efficacy of the oral formulation of medicinal products containing norfloxacin in the treatment of acute and chronic complicated pyelonephritis. Therefore the CHMP remained of the opinion that this indication should be withdrawn.

However the CHMP welcomed the idea to update the MIC breakpoints in section 5.1 of the SPC to include the clinical MIC breakpoints as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in section 5.1 of the SPC as these breakpoints are not only related to the pathogens found in complicated pyelonephritis, but to common urinary pathogens found in other urinary indications. This could indeed be done through a type II variation at national level.

### **Benefit/risk**

Having considered the overall data provided in February and June 2008, the CHMP concluded that the marketing authorisations for the oral formulations of medicinal products containing norfloxacin, when used in the treatment of acute or chronic complicated pyelonephritis, should be withdrawn because the efficacy can no longer be demonstrated in this indication.

The CHMP therefore concluded on 24 July 2008 that for oral norfloxacin containing medicinal products the benefit does not outweigh the risk in complicated pyelonephritis.

Therefore, the CHMP recommended the removal of the therapeutic indication “acute and chronic complicated pyelonephritis” for products containing norfloxacin throughout Europe.

### **GROUND FOR THE REMOVAL OF THE THERAPEUTIC INDICATION “ACUTE AND CHRONIC COMPLICATED PYELONEPHRITIS”**

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing norfloxacin;
- The Committee considered that Marketing Authorisation Holders did not present data demonstrating that norfloxacin taken orally presents efficacy in the treatment of acute or chronic complicated pyelonephritis due to susceptible organisms;
- The Committee concluded that the oral use of norfloxacin containing medicinal products in the treatment of acute or chronic complicated pyelonephritis due to susceptible organisms could no longer be supported;
- The Committee, as a consequence, concluded that the benefit/risk balance of oral norfloxacin containing medicinal products is negative in the above indication.

The CHMP has recommended the removal of the therapeutic indication “acute and chronic complicated pyelonephritis” for the medicinal products containing norfloxacin taken orally (referred to medicinal products listed in Annex I).