Annex I

List of medicinal products and presentations

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Austria	G.L. Pharma Gmbh	Convulex	Sodium Valproate 500mg/5 Ml	Solution For Injection/Infusion	Intravenous Use
Austria	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Austria	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Austria	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Austria	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Austria	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Austria	G.L. Pharma Gmbh	Convulex	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Austria	G.L. Pharma Gmbh	Convulex Für Kinder	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Austria	sanofi-aventis GmbH	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Austria	sanofi-aventis GmbH	Depakine	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Austria	sanofi-aventis GmbH	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Austria	sanofi-aventis GmbH	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Austria	sanofi-aventis GmbH	Depakine Chronosphere	Valproic Acid 14.51mg Sachet, Sodium Valproate 33.33mg Sachet	Modified-Release Granules	Oral Use
Austria	sanofi-aventis GmbH	Depakine Chronosphere	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Austria	sanofi-aventis GmbH	Depakine Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Austria	G.L. Pharma Gmbh	Natriumvalproat G.L.	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Austria	G.L. Pharma Gmbh	Natriumvalproat G.L.	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule	Oral Use
Belgium	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule	Oral Use
Belgium	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Hard	Oral Use
Belgium	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Hard	Oral Use
Belgium	Sanofi Belgium	Depakine	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Belgium	Sanofi Belgium	Depakine	Sodium Valproate 60mg/Ml	Syrup	Oral Use
Belgium	Sanofi Belgium	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	Sanofi Belgium	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	Sanofi Belgium	Depakine Enteric	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Belgium	Sanofi Belgium	Depakine Enteric	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Belgium	Sanofi Belgium	Depakine Enteric	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Belgium	Sanofi Belgium	Depakine I.V.	Sodium Valproate 400mg Container	Powder And Solvent For Solution For Injection	Intravenous Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Belgium	Sandoz N.V.	Valproate	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	Sandoz N.V.	Valproate	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	Mylan Bvba/Sprl	Valproate Mylan	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Belgium	Eurogenerics N.V./S.A.	Valproate Retard Eg	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	Eurogenerics N.V./S.A.	Valproate Retard Eg	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	Mylan Bvba/Sprl	Valproate Retard Mylan	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Belgium	Mylan Bvba/Sprl	Valproate Retard Mylan	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Bulgaria	Sanofi Bulgaria Eood	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Bulgaria	Sanofi Bulgaria Eood	Depakine	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Bulgaria	Sanofi Bulgaria Eood	Depakine	Sodium Valproate 57.64mg/Ml	Syrup	Oral Use
Bulgaria	Sanofi Bulgaria Eood	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Bulgaria	Sanofi Bulgaria Eood	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Bulgaria	G.L. Pharma Gmbh	Конвулекс хроно	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Bulgaria	G.L. Pharma Gmbh	конвулекс	Sodium Valproate 500mg/5 Ml	Solution For Injection/Infusion	Intravenous Use
Bulgaria	G.L. Pharma Gmbh	конвулекс	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Bulgaria	G.L. Pharma Gmbh	конвулекс	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Bulgaria	G.L. Pharma Gmbh	конвулекс	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Bulgaria	G.L. Pharma Gmbh	конвулекс хроно	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Croatia	Sanofi-Aventis Croatia D.O.O.	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Croatia	Sanofi-Aventis Croatia D.O.O.	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Cyprus	Sanofi-Aventis Cyprus Ltd	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Cyprus	Remedica Ltd	Petilin	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Cyprus	Remedica Ltd	Petilin	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Cyprus	Remedica Ltd	Petilin	Sodium Valproate 200mg/5 Ml	Syrup	Oral Use
Czech Republic	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Czech Republic	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Czech Republic	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Czech Republic	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Czech Republic	G.L. Pharma Gmbh	Convulex	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Czech Republic	G.L. Pharma Gmbh	Convulex Cr	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Czech Republic	G.L. Pharma Gmbh	Convulex Cr	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Czech Republic	Sanofi-Aventis Sro	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Czech Republic	Sanofi-Aventis Sro	Depakine	Sodium Valproate 57.64mg/Ml	Syrup	Oral Use
Czech Republic	Sanofi-Aventis Sro	Depakine Chrono Secable	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Czech Republic	Sanofi-Aventis Sro	Depakine Chrono Secable	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril I.V.	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 1000mg Tablet	Prolonged-Release Tablet	Oral Use
Czech Republic	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Czech Republic	Ratiopharm Gmbh	Valproat	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Czech Republic	Ratiopharm Gmbh	Valproat	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Czech Republic	Sandoz Gmbh	Valproat Chrono Sandoz	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Czech Republic	Sandoz Gmbh	Valproat Chrono Sandoz	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Denmark	Orion Corporation	Delepsine	Sodium Valproate 100mg Tablet	Gastro-Resistant Tablet	Oral Use
Denmark	Orion Corporation	Delepsine	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Denmark	Orion Corporation	Delepsine	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Denmark	Orion Corporation	Delepsine	Sodium Valproate 200mg/Ml	Oral Drops, Solution	Oral Use
Denmark	Orion Corporation	Delepsine	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Denmark	Orion Corporation	Delepsine	Sodium Valproate 300mg Suppository	Suppository	Rectal Use
Denmark	Orion Corporation	Delepsine Retard	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Denmark	Sanofi-Aventis Denmark A/S	Deprakine	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Denmark	Sanofi-Aventis Denmark A/S	Deprakine	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Denmark	Sanofi-Aventis Denmark A/S	Deprakine Retard	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Denmark	Sanofi-Aventis Denmark A/S	Deprakine Retard	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Denmark	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 1000mg Container	Prolonged-Release Granules	Oral Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Container	Prolonged-Release Granules	Oral Use
Denmark	Desitin Arzneimittel Gmbh	Orfiril Retard	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Estonia	G.L. Pharma Gmbh	Convulex	Sodium Valproate 500mg/5 Ml	Concentrate For Solution For Injection/Infusion	Intravenous Use
Estonia	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Estonia	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Estonia	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Estonia	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Estonia	G.L. Pharma Gmbh	Convulex	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Estonia	G.L. Pharma Gmbh	Convulex Retard	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Estonia	G.L. Pharma Gmbh	Convulex Retard	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Estonia	Sanofi-Aventis Estonia Oü	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Estonia	Sanofi-Aventis Estonia Oü	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Estonia	Sanofi-Aventis Estonia Oü	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Container	Prolonged-Release Granules	Oral Use
Estonia	Desitin Arzneimittel Gmbh	Orfiril Saft	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Estonia	Sandoz Pharmaceuticals D.D.	Valproate Sodium Sandoz	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Finland	Orion Oyj	Absenor	Sodium Valproate 100mg Tablet	Gastro-Resistant Tablet	Oral Use
Finland	Orion Oyj	Absenor	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Finland	Orion Oyj	Absenor	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Finland	Orion Oyj	Absenor	Sodium Valproate 200mg/Ml	Oral Drops, Solution	Oral Use
Finland	Orion Oyj	Absenor	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Finland	Orion Oyj	Absenor	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Finland	Orion Oyj	Absenor	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Finland	Sanofi Oy	Deprakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Finland	Sanofi Oy	Deprakine	Sodium Valproate 100mg Tablet	Gastro-Resistant Tablet	Oral Use
Finland	Sanofi Oy	Deprakine	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Finland	Sanofi Oy	Deprakine	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Finland	Sanofi Oy	Deprakine	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Finland	Sanofi Oy	Deprakine	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Finland	Sanofi Oy	Deprakine	Sodium Valproate 200mg/Ml	Oral Drops, Solution	Oral Use
Finland	Sanofi Oy	Deprakine	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Finland	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Finland	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Finland	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Finland	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Container	Prolonged-Release Granules	Oral Use
Finland	Sandoz A/S	Valproat Sandoz	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Finland	Sandoz A/S	Valproat Sandoz	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
France	Sanofi-Aventis France	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
France	Sanofi-Aventis France	Depakine	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
France	Sanofi-Aventis France	Depakine	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
France	Sanofi-Aventis France	Depakine	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
France	Sanofi-Aventis France	Depakine	Sodium Valproate 57.64mg/Ml	Syrup	Oral Use
France	Sanofi-Aventis France	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
France	Sanofi-Aventis France	Depakote	Valproate Semisodium 250mg Tablet	Gastro-Resistant Tablet	Oral Use
France	Sanofi-Aventis France	Depakote	Valproate Semisodium 500mg Tablet	Gastro-Resistant Tablet	Oral Use
France	Sanofi-Aventis France	Depamide	Valpromide 300mg Tablet	Gastro-Resistant Tablet	Oral Use
France	Sanofi-Aventis France	Micropakine L.P.	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Prolonged-Release Granules	Oral Use
France	Sanofi-Aventis France	Micropakine L.P.	Valproic Acid 217.75mg Sachet, Sodium Valproate 500.06mg Sachet	Prolonged-Release Granules	Oral Use
France	Sanofi-Aventis France	Micropakine L.P.	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Prolonged-Release Granules	Oral Use
France	Sanofi-Aventis France	Micropakine L.P.	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Prolonged-Release Granules	Oral Use
France	Sanofi-Aventis France	Micropakine L.P.	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Prolonged-Release Granules	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
France	Laboratoire Aguettant	Valproate De Sodium Aguettant	Sodium Valproate 400mg/4 Ml	Solution For Injection	Intravenous Use
France	Arrow Generiques	Valproate De Sodium Arrow	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
France	Eg Labo Laboratoires Eurogenerics	Valproate De Sodium Eg L.P.	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
France	Arrow Generiques	Valproate De Sodium L.P Arrow	Sodium Valproate 500mg Tablet	Film-Coated Tablet	Oral Use
France	Biogaran	Valproate De Sodium L.P. Biogaran	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
France	Sanofi-Aventis France	Valproate De Sodium Lp Zentiva	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
France	Mylan S.A.S	Valproate De Sodium Mylan	Sodium Valproate 500mg Tablet	Modified-Release Tablet	Oral Use
France	Sandoz	Valproate De Sodium Sandoz	Sodium Valproate 500mg Tablet	Modified-Release Tablet	Oral Use
France	Ratiopharm Gmbh	Valproate De Sodium Teva	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
France	Sanofi-Aventis France	Valproate De Sodium Zentiva	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
France	Sanofi-Aventis France	Valproate De Sodium Zentiva	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
France	Sanofi-Aventis France	Valproate De Sodium Zentiva	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
Germany	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Germany	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg Capsule	Prolonged-Release Tablet	Oral Use
Germany	G.L. Pharma Gmbh	Convulex	Sodium Valproate 500mg Capsule	Prolonged-Release Tablet	Oral Use
Germany	G.L. Pharma Gmbh	Convulex®	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule	Oral Use
Germany	G.L. Pharma Gmbh	Convulex®	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule	Oral Use
Germany	G.L. Pharma Gmbh	Convulex®	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl	Sodium Valproate 400mg Container	Powder And Solvent For Solution For Injection	Intravenous Use
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Sanofi-Aventis Deutschland Gmbh	Ergenyl Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Aristo Pharma Gmbh (Art 57)	Espa-Valep Retard	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Aristo Pharma Gmbh (Art 57)	Espa-Valept	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Aristo Pharma Gmbh (Art 57)	Espa-Valept	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Aristo Pharma Gmbh (Art 57)	Espa-Valept Retard	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Riemser Pharma Gmbh	Leptilan	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Riemser Pharma Gmbh	Leptilan	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Riemser Pharma Gmbh	Leptilan	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Aristo Pharma Gmbh (Art 57)	Natriumvalproat Aristo	Sodium Valproate 300mg G	Oral Drops, Solution	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Germany	Hexal Ag	Natriumvalproat Hexal	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Germany	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 1000mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Orfiril Saft	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Germany	Iip - Institut Für Industrielle Pharmazie Forschungs- Und Entwicklungsgesellschaf t Mbh	Valhel Pr	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Iip - Institut Für Industrielle Pharmazie Forschungs- Und Entwicklungsgesellschaf t Mbh	Valhel Pr	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Aliud Pharma Gmbh	Valpro	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Betapharm Arzneimittel Gmbh	Valpro	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Germany	Aliud Pharma Gmbh	Valpro Al	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Betapharm Arzneimittel Gmbh	Valpro Beta	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Betapharm Arzneimittel Gmbh	Valpro Beta	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Betapharm Arzneimittel Gmbh	Valpro Beta	Sodium Valproate 300mg/Ml	Oral Drops, Solution	Oral Use
Germany	Betapharm Arzneimittel Gmbh	Valpro Chrono	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Betapharm Arzneimittel Gmbh	Valpro Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Tad Pharma Gmbh	Valpro Tad	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Germany	Tad Pharma Gmbh	Valpro Tad	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Capsule	Oral Use
Germany	Tad Pharma Gmbh	Valpro Tad	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Capsule	Oral Use
Germany	Abz-Pharma Gmbh	Valproat	Sodium Valproate 150mg Tablet	Film-Coated Tablet	Oral Use
Germany	Abz-Pharma Gmbh	Valproat	Valproic Acid 145mg G, Sodium Valproate 333mg G	Prolonged-Release Tablet	Oral Use
Germany	Abz-Pharma Gmbh	Valproat	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Ratiopharm Gmbh	Valproat	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Germany	Ratiopharm Gmbh	Valproat	Valproic Acid 87mg G, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Stadapharm Gmbh	Valproat	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Stadapharm Gmbh	Valproat	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	1 A Pharma Gmbh	Valproat 1 A Pharma	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	1 A Pharma Gmbh	Valproat 1 A Pharma	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	1 A Pharma Gmbh	Valproat 1 A Pharma	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	1 A Pharma Gmbh	Valproat 1 A Pharma	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	1 A Pharma Gmbh	Valproat 1 A Pharma	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Aristo Pharma Gmbh (Art 57)	Valproat Aristo	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Aristo Pharma Gmbh (Art 57)	Valproat Aristo	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Abz-Pharma Gmbh	Valproat Chrono	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Abz-Pharma Gmbh	Valproat Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Valproat Chrono	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Desitin Arzneimittel Gmbh	Valproat Chrono	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Glenmark Pharmaceuticals Europe Limited	Valproat Chrono	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Germany	Glenmark Pharmaceuticals Europe Limited	Valproat Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Winthrop Arzneimittel Gmbh	Valproat Chrono	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Winthrop Arzneimittel Gmbh	Valproat Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Hexal Ag	Valproat Chrono Hexal	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Hexal Ag	Valproat Chrono Hexal	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Germany	Hexal Ag	Valproat Hexal	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Hexal Ag	Valproat Hexal	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Hexal Ag	Valproat Hexal	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Valproat Neuraxpharm	Sodium Valproate 150mg Units	Gastro-Resistant Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Valproat Neuraxpharm	Sodium Valproate 300mg Units	Gastro-Resistant Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Valproat Neuraxpharm	Sodium Valproate 600mg Units	Gastro-Resistant Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Valproat Neuraxpharm	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Valproat Neuraxpharm	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Valproat Neuraxpharm	Sodium Valproate 300mg Units	Prolonged-Release Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Valproat Neuraxpharm	Sodium Valproate 500mg Units	Prolonged-Release Tablet	Oral Use
Germany	Orion Corporation	Valproat Orion	Sodium Valproate 300mg Tablet	Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Germany	Orion Corporation	Valproat Orion	Sodium Valproate 500mg Tablet	Tablet	Oral Use
Germany	Abz-Pharma Gmbh	Valproat-Ct	Sodium Valproate 300mg Tablet	Film-Coated Tablet	Oral Use
Germany	Abz-Pharma Gmbh	Valproat-Ct	Sodium Valproate 600mg Tablet	Film-Coated Tablet	Oral Use
Germany	Ratiopharm Gmbh	Valproinsäure	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Germany	Ratiopharm Gmbh	Valproinsäure Ratiopharm	Sodium Valproate 150mg Tablet	Film-Coated Tablet	Oral Use
Germany	Ratiopharm Gmbh	Valproinsäure Ratiopharm	Sodium Valproate 300mg Tablet	Film-Coated Tablet	Oral Use
Germany	Ratiopharm Gmbh	Valproinsäure Ratiopharm	Sodium Valproate 600mg Tablet	Film-Coated Tablet	Oral Use
Greece	Sanofi-Aventis Aebe	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Greece	Sanofi-Aventis Aebe	Depakine	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Greece	Sanofi-Aventis Aebe	Depakine	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Greece	Sanofi-Aventis Aebe	Depakine	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
Greece	Sanofi-Aventis Aebe	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Greece	Sanofi-Aventis Aebe	Depakine Chronosphere	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Modified-Release Granules	Oral Use
Greece	Sanofi-Aventis Aebe	Depakine Chronosphere	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Modified-Release Granules	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Greece	Sanofi-Aventis Aebe	Depakine Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Greece	Demo Abee	Hexaquin	Sodium Valproate 400mg Vial	Powder And Solvent For Solution For Injection	Intravenous Use
Hungary	G.L. Pharma Gmbh	Convulex	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Hungary	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Hungary	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Hungary	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Hungary	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Hungary	G.L. Pharma Gmbh	Convulex	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Hungary	G.L. Pharma Gmbh	Convulex	Valproic Acid 43.38mg/Ml	Syrup	Oral Use
Hungary	Sanofi-Aventis Zrt	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Hungary	Sanofi-Aventis Zrt	Depakine	Valproic Acid 50mg/Ml	Syrup	Oral Use
Hungary	Sanofi-Aventis Zrt	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Hungary	Sanofi-Aventis Zrt	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Iceland	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Iceland	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Iceland	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Iceland	Desitin Arzneimittel Gmbh	Orfiril Retard	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim	Sodium Valproate 40mg/Ml	Oral Solution	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim	Sodium Valproate 40mg/Ml	Syrup	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim	Sodium Valproate 100mg Tablet	Tablet	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Chrono	Valproic Acid 58mg Tablet, Sodium Valproate 133.2mg Tablet	Prolonged-Release Tablet	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Chronosphere	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Prolonged-Release Granules	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Chronosphere	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Prolonged-Release Granules	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Prolonged-Release Granules	Oral Use
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Enteric	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Ireland	Sanofi-Aventis Ireland Ltd. T/A SANOFI	Epilim Enteric	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Eg S.P.A.	Acido Valproico E Sodio Valproato Eg	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Eg S.P.A.	Acido Valproico E Sodio Valproato Eg	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Ratiopharm Gmbh	Acido Valproico E Sodio Valproato Ratiopharm	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Ratiopharm Gmbh	Acido Valproico E Sodio Valproato Ratiopharm	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Ratiopharm Gmbh	Acido Valproico E Sodio Valproato Ratiopharm Ratiopharm	Valproic Acid 145mg G, Sodium Valproate 333mg G	Prolonged-Release Tablet	Oral Use
Italy	Sandoz S.P.A.	Acido Valproico Sandoz	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Sandoz S.P.A.	Acido Valproico Sandoz	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Sanofi Spa	Depakin	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Italy	Sanofi Spa	Depakin	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Sanofi Spa	Depakin	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Sanofi Spa	Depakin	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use
Italy	Sanofi Spa	Depakin	Valproic Acid 217.75mg Sachet, Sodium Valproate 500.06mg Sachet	Modified-Release Granules	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Italy	Sanofi Spa	Depakin	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Modified-Release Granules	Oral Use
Italy	Sanofi Spa	Depakin	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Modified-Release Granules	Oral Use
Italy	Sanofi Spa	Depakin	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Italy	Sanofi Spa	Depakin	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
Italy	Sanofi Spa	Depakin Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Sanofi Spa	Depakin Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Alfasigma S.p.A.	Depamag	Valproate Magnesium 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Alfasigma S.p.A.	Depamag	Valproate Magnesium 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Alfasigma S.p.A.	Depamag	Valproate Magnesium 10000mg/100 Ml	Oral Solution	Oral Use
Italy	Sanofi Spa	Depamide	Valpromide 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Zentiva Italia Srl	Sodio Valproato	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Zentiva Italia Srl	Sodio Valproato	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Italy	Zentiva Italia Srl	Sodio Valproato	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Italy	Zentiva Italia Srl	Sodio Valproato	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Italy	Zentiva Italia Srl	Sodio Valproato	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Latvia	Orion Corporation	Absenor	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Latvia	G.L. Pharma Gmbh	Convulex	Sodium Valproate 500mg/5 Ml	Concentrate For Solution For Injection/Infusion	Intravenous Use
Latvia	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Latvia	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Latvia	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Latvia	G.L. Pharma Gmbh	Convulex	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Latvia	G.L. Pharma Gmbh	Convulex®	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Latvia	G.L. Pharma Gmbh	Convulex® Retard	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Latvia	G.L. Pharma Gmbh	Convulex® Retard	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Latvia	Sanofi-Aventis Latvia Sia	Depakine	Sodium Valproate 57.64mg/Ml	Syrup	Oral Use
Latvia	Sanofi-Aventis Latvia Sia	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Latvia	Sanofi-Aventis Latvia Sia	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Lithuania	Orion Corporation	Absenor	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Lithuania	G.L. Pharma Gmbh	Convulex	Sodium Valproate 100mg/Ml	Solution For Injection/Infusion	Intravenous Use
Lithuania	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Lithuania	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Lithuania	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Lithuania	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Lithuania	G.L. Pharma Gmbh	Convulex	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Lithuania	G.L. Pharma Gmbh	Convulex Retard	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Lithuania	G.L. Pharma Gmbh	Convulex Retard	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Lithuania	Uab „Sanofi-Aventis Lietuva“	Depakine	Sodium Valproate 57.64mg/Ml	Syrup	Oral Use
Lithuania	Uab „Sanofi-Aventis Lietuva“	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Lithuania	Uab „Sanofi-Aventis Lietuva“	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Lithuania	Uab „Sanofi-Aventis Lietuva“	Depakine Chronosphere	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use
Lithuania	Uab „Sanofi-Aventis Lietuva“	Depakine Chronosphere	Valproic Acid 217.75mg Sachet, Sodium Valproate 500.06mg Sachet	Modified-Release Granules	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Lithuania	Uab „Sanofi-Aventis Lietuva“	Depakine Chronosphere	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Modified-Release Granules	Oral Use
Lithuania	Uab „Sanofi-Aventis Lietuva“	Depakine Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Lithuania	Sandoz Pharmaceuticals D.D.	Valproate Sodium Sandoz	Sodium Valproate 500mg Tablet	Modified-Release Tablet	Oral Use
Luxembourg	Sanofi Belgium	Depakine	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Luxembourg	Sanofi Belgium	Depakine	Sodium Valproate 60mg/Ml	Syrup	Oral Use
Luxembourg	Sanofi Belgium	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Luxembourg	Sanofi Belgium	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Luxembourg	Sanofi Belgium	Depakine Enteric	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Luxembourg	Sanofi Belgium	Depakine Enteric	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Luxembourg	Sanofi Belgium	Depakine Enteric	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Luxembourg	Sanofi Belgium	Depakine I.V.	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Luxembourg	Ratiopharm Gmbh	Valproat	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Luxembourg	Ratiopharm Gmbh	Valproat Ratiopharm	Valproic Acid 145mg G, Sodium Valproate 333mg G	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Luxembourg	Eurogenerics N.V./S.A.	Valproate Retard Eg	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Luxembourg	Eurogenerics N.V./S.A.	Valproate Retard Eg	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Luxembourg	Mylan Bvba/Sprl	Valproate Retard Mylan	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Luxembourg	Mylan Bvba/Sprl	Valproate Retard Mylan	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Malta	Sanofi Malta Ltd	Epilim	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Malta	Sanofi Malta Ltd	Epilim	Sodium Valproate 200mg/5 Ml	Oral Solution	Oral Use
Malta	Sanofi Malta Ltd	Epilim Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Malta	Sanofi Malta Ltd	Epilim Chrono	Valproic Acid 58mg Tablet, Sodium Valproate 133.2mg Tablet	Modified-Release Tablet	Oral Use
Malta	Sanofi Malta Ltd	Epilim Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Malta	Wockhardt Uk Ltd	Sodium Valproate Wockhardt Uk	Sodium Valproate 100mg/Ml	Solution For Injection/Infusion	Intravenous Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine	Sodium Valproate 40mg/Ml	Syrup	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Chronosphere	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Chronosphere	Valproic Acid 217.75mg Sachet, Sodium Valproate 500.06mg Sachet	Modified-Release Granules	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Chronosphere	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Modified-Release Granules	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Chronosphere	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Modified-Release Granules	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Enteric	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Enteric	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Netherlands	Sanofi-Aventis Netherlands B.V.	Depakine Enteric	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Netherlands	Apotex Europe B.V.	Natriumvalproaat Apotex	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Netherlands	Apotex Europe Bv	Natriumvalproaat Apotex	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Netherlands	Apotex Europe Bv	Natriumvalproaat Apotex	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Netherlands	Apotex Europe Bv	Natriumvalproaat Apotex	Sodium Valproate 300mg/5 Ml	Oral Solution	Oral Use
Netherlands	Teva Nederland B.V.	Natriumvalproaat Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Netherlands	Centrafarm B.V.	Natriumvalproaat Chrono Cf	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Netherlands	Centrafarm B.V.	Natriumvalproaat Chrono Cf	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Netherlands	Sandoz B.V.	Natriumvalproaat Chrono Sandoz	Sodium Valproate 300mg Tablet	Modified-Release Tablet	Oral Use
Netherlands	Sandoz B.V.	Natriumvalproaat Chrono Sandoz	Sodium Valproate 500mg Tablet	Modified-Release Tablet	Oral Use
Netherlands	Sandoz B.V.	Natriumvalproaat Sandoz	Sodium Valproate 300mg Tablet	Modified-Release Tablet	Oral Use
Netherlands	Sandoz B.V.	Natriumvalproaat Sandoz	Sodium Valproate 500mg Tablet	Modified-Release Tablet	Oral Use
Netherlands	Teva Nederland B.V.	Natriumvalproaat Teva	Valproic Acid 145mg G, Sodium Valproate 333mg G	Prolonged-Release Tablet	Oral Use
Netherlands	Pharmachemie B.V	Orfiril	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Netherlands	Pharmachemie B.V	Orfiril Cr	Sodium Valproate 300mg Capsule	Modified-Release Capsule, Hard	Oral Use
Netherlands	Pharmachemie B.V	Orfiril Cr	Sodium Valproate 1000mg Sachet	Modified-Release Granules	Oral Use
Netherlands	Pharmachemie B.V	Orfiril Cr	Sodium Valproate 500mg Sachet	Modified-Release Granules	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Norway	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg	Prolonged-Release Capsule	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 1000mg Container	Prolonged-Release Granules	Oral Use
Norway	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Container	Prolonged-Release Granules	Oral Use
Poland	Orion Corporation	Absenor	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Poland	Orion Corporation	Absenor	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Poland	G.L. Pharma Gmbh	Convival Chrono	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Poland	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Capsule, Soft	Oral Use
Poland	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Capsule, Soft	Oral Use
Poland	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Capsule, Soft	Oral Use
Poland	G.L. Pharma Gmbh	Convulex	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Poland	Sanofi-Aventis France	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Poland	Sanofi-Aventis France	Depakine	Sodium Valproate 40mg/Ml	Syrup	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Poland	Sanofi-Aventis Sp Z.O.O.	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Poland	Sanofi-Aventis Sp Z.O.O.	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Poland	Sanofi-Aventis Sp Z.O.O.	Depakine Chronosphere	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use
Poland	Sanofi-Aventis Sp Z.O.O.	Depakine Chronosphere	Valproic Acid 217.75mg Sachet, Sodium Valproate 500.06mg Sachet	Modified-Release Granules	Oral Use
Poland	Sanofi-Aventis Sp Z.O.O.	Depakine Chronosphere	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Modified-Release Granules	Oral Use
Poland	Sanofi-Aventis Sp Z.O.O.	Depakine Chronosphere	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Modified-Release Granules	Oral Use
Poland	Sanofi-Aventis Sp Z.O.O.	Depakine Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Poland	Pharmaswiss česká Republika S.R.O.	Dipromal	Valproate Magnesium 200mg Tablet	Film-Coated Tablet	Oral Use
Poland	Sandoz Gmbh	Valprolek	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Poland	Sandoz Gmbh	Valprolek	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Generis Farmacêutica, S.A.	ácido Valpróico Generis	Valproic Acid 400mg/4 Ml	Powder And Solvent For Solution For Injection	Intravenous Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Portugal	Generis Farmacêutica, S.A.	ácido Valpróico Generis	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Generis Farmacêutica, S.A.	ácido Valpróico Generis	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Sandoz Farmacêutica Lda.	ácido Valpróico Sandoz	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Sandoz Farmacêutica Lda.	ácido Valpróico Sandoz	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine	Sodium Valproate 40mg/Ml	Syrup	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chrono 300	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chrono 300	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chrono 500	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chronosphere	Valproic Acid 14.51mg Sachet, Sodium Valproate 33.33mg Sachet	Modified-Release Granules	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chronosphere	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chronosphere	Valproic Acid 217.75mg Sachet, Sodium Valproate 500.06mg Sachet	Modified-Release Granules	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chronosphere	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Modified-Release Granules	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chronosphere	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Modified-Release Granules	Oral Use
Portugal	Sanofi - Produtos Farmaceuticos Lda	Depakine Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 200mg Tablet	Coated Tablet	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 1000mg Sachet	Prolonged-Release Granules	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil	Sodium Valproate 500mg Sachet	Prolonged-Release Granules	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil-R	Valproate Semisodium 269.1mg Tablet	Gastro-Resistant Tablet	Oral Use
Portugal	Tecnifar, Indústria Técnica Farmacêutica, Sa	Diplexil-R	Valproate Semisodium 538.2mg Tablet	Gastro-Resistant Tablet	Oral Use
Portugal	Ratiopharm-Comercio E Industria De Produtos Farmaceuticos Lda	Ácido Valpróico Ratiopharm 500 mg Comprimidos de libertação prolongada	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Portugal	Ratiopharm-Comercio E Industria De Produtos Farmaceuticos Lda	Ácido Valpróico Ratiopharm 300 mg Comprimidos de libertação prolongada	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Romania	Lannacher Heilmittel Ges.M.B.H.,	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Romania	Lannacher Heilmittel Ges.M.B.H.,	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Romania	Lannacher Heilmittel Ges.M.B.H.,	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Romania	Sanofi-Aventis France	Depakine	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Romania	Sanofi-Aventis France	Depakine	Sodium Valproate 57.64mg/Ml	Syrup	Oral Use
Romania	Sanofi-Aventis France	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Romania	Sanofi-Aventis France	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
Romania	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg/5 Ml	Oral Solution	Oral Use
Romania	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Romania	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Romania	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 1000mg Sachet	Prolonged-Release Granules In Sachet	Oral Use
Romania	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Sachet	Prolonged-Release Granules In Sachet	Oral Use
Romania	Arena Group S.A	Valepil	Sodium Valproate 200mg/5 Ml	Syrup	Oral Use
Slovakia	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Slovakia	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Slovakia	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
Slovakia	G.L. Pharma Gmbh	Convulex	Sodium Valproate 300mg/Ml	Oral Solution	Oral Use
Slovakia	G.L. Pharma Gmbh	Convulex	Sodium Valproate 50mg/Ml	Syrup	Oral Use
Slovakia	G.L. Pharma Gmbh	Convulex Cr	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Slovakia	Sanofi-Aventis Slovakia Sro	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
Slovakia	Sanofi-Aventis Slovakia Sro	Depakine	Sodium Valproate 57.64mg/Ml	Syrup	Oral Use
Slovakia	Sanofi-Aventis Slovakia Sro	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Slovakia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
Slovakia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Slovakia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Slovakia	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 600mg Tablet	Gastro-Resistant Tablet	Oral Use
Slovakia	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule	Oral Use
Slovakia	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule	Oral Use
Slovakia	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 1000mg Tablet	Prolonged-Release Tablet	Oral Use
Slovakia	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Slovakia	Ratiopharm Gmbh	Valpro	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Slovakia	Sandoz Pharmaceuticals D.D.	Valproát Chrono Sandoz	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Slovakia	Sandoz Pharmaceuticals D.D.	Valproát Chrono Sandoz	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Slovenia	Sanofi-Aventis D.O.O.	Depakine Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Slovenia	Sanofi-Aventis D.O.O.	Depakine Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Spain	G.E.S. Genéricos Españoles Laboratorio, S.A.	ácido Valproico G.E.S	Sodium Valproate 400mg Vial	Powder And Solvent For Solution For Injection	Intravenous Use
Spain	Sanofi-Aventis, S.A.	Depakine	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Spain	Sanofi-Aventis, S.A.	Depakine	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
Spain	Sanofi-Aventis, S.A.	Depakine	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Spain	Sanofi-Aventis, S.A.	Depakine	Sodium Valproate 200mg/Ml	Oral Solution	Oral Use
Spain	Sanofi-Aventis, S.A.	Depakine Crono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Spain	Sanofi-Aventis, S.A.	Depakine Crono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Spain	Sanofi-Aventis, S.A.	Depakine Crono	Valproic Acid 145mg Tablet, Sodium Valproate 333mg Tablet	Prolonged-Release Tablet	Oral Use
Spain	Sanofi-Aventis, S.A.	Depakine Crono	Valproic Acid 87mg Tablet, Sodium Valproate 200mg Tablet	Prolonged-Release Tablet	Oral Use
Sweden	Orion Corporation	Absenor	Sodium Valproate 100mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Orion Corporation	Absenor	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Orion Corporation	Absenor	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Orion Corporation	Absenor	Sodium Valproate 200mg/Ml	Oral Drops, Solution	Oral Use
Sweden	Orion Corporation	Absenor	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Sweden	Orion Corporation	Absenor Depot	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
Sweden	Orion Corporation	Absenor Depot	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
Sweden	Sanofi Ab	Ergenyl	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Sweden	Sanofi Ab	Ergenyl	Sodium Valproate 100mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Sanofi Ab	Ergenyl	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Sanofi Ab	Ergenyl	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Sanofi Ab	Ergenyl	Sodium Valproate 200mg/Ml	Oral Drops, Solution	Oral Use
Sweden	Sanofi Ab	Ergenyl	Sodium Valproate 60mg/Ml	Oral Solution	Oral Use
Sweden	Sanofi Ab	Ergenyl Retard	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use
Sweden	Sanofi Ab	Ergenyl Retard	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Modified-Release Granules	Oral Use
Sweden	Sanofi Ab	Ergenyl Retard	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
Sweden	Sanofi Ab	Ergenyl Retard	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Modified-Release Tablet	Oral Use
Sweden	Sanofi Ab	Ergenyl Retard	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Modified-Release Tablet	Oral Use
Sweden	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 150mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Desitin Arzneimittel Gmbh	Orfiril	Sodium Valproate 300mg Tablet	Gastro-Resistant Tablet	Oral Use
Sweden	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
Sweden	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
Sweden	Desitin Arzneimittel Gmbh	Orfiril Long	Sodium Valproate 500mg Container	Prolonged-Release Granules	Oral Use
United Kingdom	G.L. Pharma Gmbh	Convulex	Valproic Acid 150mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
United Kingdom	G.L. Pharma Gmbh	Convulex	Valproic Acid 300mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
United Kingdom	G.L. Pharma Gmbh	Convulex	Valproic Acid 500mg Capsule	Gastro-Resistant Capsule, Soft	Oral Use
United Kingdom	Aventis Pharma Ltd	Depakote	Valproate Semisodium 269.1mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Aventis Pharma Ltd	Depakote	Valproate Semisodium 538.2mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim	Sodium Valproate 400mg/Ml	Powder And Solvent For Solution For Injection	Intravenous Use
United Kingdom	Aventis Pharma Ltd	Epilim	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim	Sodium Valproate 40mg/Ml	Oral Solution	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim	Sodium Valproate 40mg/Ml	Syrup	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim	Sodium Valproate 100mg Tablet	Tablet	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chrono	Valproic Acid 145.14mg Tablet, Sodium Valproate 333.3mg Tablet	Prolonged-Release Tablet	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chrono	Valproic Acid 58mg Tablet, Sodium Valproate 133.2mg Tablet	Prolonged-Release Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
United Kingdom	Aventis Pharma Ltd	Epilim Chrono	Valproic Acid 87mg Tablet, Sodium Valproate 199.8mg Tablet	Prolonged-Release Tablet	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chronosphere	Valproic Acid 14.51mg Sachet, Sodium Valproate 33.33mg Sachet	Modified-Release Granules	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chronosphere	Valproic Acid 145.14mg Sachet, Sodium Valproate 333.3mg Sachet	Modified-Release Granules	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chronosphere	Valproic Acid 217.75mg Sachet, Sodium Valproate 500.06mg Sachet	Modified-Release Granules	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chronosphere	Valproic Acid 29.03mg Sachet, Sodium Valproate 66.66mg Sachet	Modified-Release Granules	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chronosphere	Valproic Acid 290.27mg Sachet, Sodium Valproate 666.6mg Sachet	Modified-Release Granules	Oral Use
United Kingdom	Aventis Pharma Ltd	Epilim Chronosphere	Valproic Acid 72.61mg Sachet, Sodium Valproate 166.76mg Sachet	Modified-Release Granules	Oral Use
United Kingdom	Desitin Arzneimittel Gmbh	Episenta	Sodium Valproate 100mg/Ml	Solution For Injection	Intravenous Use
United Kingdom	Desitin Arzneimittel Gmbh	Episenta	Sodium Valproate 150mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
United Kingdom	Desitin Arzneimittel Gmbh	Episenta	Sodium Valproate 300mg Capsule	Prolonged-Release Capsule, Hard	Oral Use
United Kingdom	Desitin Arzneimittel Gmbh	Episenta	Sodium Valproate 1000mg Sachet	Prolonged-Release Granules	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
United Kingdom	Desitin Arzneimittel Gmbh	Episenta	Sodium Valproate 500mg Sachet	Prolonged-Release Granules	Oral Use
United Kingdom	G.L. Pharma Gmbh	Epival Cr	Sodium Valproate 300mg Tablet	Prolonged-Release Tablet	Oral Use
United Kingdom	G.L. Pharma Gmbh	Epival Cr	Sodium Valproate 500mg Tablet	Prolonged-Release Tablet	Oral Use
United Kingdom	Norton Healthcare Ltd T/A Ivax Pharmaceuticals Uk	Kentlim Opd	Sodium Valproate Bp 200mg	Oral Solution	Oral Use
United Kingdom	Winthrop Pharmaceuticals Uk Ltd	Sodium Valproate	Sodium Valproate 40mg/Ml	Oral Solution	Oral Use
United Kingdom	Norton Healthcare Ltd T/A Ivax Pharmaceuticals Uk	Sodium Valproate Ivax	Sodium Valproate 200mg/5 Ml	Oral Solution	Oral Use
United Kingdom	Noridem Enterprises Ltd	Sodium Valproate Noridem Enterprises	Sodium Valproate 400mg Vial	Powder And Solvent For Solution For Injection/Infusion	Intravenous Use
United Kingdom	Teva Uk Limited	Sodium Valproate Teva	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Teva Uk Limited	Sodium Valproate Teva	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Winthrop Pharmaceuticals Uk Ltd	Sodium Valproate Winthrop	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Winthrop Pharmaceuticals Uk Ltd	Sodium Valproate Winthrop	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Wockhardt Uk Ltd	Sodium Valproate Wockhardt	Sodium Valproate 100mg/Ml	Solution For Injection/Infusion	Intravenous Use
United Kingdom	Wockhardt Uk Ltd	Sodium Valproate Wockhardt	Sodium Valproate 200mg	Gastro-Resistant Tablet	Oral Use
United Kingdom	Wockhardt Uk Ltd	Sodium Valproate Wockhardt	Sodium Valproate 200mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Wockhardt Uk Ltd	Sodium Valproate Wockhardt	Sodium Valproate 500mg Tablet	Gastro-Resistant Tablet	Oral Use
United Kingdom	Wockhardt Uk Ltd	Sodium Valproate Wockhardt	Sodium Valproate 200mg/5 Ml	Oral Solution	Oral Use
United Kingdom	Wockhardt Uk Ltd	Sodium Valproate Wockhardt Uk	Sodium Valproate 500mg	Gastro-Resistant Tablet	Oral Use

Member State in EU/EEA	Marketing Authorisation holder	Invented name	INN + Strength	Pharmaceutical form	Route of Administration
United Kingdom	Norton Healthcare Ltd T/A Ivax Pharmaceuticals Uk	Valpal	Sodium Valproate 200mg/5 Ml	Oral Solution	Oral Use

Annex II

Scientific conclusions

Scientific conclusions

On 08 March 2017 France triggered a procedure under Article 31 of Directive 2001/83/EC, and requested the PRAC to assess the impact on the concerns regarding the effectiveness of the risk minimisation measures on the benefit-risk balance of medicinal products containing substances related to valproate and issue a recommendation on whether the marketing authorisation(s) of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 08 February 2018 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

In the course of the consultations that PRAC had in this procedure, some additional concerns have arisen, other than the well-known and documented harm to the foetus during *in utero* exposure. The potential impact of paternal use of valproate, the potential effect on the third generation offspring and the potential effects on mitochondria (mitochondrial toxicity) were discussed.

Regarding exposure via seminal fluid, estimation was made of the area under curve (AUC) for valproate in a woman following vaginal exposure to valproate via seminal fluid of a man treated with valproate. This resulted in a value which was more than 25,000 times lower than the AUC in a woman treated orally with an equal dose (single oral dose 500 mg). It can be concluded that it is extremely unlikely that valproate, when used by a male patient, could cause adverse effects to the embryo/foetus by this route. The PRAC requested the conduct of a retrospective observational study to further characterise this theoretical risk.

Genetic changes can be divided in gene mutations and chromosome aberrations. It seems theoretically possible that gene mutations in sperm cells could be transmitted to the offspring. However, tests for gene mutations were negative. Therefore, this type of transmission is not likely to occur for valproate. The PRAC therefore recommends that other tests could be performed (e.g. *in vitro* mouse lymphoma assay) to further explore this hypothesis. Several tests for chromosome damage were positive. Severe chromosome damage is expected to lead to death of sperm cells / reduced fertility and not to transmission of mutations to the offspring. It is unknown whether slight chromosome damage might be transmitted to the offspring. Further investigation is recommended by PRAC.

The epigenetic mechanism refers to the possibility that changes in the gene expression in the gametes are transmitted to the gene expression in the embryo (for example by changes in DNA methylation). Theoretically this is possible by changes to the gene expression in sperm cells of adult males or by changes to the developing germ cells in the embryo. In one experiment it was shown that a change in gene expression (one gene) in male mice after exposure to a histone deacetylases (HDAC) inhibitor (not valproate) was observed also in the offspring of these mice (Jia et al, 2015)[1], so possible in principle. It was shown in a transgenerational experiment in mice that administration of valproate during pregnancy (day 10) produced autism-like symptoms and increased expression of several proteins in the brains up to the third generation offspring. This was not shown for teratogenic effects as malformations in the first generation offspring was not observed in the second and third generation offspring (Choi et al, 2016)[2]. Although several limitations exist, the study suggests that there was some transgenerational effect. The PRAC agrees that more research is necessary to evaluate whether

[1] Jia H, Morris CD, Williams RM, Loring JF, Thomas EA. HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation. Proc Natl Acad Sci U S A. 2015 Jan 6;112(1):E56-64.

[2] Choi CS, Gonzales EL, Kim KC, Yang SM, Kim JW, Mabunga DF, et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. Sci Rep. 2016 Nov 7;6:36250

valproate indeed may induce transgenerational alterations of gene expression to the offspring and the types of consequent effects.

Furthermore, in a literature overview regarding effects on mitochondria, known side effects were described such as liver toxicity, Reye-like syndrome, pancreatitis and immune deficiency (leukopenia). There is no clear evidence that mitochondrial dysfunction caused by valproate is associated with the development of autism. The PRAC is of the opinion that the currently available data do not warrant further investigation regarding the potential association between mitochondrial dysfunction and autism.

In the previous European review (2014)[3], several educational measures for patients and healthcare professionals (HCPs) were recommended. Nevertheless, as shown in the data reviewed in this procedure educational measures did not reach the targeted audience in a satisfactory rate in order to have any significant impact on prescriptions.

Usage data from the ongoing joint drug utilisation study (DUS) as well as other data (surveys, national surveys, anecdotal evidence etc.) that have been evaluated in the current referral indicate that valproate is still used by a considerable proportion of WCBP in different MSs for both epilepsy and bipolar disorder indications.

A wide consultation was done on the request of PRAC to gather all the latest information in terms of scientific and clinical knowledge with the consultation of two scientific groups (neurology and psychiatry), and to collect information from healthcare professionals, female patients themselves as well their families, from patient organisations (public hearing, stake holders meeting) who are advocating to better characterise and increase the awareness on the risk of harm to the foetus when using valproate during pregnancy. From these consultations it was evident that the specialists are aware of the risks discussed, but the information is not adequately reaching the patients timely and effectively.

In addition to the measures to increase awareness about risks of valproate, the different expert consultations provided clear recommendations to restrict the use of valproate. They also provided experience from clinical practice on the management of women who wish to become pregnant or are pregnant. In particular, experience from HCPs regarding the discontinuation of valproate or switch to other treatment was provided. To obtain additional robust information on the switch and discontinuation of valproate, the PRAC requested the conduct of an observational study to identify and evaluate the best practices for switching of valproate in clinical practice.

Regarding pregnancy/family planning in epilepsy, the PRAC also highlighted that, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

In view of the above, the PRAC recommended amendments to the product information, in particular to contraindicate its use to women of childbearing potential that do not fulfil the conditions of a pregnancy prevention program, and communication to healthcare professionals through a direct healthcare professional communication (DHPC). A pregnancy prevention programme will be implemented accordingly to prevent valproate exposure during pregnancy given that significant risk of lifelong harm is associated with its use. Educational measures are necessary in order to ensure that healthcare professionals and patients are informed about the risks associated with valproate in

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f

pregnant women and women of childbearing potential and on the measures necessary to minimise the risk of exposure on valproate in pregnancy. The PRAC re-iterate that a single version of educational materials is disseminated in each member state, where appropriate. The MAHs are encouraged to collaborate and liaise with the national competent authorities to facilitate the dissemination of the agreed educational material.

The PRAC recommended the improvement of a HCP guide to make sure that valproate prescribers are aware of the risks associated with the use of this product in female children, women of childbearing potential and pregnant women and requested that the patients are also informed about these risks appropriately. The guide should explain the pregnancy prevention programme and the conditions to be met prior to starting treatment with valproate. At least annual re-assessment of the need for valproate therapy and consideration of alternative treatment options in female children who experienced menarche and women of childbearing potential should be included. In addition, the guide should familiarise the prescribers with key actions to mitigate the risks associated with the use of valproate in exposed girls and women by using the patient guide and the risk acknowledgment form. The HCP guide should include the recommendation to inform the parents of young girls using valproate about the need to contact their specialist once their daughter has experienced menarche, information on need for switching when pregnancy planning, on the need to go through the risk acknowledgement form and the patient card, at least annually.

The PRAC recommended that a patient card to be made available in all MSs and for all patients who receive valproate. Information on the patient card should be brief and concise regarding the efficacy of the product but also the harm to an unborn child when taken during pregnancy. The use of effective contraception without interruption during the all course of treatment should be included as well as a reminder for annual re-assessment. Advice on non-interruption of treatment as well as the need to contact the doctor when a pregnancy is planned or suspected should also be included. This patient card should be attached at the outer carton to prompt as a reminder the discussion between the pharmacist and the patient at the time of the product dispensing.

The PRAC recommended that the patient guide for female children, adolescents and women who are being prescribed valproate is further developed and improved. The patient guide should provide comprehensive information on risks to the unborn child due to *in utero* exposure to valproate and related substances, the details of the pregnancy prevention programme to avoid valproate exposure during pregnancy and the required actions in terms of pregnancy or intention to become pregnant. In order to provide adequate information, it should be tailored for different situations in the life-time of a woman and be age-appropriate: the first prescription, women continuing valproate treatment and not trying to have a child, women of childbearing potential continuing valproate treatment and considering trying to have a child, pregnant women (unplanned pregnancy) whilst continuing valproate treatment. This guide should be handed over to the patient.

The PRAC also reviewed the annual risk acknowledgement form which should be used and documented at initiation and during each annual review of valproate treatment by a specialist.

The PRAC taking into account all the evidence as well the areas where information is limited requested several measures in order to further characterise the risks, increase the awareness of the risks, restrict the use and measure the effectiveness of the currently proposed measures. The current ongoing drug utilisation study (DUS) should be adapted and continued to assess the effectiveness of the updated risk minimisation measures including the pregnancy prevention programme conditions and to further characterise the prescribing patterns for valproate. A survey among HCP to assess their knowledge and behaviour with regard to the new product information restrictions and whether they received the direct healthcare professional communication (DHPC) and educational materials, and another survey among patients to assess the receipt of the educational materials should be performed. A post-authorisation

safety study (PASS) using data preferably from existing registries should be performed to further characterise the foetal anticonvulsant syndrome in children with valproate *in utero* exposure as compared to other anti-epileptic drugs. In addition in an effort to increase the knowledge on the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, a retrospective observational study is recommended. Further, an observational study to evaluate and identify the best practice for discontinuation and switching of valproate treatment will be conducted.

The MAHs are strongly encouraged to collaborate on the requested measures and to perform joint studies.

Among the requests from the patients and family members who were consulted was the implementation of a visual reminder on the outer package to warn the women on the harm to the unborn baby and to also promptly advise them to use effective contraception. The PRAC agreed that such visual reminder on the outer carton is important to warn the patient on the risk and to prompt to consult a physician and requested the inclusion of a visual reminder on the outer packaging. In addition to the boxed text this may include a symbol/pictogram, with the details to be adapted at national level.

In view of the safety issues in discussion and the whole set of conditions for the risk minimisation aiming at minimising exposure in pregnancy, all MAHs need to have in place a risk management plan.

The medicinal products will continue to be listed in the additional monitoring list.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products containing substances related to valproate.
- The PRAC considered the totality of the data submitted for valproate and related substances with regard to the teratogenic and neurodevelopmental risks, the use in clinical practice and the effectiveness of the risk minimisation measures in place. This included the responses submitted by the marketing authorisation holders in writing as well as the outcomes of the scientific advisory groups in neurology and psychiatry. In addition, the PRAC considered the views of patient organisations, patients, families and carers, and the views of healthcare professionals in a public hearing and dedicated meeting.
- The PRAC confirmed the known risk of intra-uterine exposure to valproate and related substances, associated with an increased risk of developmental disorders and congenital anomalies in the offspring. No new significant information was identified regarding this risk.
- The PRAC concluded that the risk minimisation measures in place have not been sufficiently effective to prevent unintended *in utero* exposure to valproate and related substances in all indications.
- The PRAC concluded that the minimisation measures for medicinal products containing valproate or related substances should be strengthened through contraindication in all indications (epilepsy, bipolar disorders and prophylaxis of migraine) in women/girls of childbearing potential unless the conditions of the pregnancy prevention programme are complied with.

- The PRAC considered that the pregnancy prevention programme should reflect that in the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
- For their use in pregnancy for the treatment of epilepsy, the PRAC concluded that these medicinal products are contraindicated unless there is no suitable alternative treatment option. For their use in the treatment of bipolar disorders and prophylaxis of migraine these products are contraindicated in pregnancy.
- In addition, the PRAC recommended other changes to the product information such as warnings and precautions for use and updated information on the risks related to exposure during pregnancy to better inform the healthcare professionals and patients.
- The PRAC also concluded that there was a need to update the educational materials aimed to fully inform patients and healthcare professionals on the risks to the unborn child when exposed *in utero* to valproate, and to implement some further risk minimisation measures such as a visual reminder on the outer packaging, a patient card and an acknowledgment form to raise awareness about the risks and the need for contraception. PRAC also recommended post-authorisation studies to assess the effectiveness of the risk minimisation measures. Core elements of a direct healthcare professional communication were agreed, together with the timelines for its distribution.
- The PRAC also reviewed the available scientific evidence on the risk of malformations and neurodevelopmental disorders to offspring after paternal exposure, the risk of malformations and neurodevelopmental disorders to the third generation offspring and considered that further research is needed before conclusions can be drawn. The PRAC requested the conduct of post-authorisation studies.

In view of the above, the Committee considers that the benefit-risk balance of medicinal products containing substances related to valproate remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for medicinal products containing substances related to valproate.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Detailed explanation of the scientific grounds for the differences from the PRAC recommendation

The CMDh acknowledges correspondence received from a MAH (Laboratoires Aguettant, France) of medicinal products containing valproate injectable (intravenous; IV) formulations, and requesting further clarity for the implementation of the pharmacovigilance activities and risk minimization measures adopted by the PRAC for these IV formulation indicated for the temporary management of epilepsy when administration via oral route is not possible.

The MAH requests CMDh to clarify the implementation of the PRAC outcome for injectable forms by further differentiating the routine/additional risk minimization activities to be considered for the non-injectable products and those also applicable to the injectable products.

The CMDh therefore clarified that the amendments to the product information and the other routine measures to inform on the risk to the foetus when valproate is taken in pregnancy to all Healthcare professionals (HCP) and patients are applicable to all medicinal products containing valproate and related substances, irrespective of the route of administration. In addition all products should have in place a risk management plan.

For the following risk minimisation measures, the CMDh clarified that:

Regarding the visual reminder on the outer packaging, it is considered that it is crucial to remind to the HCPs that valproate should not be administered to women of childbearing potential (WCBP) who do not fulfil the pregnancy prevention plan requirements, or to pregnant patients, thus initiating a discussion about the risks of valproate with the patient. This may be particularly important as the prescribers of IV formulations of valproate are expected to be different from the usual prescribers targeted during the implementation of additional risk minimisation measures. The visual reminder is considered important and required to be implemented on the outer packaging of any valproate formulation and presentation.

With regards to the educational materials (i.e. HCP guide and patient guide), these are also considered relevant for the injectable forms of products containing valproate and related substances and therefore should be implemented. Indeed, the HCP guide will provide a reminder to the HCP of the conditions that apply for the administration of valproate (e.g. pregnancy prevention plan), the need to discuss the risks with the patient and check her pregnancy status. Additionally, as the IV valproate formulations will likely be administered by different HCPs than the usual treating physicians, having a HCP guide in place for these products is crucial and therefore such HCP guide will also be provided to prescribers of IV formulation of valproate containing products. For the female patients, there may be situations in which valproate treatment is initiated with the IV formulation (before discharge on valproate oral administration). An early communication of complete information about the risks of valproate is considered essential.

Regarding the circulation of the DHPC, all MAHs are encouraged to collaborate in order to prepare and circulate a single DHPC in each Member State and all MAHs marketing products containing valproate and related substances are required to participate in the dissemination of the information, regardless of the route of administration of their medicinal product(s). The information through the DHPC about risks and the new contraindications and other risk minimization measures is applicable to all formulations.

With regards to the patient card, the CMDh clarifies that the information is intended to act as a reminder for long-term use of valproate. As the injectable formulations are indicated only for short use, the patient card is most likely to be of limited value. Additionally, such patient card is to be attached to the packaging of valproate and related substances containing medicines, and serve as an additional reminder during the dispensing. In cases of patients for whom treatment is initiated with IV valproate formulations and then transferred to oral forms of valproate products, the patient card will be disclosed at the time of dispensing the oral valproate-containing products. Therefore, it is considered that the patient card is not required for injectable formulations products containing valproate and related substances.

The annual risk acknowledgement form for injectable formulations of valproate and related substances containing products is intended to act as a periodic reminder and acknowledgement of the risks of valproate for women of childbearing potential (WCBP). Since the injectable formulations are indicated for short-term use with a short treatment duration, this annual risk acknowledgement form is not considered relevant therefore not applicable. Finally, as the patients will be transferred eventually to non-injectable form of valproate, it is considered that the annual review will be carried out as part of RMMs recommended for oral treatment where the annual risk acknowledgment form will then be used. Consequently, the annual risk acknowledgment form is not required for the injectable formulations.

With regards to the other pharmacovigilance activities and the studies are required to further investigate potential risks with products containing valproate and related substances and to measure the effectiveness of the RMMs, the CMDh clarified that these studies would not be relevant for the injectable products as the information that could be collected for these products would be limited and unlikely to be meaningful in view of the short duration of use, often in urgent situations and only when the oral formulations cannot be administered. Therefore, the adapted PASS study on the drug utilisation, the two surveys targeting HCPs or patients, the PASS from registries in order to characterise the foetal anticonvulsant syndrome in children with anti-epileptic drugs *in utero* exposure, the retrospective observational study on the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring and, the observational study to evaluate and identify the best practice for discontinuation and switching of valproate treatment, are not applicable to the injectable formulations.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of medicinal products containing substances related to valproate remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CMDh recommends the variation to the terms of the marketing authorisations for medicinal products containing substances related to valproate.

Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

MAHs of all valproate and related substances containing products authorised in the EU should amend the product information (insertion, replacement or deletion of the text, as appropriate) to reflect the wording as provided below, and in conjunction to the Scientific conclusions:

Summary of product characteristics

[…]

Section 4.2 Posology and method of administration

[…]

Female children and women of childbearing potential

Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy, bipolar disorder or <migraine>. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).

[…]

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

[…]

Section 4.3 Contraindications

[…]

<Invented name> is contraindicated in the following situations:

[…]

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.4 and 4.6).

Treatment of bipolar disorder <and prophylaxis of migraine attacks>

- in pregnancy (see section 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.4 and 4.6).

[…]

Section 4.4 Special warnings and precautions for use

[…]

[This section should be amended to include the following box]

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

<Invented name> is contraindicated in the following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder <and prophylaxis of migraine attacks>

- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders <or migraine>.
- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician in case of pregnancy.
- the patient has received the patient guide.

- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

- The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist

The specialist should at least annually review whether valproate is the most suitable treatment

for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning.

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the indication*(s)* <bipolar disorder> <*and*> < *migraine*> if a woman is planning to become pregnant a specialist experienced in the management of <bipolar disorder> <migraine> must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology> {to be adapted depending on health care system} for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that

- the patient card is provided with every valproate dispensing and that the patients understand its content.
- the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programmeme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

An annual risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

[…]

[…]

Section 4.6 Fertility, pregnancy and lactation

[…]

[This section should be amended to include the following wording]

Valproate is contraindicated as treatment for bipolar disorder <and migraine> during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and Developmental Effects

[…]

If a woman plans a pregnancy

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the indication*(s)* <bipolar disorder> <*and*> < *migraine*> if a woman is planning to become pregnant a specialist experienced in the management of <bipolar disorder> <migraine> must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

Pregnant women

Valproate as treatment for bipolar disorder <and prophylaxis of migraine attacks> is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology> {to be adapted depending on health care system} for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies.

However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

[…]

PACKAGE LEAFLET

[Quick Response (QR) code: A QR code should be included in the packaging material and/or the package leaflet, and its location should take into account the overall readability.]

WARNING

<Invented name> , <INN> can seriously harm an unborn child when taken during pregnancy. If you are a female able to have a baby you must use effective method of birth control (contraception) without interruptions during your entire treatment with <Invented name>. Your doctor will discuss this with you but you must also follow the advice in section 2 of this leaflet.

Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.

Do not stop taking <Invented name> unless your doctor tells you to as your condition may become worse.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms seem the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

[…]

2. What you need to know before you take <invented name>

[…]

Do not take <invented name>

[This section should be amended to include the below wording]

[…]

Bipolar disorder <and> <migraine>

- For bipolar disorder <and> <migraine>, you must not use <Invented name> if you are pregnant.
- For bipolar disorder <and> <migraine>, if you are a woman able to have a baby, you must not take <Invented name>, unless you use effective method of birth control (contraception) during your entire treatment with <Invented name>). Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further (see below under “Pregnancy, breast-feeding and fertility – Important advice for women”).

Epilepsy

- For epilepsy, you must not use <Invented name> if you are pregnant, unless nothing else works for you.
- For epilepsy, if you are a woman able to have a baby, you must not take <Invented name> unless you use effective method of birth control (contraception) during your entire treatment with <Invented name>). Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further (see below under "Pregnancy, breast-feeding and fertility – Important advice for women").

[…]

Pregnancy, breast feeding and fertility

[This section should be amended to include the below wording]

[…]

Important advice for women

Bipolar disorder <and> <migraine>

- For bipolar disorder <and> <migraine>, you must not use <Invented name> if you are pregnant.
- For bipolar disorder <and> <migraine>, if you are a woman able to have a baby, you must not take <Invented name>, unless you use effective method of birth control (contraception) during your entire treatment with <Invented name>). Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

Epilepsy

- For epilepsy, you must not use <Invented name> if you are pregnant, unless nothing else works for you.
- For epilepsy, if you are a woman able to have a baby, you must not take <Invented name> unless you use effective method of birth control (contraception) during your entire treatment with <Invented name>). Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy (irrespective of the disease for which valproate is used)

- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2 to 3 babies in every 100 born to women who don't have epilepsy.

- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a baby you must not stop taking your medicine or your method of contraception until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact the doctor once your child using valproate experiences menarche.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose and read the situations which apply to you from the situations described below:

0 I AM STARTING TREATMENT WITH <INVENTED NAME>
0 I AM TAKING <INVENTED NAME> AND NOT PLANNING TO HAVE A BABY
0 I AM TAKING <INVENTED NAME> AND PLANNING TO HAVE A BABY
0 I AM PREGNANT AND I AM TAKING <INVENTED NAME>

I AM STARTING TREATMENT WITH <invented name>

If this is the first time you have been prescribed <Invented name> your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of contraception without interruption throughout your treatment with <Invented name>. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Pregnancy must be excluded before start of treatment with <Invented name> with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with <Invented name>.
- You must discuss the appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control.
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder or epilepsy <*or*> < *migraine*>*.* During this visit your doctor will make sure you are well aware and have understood all the risks and advices related to the use of valproate during pregnancy.

- Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING <invented name> AND NOT PLANNING TO HAVE A BABY

If you are continuing treatment with <Invented name> but you are not planning to have a baby make sure you are using an effective method of contraception without interruption during your entire treatment with <Invented name>. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- You must use an effective method of birth control (contraception) during your entire treatment with <Invented name>.
- You must discuss contraception (birth control) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control.
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder or epilepsy <*or*> < *migraine*>*.* During this visit your doctor will make sure you are well aware and have understood all the risks and advices related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING <invented name> AND PLANNING TO HAVE A BABY

If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of bipolar disorder <or>< *migraine*> or epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your specialist may decide to change the dose of <Invented name> or switch you to another medicine, or stop treatment with <Invented name>, a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when planning to have a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop taking <Invented name> unless your doctor tells you to.

- Do not stop using your methods of birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware and have understood all the risks and advices related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine, or stop treatment with <Invented name> a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING <INVENTED NAME>

Do not stop taking <Invented name>, unless your doctor tells you to as your condition may become worse. Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating.

You will be referred to a specialist experienced in the management of bipolar disorder, <migraine> or epilepsy, so that alternative treatment options can be evaluated.

In the exceptional circumstances when <Invented name> is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing. You and your partner could receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking <Invented name> unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of epilepsy, bipolar disorder <or migraine> to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of <Invented name> during pregnancy, including teratogenicity and developmental effects in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

[This sentence below should be adapted to National requirements]

Make sure you read the patient guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You

will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

[…]

3. How to take <invented name>

[…]

<Invented name> treatment must be started and supervised by a doctor specialised in the treatment of <epilepsy> <or> <bipolar disorders> <or> <migraine>.

[…]

4. Possible side effects

[This section should be amended to include the below wording in all indications]

[…]

Reporting of side effects

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

*[*For the printed material, please refer to the guidance of the annotated QRD template.]*

Annex IV

Conditions to the marketing authorisation

Conditions to the marketing authorisation(s)

The marketing authorisation holders shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

A visual reminder on the outer package to warn patient about the harm to unborn baby and the need for effective contraception when using the medicinal product should be implemented in all medicinal products containing substances related to valproate. The details of the visual reminder should be agreed at national level and be subject to a user test taking into account input from local patient representatives.	Within 3 months after Commission decision
The MAHs of medicinal products with substances related to valproate shall perform a drug utilisation study to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate. MAHs are encouraged to extend the ongoing drug utilisation study (DUS). Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC : Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	 Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol. Within 48 months after endorsement of the study protocol
The MAHs of medicinal products with substances related to valproate shall develop and submit educational materials according to agreed core elements. These materials should ensure that prescriber are informed and the patients understand and acknowledge the risks associated with valproate in-utero exposure. These should be submitted to the National Competent Authorities:	 Within 1 month of the Commission decision.
The MAHs of medicinal products with substances related to valproate shall conduct an observational study to evaluate and identify the best practices for switching of valproate in clinical practice.	

Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC : Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	Within 6 months after Commission decision Within 12 months after endorsement of the study protocol. Within 48 months after endorsement of the study protocol
The MAHs of medicinal products with substances related to valproate shall perform a survey among HCP to assess knowledge of HCP and behaviour with regard to PPP as well as receipt/use of DHPC and educational materials. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The final study report shall be submitted to the PRAC:	 Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol.
The MAHs of medicinal products with substances related to valproate shall perform a survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The final study report shall be submitted to the PRAC:	 Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol.
The MAHs of medicinal products with substances related to valproate shall conduct a PASS preferably based on existing registries to further characterise the foetal anticonvulsant syndrome in children with valproate *in utero* exposure as compared to other anti-epileptic drugs. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC :	 Within 6 months after Commission decision Within 12 months after endorsement of the study protocol.

Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	 Within 48 months after endorsement of the study protocol
The MAHs of medicinal products with substances related to valproate shall conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The first interim report shall be submitted to the PRAC : Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years The final study report shall be submitted to the PRAC:	 Within 6 months after Commission decision Within 12 months after endorsement of the study protocol. Within 48 months after endorsement of the study protocol
All MAHs should have in place a Risk management plan (RMP).	Within 3 months after Commission decision

With regards to the studies abovementioned, the MAHs are strongly encouraged to collaborate and perform joint studies.