ANNEX I

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

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien, Austria	Topamax 100 mg – Filmtabletten	100 milligram(s)	Film-coated tablet	Oral use
Austria	Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien, Austria	Topamax 200 mg - Filmtabletten	200 milligram(s)	Film-coated tablet	Oral use
Austria	Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien, Austria	Topamax 25 mg - Filmtabletten	25 milligram(s)	Film-coated tablet	Oral use
Austria	Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien, Austria	Topamax 50 mg - Filmtabletten	50 milligram(s)	Film-coated tablet	Oral use
Austria	Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien, Austria	Topamax 15 mg - Granulat in Kapseln	15 milligram(s)	granuals in capsule	Oral use
Austria	Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien, Austria	Topamax 25 mg - Granulat in Kapseln	25 milligram(s)	granuals in capsule	Oral use
Austria	Janssen-Cilag Pharma GmbH - Pfarrgasse 75 A-1232 Wien, Austria	Topamax 50 mg - Granulat in Kapseln	50 milligram(s)	granuals in capsule	Oral use
Belgium	Janssen-Cilag NV – BE Roderveldlaan 1 B-2600 Berchem, Belgium	Topamax 15mg harde capsules	15 milligram(s)	Capsule, hard	Oral use
Belgium	Janssen-Cilag NV – BE Roderveldlaan 1 B-2600 Berchem, Belgium	Topamax 25mg harde capsules	25 milligram(s)	Capsule, hard	Oral use
Belgium	Janssen-Cilag NV – BE Roderveldlaan 1 B-2600 Berchem, Belgium	Topamax 50mg harde capsules	50 milligram(s)	Capsule, hard	Oral use
Belgium	Janssen-Cilag NV – BE Roderveldlaan 1 B-2600 Berchem, Belgium	Topamax 100mg tabletten	100 milligram(s)	Tablet	Oral use
Belgium	Janssen-Cilag NV – BE Roderveldlaan 1 B-2600 Berchem, Belgium	Topamax 200mg tabletten	200 milligram(s)	Tablet	Oral use
Belgium	Janssen-Cilag NV – BE	Topamax 25mg tabletten	25 milligram(s)	Tablet	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	Roderveldlaan 1 B-2600 Berchem, Belgium				
Belgium	Janssen-Cilag NV – BE Roderveldlaan 1 B-2600 Berchem, Belgium	Topamax 50mg tabletten	50 milligram(s)	Tablet	Oral use
Bulgaria	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. - SI Smartinska cesta 53, 1000 Ljubljana, Slovenia	TOPAMAX	15 milligram(s)	Capsule	Oral use
Bulgaria	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. - SI Smartinska cesta 53, 1000 Ljubljana, Slovenia	TOPAMAX	25 milligram(s)	Capsule	Oral use
Bulgaria	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. - SI Smartinska cesta 53, 1000 Ljubljana, Slovenia	TOPAMAX	100 milligram(s)	Tablet	Oral use
Bulgaria	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. - SI Smartinska cesta 53, 1000 Ljubljana, Slovenia	TOPAMAX	25 milligram(s)	Tablet	Oral use
Bulgaria	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. - SI Smartinska cesta 53, 1000 Ljubljana, Slovenia	TOPAMAX	50 milligram(s)	Tablet	Oral use
Cyprus	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	TOPAMAX 100 mg tabs	100 milligram(s)	Tablet	Oral use
Cyprus	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	TOPAMAX 200 mg tabs	200 milligram(s)	Tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Cyprus	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	TOPAMAX 25 mg tabs	25 milligram(s)	Film-coated tablet	Oral use
Cyprus	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	TOPAMAX 50 mg tabs	50 milligram(s)	Film-coated tablet	Oral use
Cyprus	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	TOPAMAX 15 mg Sprinkles	15 milligram(s)	Sprinkle capsule	Oral use
Cyprus	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	TOPAMAX 25 mg Sprinkles	25 milligram(s)	Sprinkle capsule	Oral use
Cyprus	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	TOPAMAX 50 mg Sprinkles	50 milligram(s)	Sprinkle capsule	Oral use
Czech Republic	Janssen-Cilag s.r.o – CZ Karla Engliše 3201/6 150 00 Praha 5	Topamax 100 mg	100 milligram(s)	Film-coated tablet	Oral use
Czech Republic	Janssen-Cilag s.r.o – CZ Karla Engliše 3201/6 150 00 Praha 5	Topamax 25 mg	25 milligram(s)	Film-coated tablet	Oral use
Czech Republic	Janssen-Cilag s.r.o – CZ Karla Engliše 3201/6 150 00 Praha 5	Topamax 50 mg	50 milligram(s)	Film-coated tablet	Oral use
Czech Republic	Janssen-Cilag s.r.o – CZ Karla Engliše 3201/6 150 00 Praha 5	Topamax 15 mg	15 milligram(s)	Capsule	Oral use
Czech Republic	Janssen-Cilag s.r.o – CZ Karla Engliše 3201/6 150 00 Praha 5	Topamax 25 mg	25 milligram(s)	Capsule	Oral use
Denmark	Janssen-Cilag A/S - DK	Topimax	15 milligram(s)	Capsule, hard	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	Hammerbakken 19, 3460 Birkerød, Denmark				
Denmark	Janssen-Cilag A/S - DK Hammerbakken 19, 3460 Birkerød, Denmark	Topimax	25 milligram(s)	Capsule, hard	Oral use
Denmark	Janssen-Cilag A/S - DK Hammerbakken 19, 3460 Birkerød, Denmark	Topimax	50 milligram(s)	Capsule, hard	Oral use
Denmark	Janssen-Cilag A/S - DK Hammerbakken 19, 3460 Birkerød, Denmark	Topimax	100 milligram(s)	Film-coated tablet	Oral use
Denmark	Janssen-Cilag A/S - DK Hammerbakken 19, 3460 Birkerød, Denmark	Topimax	200 milligram(s)	Film-coated tablet	Oral use
Denmark	Janssen-Cilag A/S - DK Hammerbakken 19, 3460 Birkerød, Denmark	Topimax	25 milligram(s)	Film-coated tablet	Oral use
Denmark	Janssen-Cilag A/S - DK Hammerbakken 19, 3460 Birkerød, Denmark	Topimax	50 milligram(s)	Film-coated tablet	Oral use
Estonia	UAB Johnson & Johnson - LT Geležinio Vilko g. 18A LT-08104 Vilnius Lithuania	TOPAMAX 100 MG	100 milligram(s)	Film-coated tablet	Oral use
Estonia	UAB Johnson & Johnson - LT Geležinio Vilko g. 18A LT-08104 Vilnius Lithuania	TOPAMAX 200 MG	200 milligram(s)	Film-coated tablet	Oral use
Estonia	UAB Johnson & Johnson - LT Geležinio Vilko g. 18A	TOPAMAX 25 MG	25 milligram(s)	Film-coated tablet	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	LT-08104 Vilnius Lithuania				
Estonia	UAB Johnson & Johnson - LT Geležinio Vilko g. 18A LT-08104 Vilnius Lithuania	TOPAMAX 50 MG	50 milligram(s)	Film-coated tablet	Oral use
Finland	Janssen-Cilag OY – FI Metsänneidonkuja 8 02130 Espoo Finland	Topimax 15 mg kapseli, kova	15 milligram(s)	Capsule, hard	Oral use
Finland	Janssen-Cilag OY – FI Metsänneidonkuja 8 02130 Espoo Finland	Topimax 100 mg tabletti, kalvopäällysteinen	100 milligram(s)	Film-coated tablet	Oral use
Finland	Janssen-Cilag OY – FI Metsänneidonkuja 8 02130 Espoo Finland	Topimax 200 mg tabletti, kalvopäällysteinen	200 milligram(s)	Film-coated tablet	Oral use
Finland	Janssen-Cilag OY – FI Metsänneidonkuja 8 02130 Espoo Finland	Topimax 25 mg tabletti, kalvopäällysteinen	25 milligram(s)	Film-coated tablet	Oral use
Finland	Janssen-Cilag OY – FI Metsänneidonkuja 8 02130 Espoo Finland	Topimax 50 mg tabletti, kalvopäällysteinen	50 milligram(s)	Film-coated tablet	Oral use
Finland	Janssen-Cilag OY – FI Metsänneidonkuja 8 02130 Espoo Finland	Topimax 25 mg kapseli, kova	25 milligram(s)	Capsule, hard	Oral use
Finland	Janssen-Cilag OY – FI Metsänneidonkuja 8 02130 Espoo Finland	Topimax 50 mg kapseli, kova	50 milligram(s)	Capsule, hard	Oral use
France	Janssen-Cilag S.A. – FR 1 rue Camille Desmoulins, TSA 91003, 92787 ISSY-Les-Moulineaux Cedex 9 France	EPITOMAX 100 MG, COMPRIME PELLICULE	100 milligram(s)	Film-coated tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France	Janssen-Cilag S.A. – FR 1 rue Camille Desmoulins, TSA 91003, 92787 ISSY-Les-Moulineaux Cedex 9 France	EPITOMAX 200 MG, COMPRIME PELLICULE	200 milligram(s)	Film-coated tablet	Oral use
France	Janssen-Cilag S.A. – FR 1 rue Camille Desmoulins, TSA 91003, 92787 ISSY-Les-Moulineaux Cedex 9 France	EPITOMAX 50 MG, COMPRIME PELLICULE	50 milligram(s)	Film-coated tablet	Oral use
France	Janssen-Cilag S.A. – FR 1 rue Camille Desmoulins, TSA 91003, 92787 ISSY-Les-Moulineaux Cedex 9 France	EPITOMAX 15 MG, GELULE	15 milligram(s)	Sprinkle capsule	Oral use
France	Janssen-Cilag S.A. – FR 1 rue Camille Desmoulins, TSA 91003, 92787 ISSY-Les-Moulineaux Cedex 9 France	EPITOMAX 25 MG, GELULE	25 milligram(s)	Sprinkle capsule	Oral use
France	Janssen-Cilag S.A. – FR 1 rue Camille Desmoulins, TSA 91003, 92787 ISSY-Les-Moulineaux Cedex 9 France	EPITOMAX 50 MG, GELULE	50 milligram(s)	Sprinkle capsule	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Cilag 25 mg Hartkapseln	25 milligram(s)	Capsule, hard	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Janssen 25 mg Hartkapseln	25 milligram(s)	Capsule, hard	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Cilag 50 mg Hartkapseln	50 milligram(s)	Capsule, hard	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8	Topiramat-Janssen 50 mg Hartkapseln	50 milligram(s)	Capsule, hard	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	41470 Neuss, Germany				
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topamax 100 mg Filmtabletten	100 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Janssen 100 mg Filmtabletten	100 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	TOPAMAX MIGRÄNE 100 mg Filmtabletten	100 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat - Cilag 100 mg Filmtabletten	100 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Cilag 100 mg Filmtabletten	100 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topamax 200 mg Filmtabletten	200 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	TOPAMAX MIGRÄNE 200 mg Filmtabletten	200 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat - Cilag 200 mg Filmtabletten	200 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Cilag 200 mg Filmtabletten	200 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Janssen 200 mg Filmtabletten	200 milligram(s)	Film-coated tablet	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topamax 25 mg Filmtabletten	25 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	TOPAMAX MIGRÄNE 25 mg Filmtabletten	25 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Cilag 25 mg Filmtabletten	25 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Janssen 25 mg Filmtabletten	25 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topamax 50 mg Filmtabletten	50 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	TOPAMAX MIGRÄNE 50 mg Filmtabletten	50 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Cilag 50 mg Filmtabletten	50 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topiramat-Janssen 50 mg Filmtabletten	50 milligram(s)	Film-coated tablet	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	Topamax 25 mg Kapseln	25 milligram(s)	Capsule hard	Oral use
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	TOPAMAX MIGRÄNE 25 mg Hartkapseln	25 milligram(s)	Capsule	Oral use
Germany	Janssen-Cilag GmbH - DE	Topamax 50 mg Kapseln	50 milligram(s)	Capsule hard	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Raiffeisenstr. 8 41470 Neuss, Germany				
Germany	Janssen-Cilag GmbH - DE Raiffeisenstr. 8 41470 Neuss, Germany	TOPAMAX MIGRÄNE 50 mg Hartkapseln	50 milligram(s)	Capsule	Oral use
Greece	Janssen-Cilag Pharmaceutical S.A.C.I. – GR 56 Eirinis Avenue 56, Pefki, 15121, Greece	TOPAMAC	100 milligram(s)	Film-coated tablet	Oral use
Greece	Janssen-Cilag Pharmaceutical S.A.C.I. – GR 56 Eirinis Avenue 56, Pefki, 15121, Greece	TOPAMAC	200 milligram(s)	Film-coated tablet	Oral use
Greece	Janssen-Cilag Pharmaceutical S.A.C.I. – GR 56 Eirinis Avenue 56, Pefki, 15121, Greece	TOPAMAC	25 milligram(s)	Film-coated tablet	Oral use
Greece	Janssen-Cilag Pharmaceutical S.A.C.I. – GR 56 Eirinis Avenue 56, Pefki, 15121, Greece	TOPAMAC	50 milligram(s)	Film-coated tablet	Oral use
Greece	Janssen-Cilag Pharmaceutical S.A.C.I. – GR 56 Eirinis Avenue 56, Pefki, 15121, Greece	TOPAMAC	15 milligram(s)	Capsule, hard	Oral use
Greece	Janssen-Cilag Pharmaceutical S.A.C.I. – GR 56 Eirinis Avenue 56, Pefki, 15121, Greece	TOPAMAC	25 milligram(s)	Capsule, hard	Oral use
Greece	Janssen-Cilag Pharmaceutical S.A.C.I. – GR	TOPAMAC	50 milligram(s)	Capsule, hard	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	56 Eirinis Avenue 56, Pefki, 15121, Greece				
Hungary	Janssen-Cilag Kft. - HU 2045 Törökbálint Tó park, Hungary	Topamax 100 mg film-coated tablet	100 milligram(s)	Film-coated tablet	Oral use
Hungary	Janssen-Cilag Kft. - HU 2045 Törökbálint Tó park, Hungary	Topamax 200 mg film-coated tablets	200 milligram(s)	Film-coated tablet	Oral use
Hungary	Janssen-Cilag Kft. - HU 2045 Törökbálint Tó park, Hungary	Topamax 25 mg film-coated tablet	25 milligram(s)	Film-coated tablet	Oral use
Hungary	Janssen-Cilag Kft. - HU 2045 Törökbálint Tó park, Hungary	Topamax 50 mg film-coated tablet	50 milligram(s)	Film-coated tablet	Oral use
Iceland	Janssen-Cilag AB - SE Box 7073 192 07 Sollentuna, Sverige	Topimax 15 mg hylki, hörð	15 milligram(s)	Capsule, hard	Oral use
Iceland	Janssen-Cilag AB - SE Box 7073 192 07 Sollentuna, Sverige	Topimax 25 mg hylki, hörð	25 milligram(s)	Capsule, hard	Oral use
Iceland	Janssen-Cilag AB - SE Box 7073 192 07 Sollentuna, Sverige	Topimax 50 mg hylki, hörð	50 milligram(s)	Capsule, hard	Oral use
Iceland	Janssen-Cilag AB - SE Box 7073 192 07 Sollentuna, Sverige	Topimax 100 mg filmuhúðaðar töflur	100 milligram(s)	Film-coated tablet	Oral use
Iceland	Janssen-Cilag AB - SE Box 7073 192 07 Sollentuna, Sverige	Topimax 200 mg filmuhúðaðar töflur	200 milligram(s)	Film-coated tablet	Oral use
Iceland	Janssen-Cilag AB - SE Box 7073 192 07 Sollentuna, Sverige	Topimax 25 mg filmuhúðaðar töflur	25 milligram(s)	Film-coated tablet	Oral use
Iceland	Janssen-Cilag AB - SE Box 7073 192 07 Sollentuna, Sverige	Topimax 50 mg filmuhúðaðar töflur	50 milligram(s)	Film-coated tablet	Oral use
Ireland	Janssen-Cilag Limited - GB Saunderton High Wycombe Buckinghamshire HP14 4HJ United Kingdom	TOPAMAX 100 mg Tablets	100 milligram(s)	Film-coated tablet	Oral use
Ireland	Janssen-Cilag Limited - GB Saunderton	TOPAMAX 200 mg Tablets	200 milligram(s)	Film-coated tablet	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	High Wycombe Buckinghamshire HP14 4HJ United Kingdom				
Ireland	Janssen-Cilag Limited - GB Saunderton High Wycombe Buckinghamshire HP14 4HJ United Kingdom	TOPAMAX 25 mg Tablets	25 milligram(s)	Film-coated tablet	Oral use
Ireland	Janssen-Cilag Limited - GB Saunderton High Wycombe Buckinghamshire HP14 4HJ United Kingdom	TOPAMAX 50 mg Tablets	50 milligram(s)	Film-coated tablet	Oral use
Ireland	Janssen-Cilag Limited - GB Saunderton High Wycombe Buckinghamshire HP14 4HJ United Kingdom	TOPAMAX Sprinkle Capsules 15 mg.	15 milligram(s)	Sprinkle capsule	Oral use
Ireland	Janssen-Cilag Limited - GB Saunderton High Wycombe Buckinghamshire HP14 4HJ United Kingdom	TOPAMAX Sprinkle Capsules 25 mg.	25 milligram(s)	Sprinkle capsule	Oral use
Ireland	Janssen-Cilag Limited - GB Saunderton High Wycombe Buckinghamshire HP14 4HJ United Kingdom	TOPAMAX Sprinkle Capsules 50 mg	50 milligram(s)	Sprinkle capsule	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 15 mg capsule rigide, 60 capsule	15 milligram(s)	Capsule, hard	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 100 mg compresse rivestite con film, 60 compresse	100 milligram(s)	Film-coated tablet	Oral use
Italy	J.C. Healthcare srl – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	EPITOMAX 100 mg compresse rivestite con film, 60 compresse	100 milligram(s)	Film-coated tablet	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 200 mg compresse rivestite con film, 60 compresse	200 milligram(s)	Film-coated tablet	Oral use
Italy	J.C. Healthcare srl – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	EPITOMAX 200 mg compresse rivestite con film, 60 compresse	200 milligram(s)	Film-coated tablet	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 25 mg compresse rivestite con film, 60 compresse	25 milligram(s)	Film-coated tablet	Oral use
Italy	J.C. Healthcare srl – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	EPITOMAX 25 mg compresse rivestite con film, 60 compresse	25 milligram(s)	Film-coated tablet	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 300 mg compresse rivestite con film, 60 compresse	300 milligram(s)	Film-coated tablet	Oral use
Italy	J.C. Healthcare srl – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	EPITOMAX 300 mg compresse rivestite con film, 60 compresse	300 milligram(s)	Film-coated tablet	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 400 mg compresse rivestite con film, 60 compresse	400 milligram(s)	Film-coated tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	J.C. Healthcare srl – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	EPITOMAX 400 mg compresse rivestite con film, 60 compresse	400 milligram(s)	Film-coated tablet	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 50 mg compresse rivestite con film, 60 compresse	50 milligram(s)	Film-coated tablet	Oral use
Italy	J.C. Healthcare srl – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	EPITOMAX 50 mg compresse rivestite con film, 60 compresse	50 milligram(s)	Film-coated tablet	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 25 mg capsule rigide, 60 capsule	25 milligram(s)	Capsule, hard	Oral use
Italy	Janssen-Cilag SpA – IT Via Michelangelo Buonarroti n. 23 Cologno Monzese, 20093, Milano, Italy	TOPAMAX 50 mg capsule rigide, 60 capsule	50 milligram(s)	Capsule, hard	Oral use
Latvia	UAB Johnson & Johnson - LT Šeimyniškių g.1A, LT-09312 Vilnius, Lithuania	Topamax 100 mg coated tablets	100 milligram(s)	Coated tablet	Oral use
Latvia	UAB Johnson & Johnson - LT Šeimyniškių g.1A, LT-09312 Vilnius, Lithuania	Topamax 25 mg coated tablets	25 milligram(s)	Coated tablet	Oral use
Latvia	UAB Johnson & Johnson - LT Šeimyniškių g.1A, LT-09312 Vilnius, Lithuania	Topamax 50 mg coated tablets	50 milligram(s)	Coated tablet	Oral use
Latvia	UAB Johnson & Johnson - LT Šeimyniškių g.1A, LT-09312 Vilnius, Lithuania	Topamax 15 mg sprinkle capsules	15 milligram(s)	Sprinkle capsule	Oral use
Latvia	UAB Johnson & Johnson - LT Šeimyniškių g.1A, LT-09312 Vilnius,	Topamax 25 mg sprinkle capsules	25 milligram(s)	Sprinkle capsule	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Lithuania				
Lithuania	UAB Johnson & Johnson Šeimyniškių g. 1A, LT-09312 Vilnius, Lithuania	Topamax	100 milligram(s)	Tablet	Oral use
Lithuania	UAB Johnson & Johnson Šeimyniškių g. 1A, LT-09312 Vilnius, Lithuania	Topamax	200 milligram(s)	Tablet	Oral use
Lithuania	UAB Johnson & Johnson Šeimyniškių g. 1A, LT-09312 Vilnius, Lithuania	Topamax	25 milligram(s)	Tablet	Oral use
Lithuania	UAB Johnson & Johnson Šeimyniškių g. 1A, LT-09312 Vilnius, Lithuania	Topamax	50 milligram(s)	Tablet	Oral use
Luxembourg	Janssen-Cilag NV – BE Roderveldlaan 1 2600 Berchem, Belgium	Topamax gélules 15 mg	15 milligram(s)	Capsule, hard	Oral use
Luxembourg	Janssen-Cilag NV – BE Roderveldlaan 1 2600 Berchem, Belgium	Topamax comprimés 100 mg	100 milligram(s)	Tablet	Oral use
Luxembourg	Janssen-Cilag NV – BE Roderveldlaan 1 2600 Berchem, Belgium	Topamax comprimés 200 mg	200 milligram(s)	Tablet	Oral use
Luxembourg	Janssen-Cilag NV – BE Roderveldlaan 1 2600 Berchem, Belgium	Topamax comprimés 25 mg	25 milligram(s)	Tablet	Oral use
Luxembourg	Janssen-Cilag NV – BE Roderveldlaan 1 2600 Berchem, Belgium	Topamax comprimés 50 mg	50 milligram(s)	Tablet	Oral use
Luxembourg	Janssen-Cilag NV – BE Roderveldlaan 1 2600 Berchem, Belgium	Topamax gélules 25 mg	25 milligram(s)	Capsule, hard	Oral use
Luxembourg	Janssen-Cilag NV – BE Roderveldlaan 1 2600 Berchem, Belgium	Topamax gélules 50 mg	50 milligram(s)	Capsule, hard	Oral use
Malta	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	Topamax	100 milligram(s)	Tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Malta	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	Topamax	200 milligram(s)	Tablet	Oral use
Malta	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	Topamax	25 milligram(s)	Tablet	Oral use
Malta	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	Topamax	50 milligram(s)	Tablet	Oral use
Malta	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	Topamax	15 milligram(s)	Hard capsule	Oral use
Malta	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	Topamax	25 milligram(s)	Hard capsule	Oral use
Malta	Janssen-Cilag International NV - BE Turnhoutseweg 30, B-2340 Beerse, Belgium	Topamax	50 milligram(s)	Hard capsule	Oral use
Netherlands	Janssen-Cilag BV – NL Dr. Paul Janssenweg 150 PO Box 90240 5000 LT Tilburg The Netherlands	Topamax omhulde tabletten 100 mg, omhulde tabletten	100 milligram(s)	Coated tablet	Oral use
Netherlands	Janssen-Cilag BV – NL Dr. Paul Janssenweg 150 PO Box 90240 5000 LT Tilburg The Netherlands	Topamax omhulde tabletten 200 mg, omhulde tabletten	200 milligram(s)	Coated tablet	Oral use
Netherlands	Janssen-Cilag BV – NL Dr. Paul Janssenweg 150 PO Box 90240	Topamax omhulde tabletten 25 mg, omhulde tabletten	25 milligram(s)	Coated tablet	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	5000 LT Tilburg The Netherlands				
Netherlands	Janssen-Cilag BV – NL Dr. Paul Janssenweg 150 PO Box 90240 5000 LT Tilburg The Netherlands	Topamax omhulde tabletten 50 mg, omhulde tabletten	50 milligram(s)	Coated tablet	Oral use
Netherlands	Janssen-Cilag BV – NL Dr. Paul Janssenweg 150 PO Box 90240 5000 LT Tilburg The Netherlands	Topamax Sprinkle capsules 15 mg, capsules	15 milligram(s)	Capsule	Oral use
Netherlands	Janssen-Cilag BV – NL Dr. Paul Janssenweg 150 PO Box 90240 5000 LT Tilburg The Netherlands	Topamax Sprinkle capsules 25 mg, capsules	25 milligram(s)	Capsule	Oral use
Netherlands	Janssen-Cilag BV – NL Dr. Paul Janssenweg 150 PO Box 90240 5000 LT Tilburg The Netherlands	Topamax Sprinkle capsules 50 mg, capsules	50 milligram(s)	Capsule	Oral use
Norway	Janssen-Cilag AS – NO Hoffsveien 1D 0275 Oslo Norway	Topimax 15 mg Kapsel, hard	15 milligram(s)	Capsule, hard	Oral use
Norway	Janssen-Cilag AS – NO Hoffsveien 1D 0275 Oslo Norway	Topimax 25 mg Kapsel, hard	25 milligram(s)	Capsule, hard	Oral use
Norway	Janssen-Cilag AS – NO Hoffsveien 1D 0275 Oslo Norway	Topimax 50 mg Kapsel, hard	50 milligram(s)	Capsule, hard	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Norway	Janssen-Cilag AS – NO Hoffsveien 1D 0275 Oslo Norway	Topimax 100 mg Tabletter filmdrasjert	100 milligram(s)	Film-coated tablet	Oral use
Norway	Janssen-Cilag AS – NO Hoffsveien 1D 0275 Oslo Norway	Topimax 200 mg Tabletter filmdrasjert	200 milligram(s)	Film-coated tablet	Oral use
Norway	Janssen-Cilag AS – NO Hoffsveien 1D 0275 Oslo Norway	Topimax 25 mg Tabletter filmdrasjert	25 milligram(s)	Film-coated tablet	Oral use
Norway	Janssen-Cilag AS – NO Hoffsveien 1D 0275 Oslo Norway	Topimax 50 mg Tabletter filmdrasjert	50 milligram(s)	Film-coated tablet	Oral use
Poland	Janssen-Cilag International NV - BE Turnhoutseweg 30 B-2340 Beerse Belgium	Topamax 100 mg tabletki powlekane	100 milligram(s)	Film-coated tablet	Oral use
Poland	Janssen-Cilag International NV - BE Turnhoutseweg 30 B-2340 Beerse Belgium	Topamax 200 mg tabletki powlekane	200 milligram(s)	Film-coated tablet	Oral use
Poland	Janssen-Cilag International NV - BE Turnhoutseweg 30 B-2340 Beerse Belgium	Topamax 25 mg tabletki powlekane	25 milligram(s)	Film-coated tablet	Oral use
Poland	Janssen-Cilag International NV - BE Turnhoutseweg 30 B-2340 Beerse Belgium	Topamax 50 mg tabletki powlekane	50 milligram(s)	Film-coated tablet	Oral use
Poland	Janssen-Cilag International NV - BE Turnhoutseweg 30 B-2340 Beerse	Topamax , 15 mg kapsulki	15 milligram(s)	Capsule	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	Belgium				
Poland	Janssen-Cilag International NV - BE Turnhoutseweg 30 B-2340 Beerse Belgium	Topamax , 25 mg kapsulki	25 milligram(s)	Capsule	Oral use
Portugal	Janssen-Cilag Farmacêutica, Lda. – PT Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo 2734-503 Barcarena Portugal	Topamax	100 milligram(s)	Film-coated tablet	Oral use
Portugal	Janssen-Cilag Farmacêutica, Lda. – PT Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo 2734-503 Barcarena Portugal	Topamax	200 milligram(s)	Film-coated tablet	Oral use
Portugal	Janssen-Cilag Farmacêutica, Lda. – PT Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo 2734-503 Barcarena Portugal	Topamax	25 milligram(s)	Film-coated tablet	Oral use
Portugal	Janssen-Cilag Farmacêutica, Lda. – PT Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo 2734-503 Barcarena Portugal	Topamax	50 milligram(s)	Film-coated tablet	Oral use
Portugal	Janssen-Cilag Farmacêutica, Lda. – PT Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo 2734-503 Barcarena Portugal	Topamax	15 milligram(s)	capsule, hard	Oral use
Portugal	Janssen-Cilag Farmacêutica, Lda. – PT Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo 2734-503 Barcarena Portugal	Topamax	25 milligram(s)	capsule, hard	Oral use
Portugal	Janssen-Cilag Farmacêutica, Lda. – PT Estrada Consiglieri Pedroso, 69 A -	Topamax	50 milligram(s)	capsule, hard	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Queluz de Baixo 2734-503 Barcarena Portugal				
Romania	Johnson & Johnson, d.o.o. – SI Smartinska cesta 53, Ljubljana, Slovenia	TOPAMAX 100 tablets	100 milligram(s)	Tablet	Oral use
Romania	Johnson & Johnson, d.o.o. – SI Smartinska cesta 53, Ljubljana, Slovenia	TOPAMAX 200 tablets	200 milligram(s)	Tablet	Oral use
Romania	Johnson & Johnson, d.o.o. – SI Smartinska cesta 53, Ljubljana, Slovenia	TOPAMAX 25 tablets	25 milligram(s)	Tablet	Oral use
Romania	Johnson & Johnson, d.o.o. – SI Smartinska cesta 53, Ljubljana, Slovenia	TOPAMAX 50 tablets	50 milligram(s)	Tablet	Oral use
Romania	Johnson & Johnson, d.o.o. – SI Smartinska cesta 53, Ljubljana, Slovenia	TOPAMAX sprinkle caps	50 milligram(s)	Sprinkle capsule	Oral use
Slovak Republic	Johnson & Johnson, s.r.o – SK Plynárenská 7/B 824 78 Bratislava Slovak Republic	Topamax 15 mg cps	15 milligram(s)	Prolonged-release capsule, hard	Oral use
Slovak Republic	Johnson & Johnson, s.r.o – SK Plynárenská 7/B 824 78 Bratislava Slovak Republic	Topamax 25 mg cps	25 milligram(s)	Prolonged-release capsule, hard	Oral use
Slovak Republic	Johnson & Johnson, s.r.o – SK	Topamax 100	100 milligram(s)	Film-coated tablet	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	Plynárenská 7/B 824 78 Bratislava Slovak Republic				
Slovak Republic	Johnson & Johnson, s.r.o – SK Plynárenská 7/B 824 78 Bratislava Slovak Republic	Topamax 200	200 milligram(s)	Film-coated tablet	Oral use
Slovak Republic	Johnson & Johnson, s.r.o – SK Plynárenská 7/B 824 78 Bratislava Slovak Republic	Topamax 25	25 milligram(s)	Film-coated tablet	Oral use
Slovak Republic	Johnson & Johnson, s.r.o – SK Plynárenská 7/B 824 78 Bratislava Slovak Republic	Topamax 50	50 milligram(s)	Film-coated tablet	Oral use
Slovenia	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. – SI Šmartinska 53, Ljubljana, Slovenia	TOPAMAX 100 mg filmsko oblozene tablete	100 milligram(s)	Film-coated tablet	Oral use
Slovenia	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. – SI Šmartinska 53, Ljubljana, Slovenia	TOPAMAX 200 mg filmsko oblozene tablete	200 milligram(s)	Film-coated tablet	Oral use
Slovenia	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. – SI Šmartinska 53, Ljubljana, Slovenia	TOPAMAX 25 mg filmsko oblozene tablete	25 milligram(s)	Film-coated tablet	Oral use
Slovenia	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. – SI Šmartinska 53, Ljubljana, Slovenia	TOPAMAX 50 mg filmsko oblozene tablete	50 milligram(s)	Film-coated tablet	Oral use
Slovenia	Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. – SI Šmartinska 53, Ljubljana, Slovenia	TOPAMAX 15 mg kapsule	15 milligram(s)	hard capsule	Oral use
Spain	Janssen-Cilag S.A. – ES	TOPAMAX 100 mg	100 milligram(s)	Coated tablet	Oral use

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration
	Paseo de las DoceEstrellas, 5-7 28042 Madrid, Spain	Comprimidos recubiertos			
Spain	Janssen-Cilag S.A. – ES Paseo de las DoceEstrellas, 5-7 28042 Madrid, Spain	TOPAMAX 200 mg Comprimidos recubiertos	200 milligram(s)	Coated tablet	Oral use
Spain	Janssen-Cilag S.A. – ES Paseo de las DoceEstrellas, 5-7 28042 Madrid, Spain	TOPAMAX 25 mg Comprimidos recubiertos	25 milligram(s)	Coated tablet	Oral use
Spain	Janssen-Cilag S.A. – ES Paseo de las DoceEstrellas, 5-7 28042 Madrid, Spain	TOPAMAX 50 mg Comprimidos recubiertos	50 milligram(s)	Coated tablet	Oral use
Spain	Janssen-Cilag S.A. – ES Paseo de las DoceEstrellas, 5-7 28042 Madrid, Spain	TOPAMAX DISPERSABLE 15 mg, cápsulas	15 milligram(s)	Sprinkle capsule	Oral use
Spain	Janssen-Cilag S.A. – ES Paseo de las DoceEstrellas, 5-7 28042 Madrid, Spain	TOPAMAX DISPERSABLE 25 mg, cápsulas	25 milligram(s)	Sprinkle capsule	Oral use
Spain	Janssen-Cilag S.A. – ES Paseo de las DoceEstrellas, 5-7 28042 Madrid, Spain	TOPAMAX DISPERSABLE 50 mg, cápsulas	50 milligram(s)	Sprinkle capsule	Oral use
Sweden	Janssen-Cilag AB – SE Box 7073 192 07 Sollentuna, Sverige	Topimax 15 mg kapslar, hårda	15 milligram(s)	Capsule, hard	Oral use
Sweden	Janssen-Cilag AB – SE Box 7073 192 07 Sollentuna, Sverige	Topimax 25 mg kapslar, hårda	25 milligram(s)	Capsule, hard	Oral use
Sweden	Janssen-Cilag AB – SE Box 7073 192 07 Sollentuna, Sverige	Topimax 50 mg kapslar, hårda	50 milligram(s)	Capsule, hard	Oral use
Sweden	Janssen-Cilag AB – SE Box 7073 192 07 Sollentuna, Sverige	Topimax 100 mg tabletter, filmdragerade	100 milligram(s)	Film-coated tablet	Oral use
Sweden	Janssen-Cilag AB – SE Box 7073 192 07 Sollentuna, Sverige	Topimax 200 mg tabletter, filmdragerade	200 milligram(s)	Film-coated tablet	Oral use
Sweden	Janssen-Cilag AB – SE	Topimax 25 mg tabletter,	25 milligram(s)	Film-coated tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Box 7073 192 07 Sollentuna, Sverige	filmdragerade			
Sweden	Janssen-Cilag AB – SE Box 7073 192 07 Sollentuna, Sverige	Topimax 50 mg tabletter, filmdragerade	50 milligram(s)	Film-coated tablet	Oral use
United Kingdom	Janssen-Cilag Limited – GB Saunderton High-Wycombe Buckinghamshire HP 14 4HJ United Kingdom	TOPAMAX 100 mg Tablets	100 milligram(s)	Tablet	Oral use
United Kingdom	Janssen-Cilag Limited – GB Saunderton High-Wycombe Buckinghamshire HP 14 4HJ United Kingdom	TOPAMAX 200 mg Tablets	200 milligram(s)	Tablet	Oral use
United Kingdom	Janssen-Cilag Limited – GB Saunderton High-Wycombe Buckinghamshire HP 14 4HJ United Kingdom	TOPAMAX 25 mg Tablets	25 milligram(s)	Tablet	Oral use
United Kingdom	Janssen-Cilag Limited – GB Saunderton High-Wycombe Buckinghamshire HP 14 4HJ United Kingdom	TOPAMAX 50 mg Tablets	50 milligram(s)	Tablet	Oral use
United Kingdom	Janssen-Cilag Limited – GB Saunderton High-Wycombe Buckinghamshire HP 14 4HJ United Kingdom	TOPAMAX Sprinkle Capsules 15 mg	15 milligram(s)	Sprinkle capsule	Oral use
United Kingdom	Janssen-Cilag Limited – GB Saunderton High-Wycombe	TOPAMAX Sprinkle Capsules 25 mg	25 milligram(s)	Sprinkle capsule	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Buckinghamshire HP 14 4HJ United Kingdom				
United Kingdom	Janssen-Cilag Limited – GB Saunderton High-Wycombe Buckinghamshire HP 14 4HJ United Kingdom	TOPAMAX Sprinkle Capsules 50 mg	50 milligram(s)	Sprinkle capsule	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF TOPAMAX AND ASSOCIATED NAMES (SEE ANNEX I)

Topiramate is a sulfamate-substituted monosaccharide. Topiramate enhances γ-aminobutyrate-activated chloride channels and inhibits excitatory neurotransmission, through actions on kainate subtypes of glutamate receptors and ∝-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. It is also an inhibitor of some isozymes of carbonic anhydrase.

The harmonisation of topiramate marketed in the EU Member States, Norway and Iceland applies to two formulations:
- tablets (25 mg, 50 mg, 100 mg, 200 mg)
- capsules (15 mg, 25 mg, 50 mg)

A number of areas of disharmony in the product information for topirmate have been evaluated by the CHMP and the revised Product Information (PI) was adopted. The main areas for harmonisation were as follows:

4.1 – Therapeutic Indications

Monotherapy for epilepsy
The evidence of the efficacy and safety of topiramate as monotherapy in the treatment of epilepsy has been presented from 4 randomised controlled studies.

In newly diagnosed patients, topiramate showed benefit in monotherapy in two (TOPMAT-EPMN-105 and TOPMAT-EPMN-106) out of the three studies conducted. Study TOPMAT-EPMN-105 provided evidence to support the extension to the wider 'epilepsy' indication as this is the only study which included patients with a variety of seizure syndromes other than partial onset seizures. Here, the seizure types studies included both partial onset seizures (defined as partial, complex partial, or partial evolving into secondarily generalized seizures) and generalized seizures (defined as generalized tonic-clonic, tonic, or clonic seizures).

The investigation of topiramate as monotherapy in the paediatric population related to a minority (~20%) of the patients evaluated in the randomized controlled studies of topiramate monotherapy who were children (≤16 years of age). About 300 patients between the age of 6 and 16 years old have been included in the clinical development of topiramate as monotherapy. The results of covariate analyses in the studies TOPMAT-EPMN-104, TOPMAT-EPMN-105 and TOPMAT-EPMN-106 indicate that the efficacy of topiramate monotherapy did not differ as a function of age. There are no data to support a claim for efficacy as monotherapy in patients younger than 6 years.

After discussion of the wording for this indication, the following text was considered to be acceptable to the CHMP for the use of topiramate in monotherapy for epilepsy:

"Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures."

Adjunctive therapy for epilepsy in children and adults
The proposed indication of adjunctive therapy is approved in all of 29 countries involved in the Article 30 procedure. A total of 9 studies have been conducted and submitted in order to explore the efficacy of topiramate as add-on (adjunctive) therapy. The clinical development in general fulfils the CHMP Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders, with respect to the key issues.

- Partial onset seizures (POS) with or without secondary generalization in Adults and Children

The results of 6 controlled studies indicate that adjunctive therapy in adults with topiramate has significant therapeutic benefit in controlling partial onset seizures with or without secondary generalisation. The efficacy of topiramate in reducing seizure frequency was consistent in all 6 studies in a large number of patients participating in these studies.

There would appear to be both a clinically and statistically significant evidence of efficacy with topiramate as add-on treatment to commonly used AEDs in POS indications. This is further supported by the low discontinuation rate due to lack of efficacy. Therefore the CHMP considered that the use of topiramate as adjunctive therapy in adults with partial onset seizures with or without secondary generalization is supported.

The evidence of the efficacy of topiramate as adjunctive therapy for partial onset seizures with or without secondarily generalised seizures in paediatric patients has been derived from a multicentre, placebo-controlled study (YP). Although not achieving statistical significance in a given age group 2-5 yrs, 6-9 yrs, 10-15 yrs and ≥16 yrs, the general trend is toward numerical superiority to placebo in each age group. The results have been presented for the entire cohort, demonstrating a statistically significant treatment effect over the whole paediatric patient group. This is seen to be supportive of the proposed indication of topimarate as adjunctive therapy for partial onset seizures with or without secondarily generalised seizures in the paediatric population.

- Adjunctive Therapy for Primary Generalized Tonic-Clonic (PGTC) Seizures in Adults and Children

Two studies YTC and YTC-E, explored the efficacy of topiramate as adjunctive therapy in primary generalised tonic-clonic (PGTC) seizures patients. One of the studies was conducted in US/Costa Rica and the other study was performed in Europe. Topiramate showed a reduction of PTGC seizures rate in the American/CR study, and when both studies were combined. The results for European trial were inconclusive mainly due to a placebo response that was greater than expected. The MAH justifies this difference stating that the imbalance in baseline seizure rate, in seizure severity and selective discontinuation rate among the groups could have contributed to the underestimation of topiramate efficacy. This explanation was considered to be reasonable and the proposed indication for the use of topiramate as adjunctive therapy in adults with primary generalized tonic-clonic seizures can be considered to be sufficiently supported.

The evidence to support paediatric use in PGTC Seizures has been provided from Studies YTC and YTC-E. The MAH has supplied the analysis of data by age group for each study. Although not achieving statistical significance in a given age group 2-5 yrs, 6-9 yrs, 10-15 yrs and ≥16 yrs, the general trend is toward numerical superiority to placebo in each age group.

The results from the ANCOVA models indicate that age did not have an impact on treatment effect (p-value>=0.20) for all three seizure types (POS, PGTS, or LGS). However there is no physiological or pharmacological reason to suspect that the mechanism of action of the drug or the pathophysiology of the illness would be any different in a child of 2 years versus a child of 10 years of age. Therefore, it is reasonable to accept that if efficacy in a given indication has been shown in the paediatric population in general, then those results can be extrapolated to a given lower age limit. There is undoubtedly statistically significant evidence of efficacy seen in the paediatric population as a whole to support the adjunctive therapy indication in children with POS, PGTS, or LGS seizure types. The youngest age involved in the clinical trials was 2 years old.

Therefore the harmonised indication for topiramate adjunctive therapy in partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures in adults and in the paediatric population was supported by the CHMP:

"Adjunctive therapy for adults, adolescents and children aged 2 years and above with partial onset seizures with or without secondary generalisation or primary generalized tonic-clonic seizures……."

Seizures associated with Lennox-Gastaut syndrome (LGS)
The use of topiramate as add-on therapy in patients (adults and paediatrics) with LGS treated with up to 2 AEDs was supported by only one, controlled, rather short study. The justification put forward by the MAH that this shortcoming is due to the limited number of subjects and qualified study centres available was considered to be acceptable. The results provided by this study reinforce those derived from the Study YP in children with Partial Onset Seizure.

Although not achieving statistical significance in a given paediatric age group, the general trend is toward numerical superiority to placebo in each age group.

Therefore the following harmonised indication for the treatment of seizures associated with Lennox-Gastaut syndrome was adopted by the CHMP. For the sake of consistency it was agreed to merge both adjunctive therapy indications to read:

"Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome."

Prophylaxis of migraine
In the adult population, topiramate at doses equal to or higher than 100 mg showed greater reductions in monthly migraine attacks than placebo. In 2 out of 4 studies these differences were statistically significant. Key secondary outcomes (responder rate, migraine attack rate, use of rescue medication) demonstrated a consistent response. The 200 mg dose did not appear to provide additional benefit. In one of the studies (TOPMAT-MIGR-003), which compared topimarate to propranolol, a similar efficacy profile was observed.

These results can be considered sufficient to support the proposed indication. This indication is endorsed by the current recommendations of the European Federation of Neurological Societies (EFNS) task force (2006) where topiramate is considered an appropriate first-line prophylactic migraine medication based on scientific evidence from clinical trials and on expert consensus of the EFNS.

In some countries, topiramate was approved as a second- line prophylactic migraine medication. The MAH disagreed with this proposal stating that in all trials, patients were not required to have failed on prophylactic migraine medications. It is true that the trials were not specifically designed for recruiting resistant patients although limited information is available regarding the kind of patients finally involved in them (naïve vs previously treated/resistant patients).

Following extensive discussion on the use of topiramate in the prophylaxis of migraine, the following text was considered to be acceptable to the CHMP:

"Topiramate is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment."

4.2 – Posology

Monotherapy for epilepsy in children and adults
Regarding the posology for topiramate, in general the titration schedules in monotherapy and adjunct therapy in Section 4.2 Posology of the SPC are consistent across MS SPCs, although there are differences depending on age range for use.

The recommended monotherapy dosage of 100 – 200 mg/day as the initial target dose and the maximum daily dose of 500mg/day in monotherapy in adults, and the initial target dose of 100 mg/day depending on clinical response in children aged 6 years and above was endorsed by the CHMP for use.

Adjunctive therapy for epilepsy in children and adults

- Partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or
- Seizures associated with Lennox-Gastaut syndrome

An effective dose range of 200-400mg/day for adults was endorsed by the CHMP. The maximum weekly incremental dose titration has been amended to 50mg/day, as opposed to the 100mg/day. The CHMP agreed the following wording for adults:

"Adults
Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was the lowest effective dose. The usual daily dose is 200-400 mg in two divided doses."

The recommended total daily dose of approximately 5 - 9 mg/kg/day in two divided doses as adjunctive therapy in the paediatric population (children aged 2 years and above) was endorsed by the CHMP.

Dose recommendations for the renally impaired have been stated. No dose adjustment is recommended for the elderly, provided that renal function is in tact. Information on dosing in patients with hepatic impairment has also been provided.

Prophylaxis of migraine
The suggested dose titration of 25mg/day for one week with 25mg weekly increments was endorsed by the CHMP.

No paediatric subjects have been investigated in any of the migraine studies and therefore no efficacy or safety claim has been made.

4.3 - Contraindications
A contraindication for the use of topiramate for the **indication of epilepsy** in pregnancy and women of childbearing potential if not using effective methods of contraception was not considered warranted by the CHMP. Appropriate advice has been included in section 4.6 about the risks to the mother and foetus of treatment and the risks of not treating epilepsy during pregnancy (see SPC section 4.6).

A contraindication for the use of topiramate for the indication of migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception has been included in the SPC in sections 4.3 and 4.6.

4.4 - Special warnings and precautions for use
Mood disturbances/depression and suicidal tendency, acute myopia and secondary angle closure glaucoma and metabolic acidosis have been included and identified as an important risk in the Risk Management Plan (RMP). Warning statements have also been included that topiramate should be used with caution in patients with conditions or treatments that represent a risk factor for the appearance of metabolic acidosis and also that the patient's history of eye disorders should be considered when treated with topiramate.

It has been noted that weight loss is a pertinent feature of treatment with topiramate in some patients and a warning stating that patients on long term topiramate treatment should be regularly weighed and monitored for continuing weight loss has been included.

Whether topiramate can exert some effect on bones (i.e. apart from that described for metabolic acidosis) and as a consequence on growth, has not been fully elucidated. The assessment of paediatric data is foreseen to take place in the near future and no additional measures seem to be required at present.

In addition the CHMP supported the deletion of any mention of the interchangeability of different products of topiramate in individual patients, in the product information.

4.5 - Interaction with other medicinal products and other forms of interaction
Data supporting the proposed text on the potential interactions of topiramate with oral contraceptives and risperidone have been presented. There would appear to be a reduction in all measured parameters (Cmax, Tmax and AUC) for Ethinyl Estradiol associated with concomitant topiramate administration in the epilepsy study. A suitable warning to the effect that the possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Topamax has been included and is supported by the CHMP.

There does not appear to be any statistically significant difference between the plasma concentration of risperidone when administered concomitantly with topiramate either in healthy subjects or in patients with Bipolar Disorder. The proposed SPC wording reflects the non-significant difference in concentration seen and appropriately concludes that the interaction is unlikely to be of clinical significance. Given that an increase in the number of adverse events (as well as the AEs leading to study discontinuation) is observed when risperidone and topiramate are administered concomitantly, the wording of this subsection has been slightly amended. The proposed wording in this section is considered to be acceptable by the CHMP.

In addition, a statement on the interaction of topiramate with St John's Wort was also included in the Product Information.

4.6 - Pregnancy and Lactation
The MAH provided a review of data collections from J&J PRD's own pharmacovigilance database and prospective pregnancy registries, which identified potential risks to the foetus of pregnant women treated with topiramate. Although a literature review presented by the MAH indicates that there is a potential benefit in using migraine prophylactic treatment in pregnant women suffering from migraine, it is fair to say that the vast majority of migraine improves during pregnancy, although the exact figures from studies vary. In those women who require prophylactic treatment for migraine, an agent not shown to be teratogenic in three animal species at low dose, is preferred.

The studies showing an association between the occurrence of gestational hypertension or pre eclampsia more commonly in women with migraine do not prove a causal relationship between migraine and either pre eclampsia or hypertension. No study has shown that good migraine control prevents gestational hypertension or pre eclampsia. Similarly, the link between migraine and ischaemic stroke is not proven. There is currently no evidence that migraine prophylaxis during pregnancy reduces the risk of stroke.

The CHMP is of the view that the contraindication for the use of topiramate for the indication of migraine prophylaxis during pregnancy and in women of child bearing potential without adequate contraception is justified based on the demonstration of teratogenicity of topiramate in three animal species and the availability of alternative acute and prophylactic treatments for migraine during pregnancy that have not been shown to be teratogenic in three animal species.

Where there is insufficient human data but evidence of risk from animal studies and the availability of safer alternative treatments a contraindication for the use in pregnancy is justified. As recommended by the

CHMP, the contraindication for the use of topiramate for migraine prophylaxis in pregnancy or women of child bearing potential without adequate contraception has been included by the MAH for the indication migraine prophylaxis.

5.3 - Preclinical safety data

As part of the initial application, the MAH submitted a full non-clinical package in support of product registration including a complete package of reproductive toxicology reports. There have been no new toxicology data produced by the MAH in support of topiramate, other than an oral toxicity study in juvenile rats.

The embryofetal studies show clear evidence of the teratogenic potential of topiramate. The fact that this effect was reproducible and has been observed in three species, both rodent and non-rodent is suggestive of a potential risk to humans.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summary of Products Characteristics, labelling and package leaflet.

- the Summary of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Topamax and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 25 mg film-coated tablets
Topamax and associated names (see Annex I) 50 mg film-coated tablets
Topamax and associated names (see Annex I) 100 mg film-coated tablets
Topamax and associated names (see Annex I) 200 mg film-coated tablets

Topamax and associated names (see Annex I) 15 mg hard capsules
Topamax and associated names (see Annex I) 25 mg hard capsules
Topamax and associated names (see Annex I) 50 mg hard capsules

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Hard capsules

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures.

Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome

Topiramate is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment.

4.2 Posology and method of administration

General

It is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Dose and titration rate should be guided by clinical response.

Topamax is available in film-coated tablets and a hard capsule formulation. It is recommended that film-coated tablets not be broken. The hard capsule formulation is provided for those patients who cannot swallow tablets, e.g. paediatric and the elderly.

Topamax hard capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This medicinal product/food mixture is to be swallowed immediately and not chewed. It must not be stored for future use.

It is not necessary to monitor topiramate plasma concentrations to optimize therapy with Topamax. On rare occasions, the addition of topiramate to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and carbamazepine to adjunctive therapy with Topamax may require adjustment of the dose of Topamax.

Topamax can be taken without regard to meals.

In patients with or without a history of seizures or epilepsy, antiepileptic drugs including topiramate should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In paediatric clinical trials, topiramate was gradually withdrawn over a 2-8 week period.

Monotherapy epilepsy

General
When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended.

When enzyme inducing medicinal products are withdrawn, topiramate levels will increase. A decrease in Topamax (topiramate) dosage may be required if clinically indicated.

Adults

Dose and titration should be guided by clinical response. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

Paediatric population (children over 6 years of age)

Dose and titration rate in children should be guided by clinical outcome. Treatment of children over 6 years of age should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1 or 2 week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used.

The recommended initial target dose range for topiramate monotherapy in children over 6 years of age is 100 mg/day depending on clinical response, (this is about 2.0mg/kg/day in children 6-16 years).

Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome)

Adults

Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was the lowest effective dose. The usual daily dose is 200-400 mg in two divided doses.

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease (see section 4.4).

Paediatric population (children aged 2 years and above)

The recommended total daily dose of Topamax (topiramate) as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response.

Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Migraine

Adults

The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.
Some patients may experience a benefit at a total daily dose of 50 mg/day. . Patients have received a total daily dose up to 200 mg/day. This dose may be benefit in some patients, nevertheless, caution is advised due to an increase incidence of side effects

Paediatric population

Topamax (topiramate) is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy.

General dosing recommendations for Topamax in special patient populations

Renal impairment

In patients with impaired renal function ($CL_{CR} \leq 60$ mL/min) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose

In patients with end-stage renal failure, since topiramate is removed from plasma by haemodialysis, a supplemental dose of Topamax equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and

completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

Hepatic impairment

In patients with moderate to severe hepatic impairment topiramate should be administered with caution as the clearance of topiramate is decreased.

Elderly

No dose adjustment is required in the elderly population providing renal function is intact.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception

4.4 Special warnings and precautions for use

In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended (see section 4.2 for further details).

As with other anti-epileptic drugs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with topiramate. These phenomena may be the consequence of an overdose, a decrease in plasma concentrations of concomitantly used anti-epileptics, progress of the disease, or a paradoxical effect.

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse reactions (see section 4.8).

Mood disturbances/depression

An increased incidence of mood disturbances and depression has been observed during topiramate treatment.

Suicide/suicide ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for topiramate.

In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) and at a nearly 3 fold higher incidence than those treated with placebo (0.2%; 8 out of 4,045 patients treated).

Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Nephrolithiasis

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain.

Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medicinal products associated with nephrolithiasis may be at increased risk.

Decreased hepatic function

In hepatically-impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Acute myopia and secondary angle closure glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of topiramate, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.

Elevated intraocular pressure of any aetiology, if left untreated, can lead to serious sequelae including permanent vision loss.

A determination should be made whether patients with history of eye disorders should be treated with topiramate.

Metabolic acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/l at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in paediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/l. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or certain medicinal products) may be additive to the bicarbonate lowering effects of topiramate.

Chronic metabolic acidosis increases the risk of renal stone formation and may potentially lead to osteopenia.

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on bone-related sequelae has not been systematically investigated in paediatric or adult populations.

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Topiramate should be used with caution in patients with conditions or treatments that represent a risk factor for the appearance of metabolic acidosis.

Nutritional supplementation

Some patients may experience weight loss whilst on treatment with topiramate. It is recommended that patients on topiramate treatment should be monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight while on topiramate.

Lactose intolerance

Topamax contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Topamax on other antiepileptic medicinal products

The addition of Topamax to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of Topamax to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

A pharmacokinetic interaction study of patients with epilepsy indicated the addition of topiramate to lamotrigine had no effect on steady state plasma concentration of lamotrigine at topiramate doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of topiramate during or after removal of lamotrigine treatment (mean dose of 327 mg/day).

Topiramate inhibits the enzyme CYP 2C19 and may interfere with other substances metabolized via this enzyme (e.g., diazepam, imipramin, moclobemide, proguanil, omeprazol).

Effects of other antiepileptic medicinal products on Topamax

Phenytoin and carbamazepine decrease the plasma concentration of topimarate. The addition or withdrawal of phenytoin or carbamazepine to Topamax therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of Topamax and, therefore, does not warrant dosage adjustment of Topamax. The results of these interactions are summarized below:

AED Coadministered	AED Concentration	Topamax Concentration
Phenytoin	↔**	↓
Carbamazepine (CBZ)	↔	↓
Valproic acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

↔ = No effect on plasma concentration (≤ 15% change)
** = Plasma concentrations increase in individual patients
↓ = Plasma concentrations decrease
NS = Not studied
AED = antiepileptic drug

Other medicinal product interactions

Digoxin

In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of Topamax. The clinical relevance of this observation has not been established. When Topamax is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

CNS depressants

Concomitant administration of Topamax and alcohol or other CNS depressant medicinal products has not been evaluated in clinical studies. It is recommended that Topamax not be used concomitantly with alcohol or other CNS depressant medicinal products.

St John's Wort (Hypericum perforatum).
A risk of decreased plasma concentrations resulting in a loss of efficacy could be observed with co-administration of topiramate and St John's Wort. There have been no clinical studies evaluating this potential interaction.

Oral contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 µg ethinyl estradiol (EE), Topamax given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in epilepsy patients taking valproic acid. In both studies, Topamax (50-200 mg/day in healthy volunteers and 200-800 mg/day in epilepsy patients) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day (in epilepsy patients), there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day (in healthy volunteers). The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Topamax. Patients taking estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

Lithium

In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with topiramate.

Risperidone

Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with bipolar disorder, yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with topiramate were not statistically significant. Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no significant changes in the systemic exposure of the risperidone total active moiety or of topiramate. When topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to topiramate (250-400 mg/day) introduction (90% and 54 % respectively). The most frequently reported AE's when topiramate was added to risperidone treatment were: somnolence (27% and 12%), paraesthesia (22% and 0%) and nausea (18% and 9% respectively).

Hydrochlorothiazide (HCTZ)

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear.

When Topamax is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In

addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When Topamax is added to pioglitazone therapy or pioglitazone is added to Topamax therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide AUC_{24} during topiramate administration. Systemic exposure of the active metabolites, 4-*trans*-hydroxy-glyburide (M1) and 3-*cis*-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

When topiramate is added to glyburide therapy or glyburide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions

Agents predisposing to nephrolithiasis

Topamax, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using Topamax, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic acid

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction. An association of hyperammonemia with topiramate monotherapy or concomitant treatment with other anti-epileptics has not been established.

Additional pharmacokinetic drug interaction studies

Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in C_{max} or AUC as a result of the interactions are summarized below. The second column (concomitant drug concentration) describes what happens to the concentration of the concomitant drug listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate.

Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

Concomitant Drug	Concomitant Drug Concentration[a]	Topiramate Concentration[a]
Amitriptyline	↔ 20% increase in C_{max} and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% increase in C_{max} for 4-OH propranolol (TPM 50 mg q12h)	9% and 16% increase in C_{max}, 9% and17% increase in AUC (40 and 80 mg propranolol q12h respectively)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔
Diltiazem	25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*	20% increase in AUC
Venlafaxine	↔	↔
Flunarizine	16% increase in AUC (TPM 50 mg q12h)[b]	↔

[a] % values are the changes in treatment mean C_{max} or AUC with respect to monotherapy
↔ = No effect on C_{max} and AUC (≤ 15% change) of the parent compound
NS = Not studied
*DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem
[b] Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

4.6 Pregnancy and lactation

Topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.

There are no adequate and well-controlled studies with Topamax in pregnant women.

Pregnancy registry data suggest that there may be an association between the use of Topamax during pregnancy and congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen. This data should be interpreted with caution, as more data is needed to identify increased risks for malformations.

In addition, data from these registries and other studies suggest that, compared with monotherapy, there may be an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy.

It is recommended that women of child bearing potential use adequate contraception.

Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since many medicinal products are excreted into human milk, a decision must be made whether to suspend breast-feeding or to discontinue/ abstain from topiramate therapy taking into account the importance of the medicinal product to the mother (section 4.4).

Indication Epilepsy

During pregnancy, topiramate should be prescribed after fully informing the woman of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the foetus.

Indication Migraine Prophylaxis

Topiramate is contraindicated in pregnancy, and in women of childbearing potential if an effective method of contraception is not used (see section 4.3 and 4.5 Interactions with oral contraceptives).

4.7 Effects on ability to drive and use machines

Topiramate acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/or blurred vision. These adverse reactions could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the medicinal products established.

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of ADRs were mild to moderate in severity. ADRs identified in clinical trials, and during post-marketing experience (as indicated by "*") are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Not known	cannot be estimated from the available data

The most common ADRs (those with an incidence of >5% and greater than that observed in placebo in at least 1 indication in double-blind controlled studies with topiramate) include: anorexia, decreased appetite, bradyphrenia, depression, expressive language disorder, insomnia, coordination abnormal, disturbance in attention, dizziness, dysarthria, dysgeusia, hypoesthesia, lethargy, memory impairment, nystagmus, paresthesia, somnolence, tremor, diplopia, vision blurred, diarrhoea, nausea, fatigue, irritability, and weight decreased.

<u>Paediatric population</u>

ADRs reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchloraemic, hypokalaemia, abnormal behaviour, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, lacrimation increased, sinus bradycardia, feeling abnormal, and gait disturbance.

ADRs that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia, and learning disability.

Table 1: Topiramate Adverse Drug Reactions

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Investigations	Weight decreased	Weight increased*	Crystal urine present, tandem gait test abnormal, white blood cell count decreased	Blood bicarbonate decreased	
Cardiac disorders			Bradycardia, sinus bradycardia, palpitations		
Blood and lymphatic system disorders		Anaemia	Leucopenia, thrombocytopenia lymphadenopathy, eosinophilia	Neutropenia*	
Nervous system disorders	Paraesthesia, somnolence Dizziness	Disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation ,	Depressed level of consciousness, grand mal convulsion, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersomnia, aphasia, repetitive speech, hypokinesia, dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysaesthesia, hypogeusia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia,	Apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli	

			formication		
Eye disorders		Vision blurred, diplopia, visual disturbance	Visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia	Blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating scotoma, eyelid oedema*, night blindness, amblyopia	Angle closure glaucoma*, Maculopathy*, eye movement disorder*
Ear and labyrinth disorders		Vertigo, tinnitus, ear pain	Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired		
Respiratory, thoracic and mediastinal disorders		Dyspnoea , epistaxis, nasal congestion, rhinorrhoea	Dyspnoea exertional, Paranasal sinus hypersecretion, dysphonia		
Gastrointestinal disorders	Nausea, diarrhoea	Vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort	Pancreatitis, flatulence, gastrooesophageal reflux disease, abdominal pain lower, hypoaesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia		
Renal and urinary disorders		Nephrolithiasis, pollakiuria, dysuria	Calculus urinary, urinary incontinence,	Calculus ureteric, renal tubular acidosis*	

			haematuria, incontinence, micturition urgency, renal colic, renal pain		
Skin and subcutaneous tissue disorders		Alopecia, rash, pruritus	Anhidrosis, hypoaesthesia facial, urticaria, erythema, pruritus generalised, rash macular, skin discolouration, dermatitis allergic, swelling face	Stevens-Johnson syndrome* erythema multiforme*, skin odour abnormal, periorbital oedema*, urticaria localised	Toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders		Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain	Joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue	Limb discomfort*	
Metabolism and nutrition disorders		Anorexia, decreased appetite	Metabolic acidosis, Hypokalaemia, increased appetite, polydipsia	Acidosis hyperchloraemic	
Infections and infestations	Nasopharyngitis *				
Vascular disorders			Hypotension, orthostatic hypotension flushing, hot flush,	Raynaud's phenomenon	
General disorders and administration site conditions	Fatigue	Pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise	Hyperthermia, thirst, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery	Face oedema, calcinosis	
Social circumstances			Learning disability		
Immune system disorders		Hypersensitivity			Allergic oedema*, conjunctival

				oedema*
Reproductive system and breast disorders			Erectile dysfunction, sexual dysfunction	
Psychiatric disorders	Depression	Bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour	Suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphemia, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood	Mania, anorgasmia, panic disorder, disturbance in sexual arousal, feeling of despair*, orgasm abnormal, hypomania, orgasmic sensation decreased

* identified as an ADR from postmarketing spontaneous reports. Its frequency was calculated based on clinical trial data.

4.9 Overdose

Signs and symptoms

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after overdoses with multiple medicinal products including topiramate.

Topiramate overdose can result in severe metabolic acidosis (see section 4.4).

Treatment

In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive and the patient should be well hydrated. Haemodialysis has been shown to be an effective means of removing topiramate from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antiepileptics, antimigraine preparations, ATC code: N03AX11

Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which topiramate exerts its antiseizure and migraine prophylaxis effects are unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of topiramate.

Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γ-aminobutyrate (GABA) activated $GABA_A$ receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter.

This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate $GABA_A$ receptors.

Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Topiramate antagonized the ability of kainate to activate the kainate/AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of excitatory amino acid (glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of topiramate were concentration-dependent over a range of 1 μM to 200 μM, with minimum activity observed at 1 μM to 10 μM.

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

In animal studies, topiramate exhibits anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests and is effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole.

Studies in mice receiving concomitant administration of topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity. In well-controlled add-on trials, no correlation has been demonstrated between

trough plasma concentrations of topiramate and its clinical efficacy. No evidence of tolerance has been demonstrated in man.

5.2 Pharmacokinetic properties

The film-coated tablet and hard capsule formulations are bioequivalent.

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

Absorption
Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of 1.5 µg/ml was achieved within 2 to 3 hours (T_{max}).

Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of ^{14}C-topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of topiramate.

Distribution
Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/ml has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 l/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

Metabolism
Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and faeces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of ^{14}C-topiramate. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.

Elimination
In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of ^{14}C-topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of topiramate the mean renal clearance was approximately 18 ml/min and 17 ml/min, respectively. There is evidence of renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. Overall, plasma clearance is approximately 20 to 30 ml/min in humans following oral administration.

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. The mean C_{max} following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 µg/ml. Following administration of multiple doses of 50 mg and 100 mg of topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.

Concomitant multiple-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function ($CL_{CR} \leq$ 60 ml/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. Topiramate is effectively removed from plasma by haemodialysis.

Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.

Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

Paediatric population (pharmacokinetics, up to 12 years of age)

The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic drugs decrease the steady-state plasma concentrations.

5.3 Preclinical safety data

In nonclinical studies of fertility, despite maternal and paternal toxicity as low as 8 mg/kg/day, no effects on fertility were observed, in male or female rats with doses up to 100 mg/kg/day.

In preclinical studies, topiramate has been shown to have teratogenic effects in the species studied (mice, rats and rabbits). In mice, fetal weights and skeletal ossification were reduced at 500 mg/kg/day in conjunction with maternal toxicity. Overall numbers of fetal malformations in mice were increased for all drug-treated groups (20, 100 and 500 mg/kg/day).

In rats, dosage-related maternal and embryo/fetal toxicity (reduced fetal weights and/or skeletal ossification) were observed down to 20 mg/kg/day with teratogenic effects (limb and digit defects) at 400 mg/kg/day and above. In rabbits, dosage-related maternal toxicity was noted down to 10 mg/kg/day with embryo/fetal toxicity (increased lethality) down to 35 mg/kg/day, and teratogenic effects (rib and vertebral malformations) at 120 mg/kg/day.

The teratogenic effects seen in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans. Effects on growth were also indicated by lower weights at birth and during lactation for pups from female rats treated with 20 or 100 mg/kg/day during gestation and lactation. In rats, topiramate crosses the placental barrier.

In juvenile rats, daily oral administration of topiramate at doses up to 300 mg/kg/day during the period of development corresponding to infancy, childhood, and adolescence resulted in toxicities similar to those in adult animals (decreased food consumption with decreased body weight gain, centrolobullar hepatocellular hypertrophy). There were no relevant effects on long bone (tibia) growth or bone (femur) mineral density, preweaning and reproductive development, neurological development (including assessments on memory and learning), mating and fertility or hysterotomy parameters.

In a battery of *in vitro* and *in vivo* mutagenicity assays, topiramate did not show genotoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 25 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 25 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 25 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 50 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 50 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 50 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 100 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 200 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 200 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Alu/alu blister

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 200 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 25 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 25 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 25 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 50 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 50 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 50 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

APPEAR ON THE OUTER PACKAGING

Carton for Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 100 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 100 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

APPEAR ON THE OUTER PACKAGING

Carton for Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 200 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 200 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 200 mg film-coated tablets
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets with desiccant
28 film-coated tablets with desiccant
50 film-coated tablets with desiccant
56 film-coated tablets with desiccant
60 film-coated tablets with desiccant
100 film-coated tablets with desiccant

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 15 mg hard capsules
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 hard capsules
28 hard capsules
50 hard capsules
60 hard capsules
100 hard capsules

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 15 mg hard capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 15 mg hard capsules
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 hard capsules
28 hard capsules
50 hard capsules
60 hard capsules
100 hard capsules

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 25 mg hard capsules
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 hard capsules
28 hard capsules
50 hard capsules
60 hard capsules
100 hard capsules

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 25 mg hard capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 25 mg hard capsules
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 hard capsules
28 hard capsules
50 hard capsules
60 hard capsules
100 hard capsules

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 50 mg hard capsules
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 hard capsules
28 hard capsules
50 hard capsules
60 hard capsules
100 hard capsules

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

Topamax and associated names (see Annex I) 50 mg hard capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Plastic bottle

1. NAME OF THE MEDICINAL PRODUCT

Topamax and associated names (see Annex I) 50 mg hard capsules
[See Annex I - To be completed nationally]
topiramate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 hard capsules
28 hard capsules
50 hard capsules
60 hard capsules
100 hard capsules

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Topamax and associated names (see Annex I) 25, 50, 100 and200 mg film-coated tablets
Topamax and associated names 15, 25 and 50 mg hard capsules

[See Annex I - To be completed nationally]

Topiramate

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT TOPAMAX IS AND WHAT IT IS USED FOR:

Topamax belongs to a group of medicines called “antiepileptic medicines.” It is used:

- alone to treat seizures in adults and children over age 6
- with other medicines to treat seizures in adults and children over age 2
- to prevent migraine headaches in adults

2. BEFORE YOU TAKE TOPAMAX

Do not take Topamax

- if you are allergic (hypersensitive) to topiramate or any of the other ingredients of Topamax (listed in section 6).
- for migraine prevention if you are pregnant or you are able to become pregnant but you are not using effective contraception (see section ‘pregnancy and breastfeeding’ for further information).

If you are not sure if the above applies to you, talk to your doctor or pharmacist before using Topamax.

Take special care with Topamax

Check with your doctor or pharmacist before taking Topamax if you:
- have kidney problems, especially kidney stones, or are getting kidney dialysis
- have a history of blood and body fluid abnormality (metabolic acidosis)
- have liver problems
- have eye problems, especially glaucoma
- have a growth problem
- are on a high fat diet (ketogenic diet)

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before using Topamax.

It is important that you do not stop taking your medicine without first consulting your doctor.

You should also to talk to your doctor before taking any medicine containing topiramate that is given to you as an alternative to Topamax.

You may loss weight if you use Topamax so your weight should be checked regularly when using this medicine. If you are losing too much weight or a child using this medicine is not gaining enough weight, you should consult your doctor.

A small number of people being treated with anti-epileptic medicines such as Topamax have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, vitamins and herbal medicines. Topamax and certain other medicines can affect each other. Sometimes the dose of some of your other medicines or Topamax will have to be adjusted.

Especially, tell your doctor or pharmacist if you are taking:
- other medicines that impair or decrease your thinking, concentration, or muscle coordination (e.g. central nervous system depressant medicines such as muscle relaxants and sedatives).
- birth control pills. Topamax may make your birth control pills less effective.

Tell your doctor if your menstrual bleeding changes while you are taking birth control pills and Topamax.

Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you start a new medicine.

Other medicines you should discuss with your doctor or pharmacist include other antiepileptic medicines, risperidone, lithium, hydrochlorothiazide, metformin, pioglitazone, glyburide, amitriptyline, propranolol, diltiazem, venlafaxine, flunarazine

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before using Topamax.

Taking Topamax with food and drink

You can take Topamax with or without food. Drink plenty of fluids during the day to prevent kidney stones while taking Topamax. You should avoid drinking alcohol when taking Topamax.

Pregnancy and breast-feeding

Talk to your doctor before using Topamax if you are pregnant, trying to become pregnant or breast-feeding. Your doctor will decide if you can take Topamax. As with other antiepilepsy medicines, there is a risk of harm to the unborn child if Topamax is used during pregnancy. Make sure you are very clear about the risks and the benefits of using Topamax for epilepsy during pregnancy.

You should not take Topamax for migraine prevention if you are pregnant or you are able to become pregnant and you are not using effective contraception.

Mothers who breastfeed while taking Topamax must tell the doctor as soon as possible if the baby experiences anything unusual.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Dizziness, tiredness, and vision problems may occur during treatment with Topamax. Do not drive or use any tools or machines without talking to your doctor first.

Important information about some of the ingredients of Topamax

[To be completed nationally]

3. HOW TO TAKE TOPAMAX

Always take Topamax exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Take Topamax exactly as prescribed. Your doctor will usually start you on a low dose of Topamax and slowly increase your dose until the best dose is found for you.
- Topamax tablets are to be swallowed whole. Avoid chewing the tablets as they may leave a bitter taste.
- Topamax hard capsules may be swallowed whole or may be opened and sprinkled on a teaspoon of soft food of any type. Examples are applesauce, custard, ice cream, porridge, pudding or yogurt. Drink fluids right after to make sure all of the food and medicine mixture is swallowed.
- Hold the hard capsule upright so that you can read the word “TOP”
- Carefully twist off the clear portion of the capsule. You may find it best to do this over the small portion of food onto which you will be pouring the sprinkles.
- Sprinkle all of the capsule’s contents onto a spoonful of soft food, taking care to see that the entire prescribed dosage is sprinkled onto the food.
- Be sure to swallow the entire spoonful of the sprinkle/food mixture immediately. Avoid chewing. Drink fluids immediately in order to make sure all of the mixture is swallowed.
- Never store any medicine and food mixture for use at a later time.
- Topamax can be taken before, during, or after a meal. Drink plenty of fluids during the day to prevent kidney stones while taking Topamax.

If you take more Topamax than you should

- See a doctor right away. Take the medicine pack with you.
- You may feel sleepy or tired, or have abnormal body movements, problems standing and walking, feel dizzy due to low blood pressure, or have abnormal heart beats or fits.

Overdose can happen if you are taking other medicines together with Topamax.

If you forget to take Topamax

- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. If you miss two or more doses, contact your doctor.
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you stop taking Topamax

Do not stop taking this medicine unless told to do so by your doctor. Your symptoms may return. If your doctor decides to stop this medication, your dose may be decreased gradually over a few days.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Topamax can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data).

Very common side effects include:

- Weight loss
- Tingling in the arms and legs
- Drowsiness or sleepiness
- Dizziness
- Diarrhoea
- Nausea
- Stuffy, runny nose and sore throat
- Tiredness
- Depression

Common side effects include:

- Changes in mood or behaviour, including anger, nervousness, sadness
- Weight gain
- Decrease or loss of appetite
- Reduced number of red blood cells
- Changes in thinking and alertness, including confusion, problems with concentration, memory or slowness in thinking
- Slurred speech
- Clumsiness, or problems with walking
- Involuntary shaking in the arms, hands or legs
- Reduced sense of touch or sensation
- Involuntary movement of the eyes
- Distorted sense of taste
- Visual disturbance, blurred vision, double vision
- Ringing sound in the ears
- Ear pain
- Shortness of breath
- Nose bleeds
- Vomiting
- Constipation
- Stomach pain
- Indigestion

- Dry mouth
- Tingling or numbness of the mouth
- Kidney stones
- Frequent urination
- Painful urination
- Hair loss
- Skin rash and/or itchy skin.
- Joint pain
- Muscle spasms, muscle twitching or muscle weakness
- Chest pain
- Fever
- Loss of strength
- General feeling of feeling unwell
- Allergic reaction

Uncommon side effects include:

- Crystals in the urine
- Abnormal blood counts, including reduced white blood cell count or platelet count, or increased eosinophils
- Irregular heartbeat or slowness of the heart beat
- Swollen glands in the neck armpit or groin
- Increase in seizures
- Problems with verbal communication
- Drooling
- Restlessness or increased mental and physical activity
- Loss of consciousness
- Fainting
- Slow or diminished movements
- Disturbed or poor quality sleep
- Impaired or distorted sense of smell
- Problems with handwriting
- Feeling of movement under the skin
- Eye problems including dry eyes, light sensitivity, involuntary twitching, tearing and decreased vision
- Decreased or loss of hearing.
- Hoarseness of the voice
- Inflammation of the pancreas
- Gas
- Heartburn
- Loss of sensitivity to touch in the mouth
- Bleeding gums
- Fullness or bloating
- Painful or burning sensations in the mouth
- Breath odour
- Leakage of urine and/or stools
- Urgent desire to urinate
- Pain in the kidney area and/or bladder caused by kidney stones
- **Decrease or loss of sweating**
- Skin discolouration
- Localized swelling in the skin
- Swelling of the face.
- Swelling of the joints.

- Musculoskeletal stiffness
- **Increased** acid levels in the blood
- Low potassium levels in the blood
- Increased appetite
- Increased thirst and drinking abnormally large amounts of fluid
- Low blood pressure or decrease in blood pressure that occurs when you stand up
- Hot flushing
- Flu like illness
- Cold extremities (e.g. hands and face)
- Problems with learning
- Disturbances in sexual function (erectile dysfunction, loss of libido)
- Hallucinations
- Decreased verbal communication

Rare side effects include:

- Excessive skin sensitivity
- Impaired sense of smell
- **Glaucoma which is a blockage of fluid in the eye causing increased pressure in the eye, pain and decreased vision**
- Renal tubular acidosis
- Severe skin reaction, including Stevens-Johnson syndrome, a life threatening skin condition in which the upper layer of the skin separates from the lower, and erythma multiforme, a condition of raised red spots that can blister
- Odour
- Swelling in the tissues around the eye
- Raynaud's syndrome. A disorder affecting the blood vessels, in the fingers, toes, ears and causing pain and cold sensitivity
- Tissue calcification (calcinosis).

Side effects of unknown frequency

- Maculopathy is a disease of the macula, the small spot in the retina where vision is keenest. You should call your doctor if you notice a change or decrease in your vision.
- Swelling of the conjunctiva of the eye.
- Toxic epidermal necrolysis which is a more severe form of Stevens-Johnson syndrome (see uncommon side effects).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TOPAMAX

Keep out of the reach and sight of children.

Do not use Topamax after the expiry date which is on the label. The expiry date refers to the last day of that month.

[To be completed nationally]

6. FURTHER INFORMATION

What Topamax contains

The active substance is topiramate.

- Each Topamax film-coated tablet contains 25, 50, 100, 200 mg of topiramate.
- Each Topamax hard capsule contains 15, 25, 50 mg of topiramate.

The other ingredients of Topamax are listed below.

[To be completed nationally]

What Topamax looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]