Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Topiramate Accord 25 mg film-coated Tablets
Topiramate Accord 50 mg film-coated Tablets
Topiramate Accord 100 mg film-coated Tablets
Topiramate Accord 200 mg film-coated Tablets

(topiramate)

UK/H/1438/001-004/DC
UK licence numbers: PL 20075/0145-0148

Accord Healthcare Limited

Lay Summary

Topiramate Accord 25 mg film-coated Tablets
Topiramate Accord 50 mg film-coated Tablets
Topiramate Accord 100 mg film-coated Tablets
Topiramate Accord 200 mg film-coated Tablets
(topiramate)

This is a summary of the Public Assessment Report (PAR) for Topiramate Accord 25 mg, 50 mg, 100 mg and 200 mg film-coated tablets (PL 20075/0145-0148). Topiramate Accord 25 mg, 50 mg, 100 mg and 200 mg film-coated tablets will be referred to as Topiramate tablets throughout this report, for ease of reading. It explains how Topiramate tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Topiramate tablets.

For practical information about using Topiramate tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Topiramate tablets and what are they used for?
Topiramate tablets are 'generic medicines'. This means that they are similar to 'reference medicines', already authorised in the European Union (EU) called Topamax 25mg, 50mg, 100mg, and 200mg film-coated tablets.

Topiramate tablets are 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

How do Topiramate tablets work?
Topiramate tablets contain the active substance topiramate, which belongs to a group of medicines called "antiepileptic medicines". The exact mechanism by which topiramate treats seizures and prevents migraine headaches is not fully understood.

How are Topiramate tablets used?
Topiramate tablets should be swallowed whole and can be taken before, during or after meals. Patients are advised to drink plenty of fluids during the day to prevent kidney stones.

The dose of Topiramate tablets should be taken as prescribed. The prescribing doctor will usually start the patient on a low dose of Topiramate tablets and slowly increase the dose until the most suitable dose for the patient is found.

Please read Section 3 of the package leaflet for further information.

Topiramate 25 mg, 50 mg, 100 mg and 200 mg tablets can only be obtained with a prescription.

What benefits of Topiramate tablets have been shown in studies?
Because Topiramate 25 mg, 50 mg, 100 mg and 200 mg tablets are generic medicines, studies in patients have been limited to tests to determine that the highest strength medicine, Topiramate 200 mg tablets, is bioequivalent to the reference medicine, Topamax 200 mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

It was concluded, from these tests, that Topiramate 25 mg, 50 mg, 100 mg and 200 mg tablets are comparable to the equivalent strengths of the reference medicines Topamax 25 mg, 50 mg and 100 mg film-coated tablets.

What are the possible side effects from Topiramate tablets?
Because Topiramate tablets are generic medicines, and are bioequivalent to the reference medicines, their benefits and possible side effects are taken as being the same as the reference medicines.

For information about side effects that may occur with using Topiranate tablets, please refer to the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why are Topiramate tablets approved?
It was concluded that, in accordance with EU requirements, Topiramate 25 mg, 50 mg, 100 mg and 200 mg tablets have been shown to have comparable quality and to be bioequivalent to Topamax 25 mg, 50 mg, 100 mg and 200 mg film-coated tablets, respectively. The MHRA, therefore, decided that, as for Topamax tablets, the benefits are greater than the risks and recommended that Topiramate tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Topiramate tablets?
A Risk Management Plan (RMP) has been developed to ensure that Topiramate tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet for Topiramate tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Topiramate tablets
Bulgaria, Germany, Italy, Lithuania, the Netherlands, Poland, Portugal, Spain and the UK agreed to grant Marketing Authorisations for Topiramate tablets on 20 September 2009.

Marketing Authorisations were granted in the UK to Accord Healthcare Limited on 20 October 2009.

The Marketing Authorisations for Topiramate tablets have subsequently been withdrawn in Germany and Poland.

The full PAR for Topiramate tablets follows this summary.

For more information about taking Topiramate tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2015.

Table of Contents

I	Introduction	Page 6
II	Quality aspects	Page 8
III	Non-clinical aspects	Page 11
IV	Clinical aspects	Page 11
V	User consultation	Page 14
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 14
	Annex - Table of content of the PAR update for MRP and DCP	Page 25

I Introduction

Based on the review of the data on quality, safety and efficacy, the MHRA granted Accord Healthcare Limited Marketing Authorisations for the medicinal products Topiramate 25 mg, 50 mg, 100 mg, and 200 mg film-coated tablets (PL 20075/0145-0148, UK/H/1438/001-004/DC) on 20th October 2009. The products are prescription-only medicines (POMs).

These are abridged applications for Topiramate 25 mg, 50 mg, 100 mg, and 200 mg film-coated tablets, four strengths of topiramate, submitted under Article 10(1) of 2001/83 EC, as amended. The applications refer to the reference products, Topamax 25mg, 50mg, 100mg, and 200mg film-coated tablets (PL 00242/0301-0304 respectively), authorised to Janssen-Cilag Limited on 18th July 1995. These are the innovator products. The innovator products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Topiramate tablets are indicated as 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. The tablets are also indicated as 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 film-coated tablets are also indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment. Therapy is initiated at a low dose followed by gradual titration to an effective dose. Dose and titration rate should be guided by clinical response.

Topiramate belongs to the pharmacotherapeutic group, anti-epileptics (ATC code N03A X11) and is classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity. Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to sustained depolarisation, indicative of state-dependent blockade of voltage-sensitive sodium channels. Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of the kainate/AMPA subtype of glutamate receptor, but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This effect is not thought to be a major component of the antiepileptic activity of topiramate.

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.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Topiramate 200mg film-coated tablets, to that of the reference product, Topamax 200mg film-coated tablets (PL 00242/0304, Janssen-Cilag Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The Marketing Authorisation holder has provided adequate justification for not submitting a Risk Management Plan (RMP).

II Quality aspects

II.1 Introduction

The drug products are presented as round, biconvex film-coated tablets with bevelled edges, each containing 25 mg, 50 mg, 100 mg, or 200 mg of the active ingredient topiramate. Full descriptions of the colours and markings of the individual tablets may be found by referring to the SmPCs / patient information leaflet.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, croscarmellose sodium, pregelatinised starch, lactose monohydrate, and magnesium stearate making up the tablet core. The film-coating comprises hypromellose, titanium dioxide (E171), and macrogol 6000 for the 25mg strength (white) tablets. For the 50mg (light yellow) and 100mg (dark yellow) strength tablets, the film-coat is made up of Opadry yellow 03F52057 and Opadry yellow 03F52056, respectively. Both Opadry yellow 03F52057 and Opadry yellow 03F52056 consist of hypromellose, macrogol 6000, titanium dioxide (E171), and iron oxide yellow (E172). For the 200mg strength (red) tablets, the film-coat is made up of Opadry pink 03F54045, which consists of hypromellose, macrogol 6000, titanium dioxide (E171), and iron oxide red (E172). Appropriate justification for the inclusion of each excipient has been provided.

The finished products are licensed for marketing in aluminium/aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The tablets are packaged in pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated. The tablets are also marketed in high density polyethylene (HDPE) bottles fitted with a white opaque polypropylene child resistant closure, supplied in cardboard cartons in pack sizes of 14, 30, 60, 100 and 200 film-coated tablets. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC, as amended, and is suitable for contact with foodstuffs.

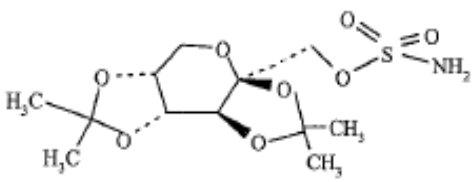
II.2 Drug Substance

Topiramate

Nomenclature:

INN:	Topiramate
Chemical name:	- 2,3:4,5-Bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate - 2,3:4,5-di-O-isopropylidene-ß-D-fructopyranose sulfamate

Structure:



Molecular formula:	$C_{12}H_{21}NO_8S$
Molecular weight:	339.36 g/mol
CAS No:	97240-79-4
Physical form:	White or off white crystalline powder
Solubility:	Soluble in methanol, acetone, dimethyl formamide, 0.1N aqueous sodium hydroxide solution and slightly soluble in water

The active substance, topiramate, is not the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in HDPE drums lined with double polythene bags. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in containers representative of the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 24 months.

II.3 Medicinal Product

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

The excipients are all controlled to the requirements of the current European Pharmacopoeia.

The coating dispersions are not compendial but the individual components comply with the requirements of the European Pharmacopoeia. Copies of the routine tests and specifications are provided. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Appropriate TSE/BSE documentation was provided for lactose monohydrate.

There were no novel excipients used and no overages.

Comparative dissolution data were provided for each of the four strengths of the generic topiramate tablets and appropriate reference tablet formulations. The dissolution profiles were found to be similar.

Comparative impurity data were also provided for the test and appropriate reference products. The impurity profiles were comparable and all impurities were within the specification limits.

A bioequivalence study was presented comparing the test product, Topiramate 200mg film-coated tablets, to the reference product, Topamax 200 mg film-coated tablets (PL 00242/0304, Janssen-Cilag Limited).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on two production scale batches for each of the strengths.

Finished Product Specification
The finished product specifications include tests and criteria to apply for both release and end of shelf life testing and are satisfactory; they provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided for two production scale batches of each of the strengths and they comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are ‘Do not store above 25°C’. Additional instructions of ‘Keep in the original pack in order to protect from moisture’ and ‘Keep the container tightly closed in order to protect from moisture’ are applied to the packaging for the blister pack and HDPE bottle pack respectively.

II.4 Discussion on chemical and pharmaceutical aspects

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Topiramate 200 mg tablets are a generic medicinal product of Topamax 200 mg film-coated tablets (PL 00242/0304, Janssen-Cilag Limited) appears justified.

Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. As the test products, Topiramate 25 mg, 50 mg, 100 mg, and 200 mg tablets, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200 mg strength were extrapolated to the 25 mg, 50 mg, and 100 mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

III Non-clinical aspects

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of topiramate, which is a widely used and well-known active substance.

A satisfactory non-clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

IV Clinical aspects

IV.1 Introduction

Topiramate tablets are indicated as 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. The tablets are also indicated as 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 tablets are also indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment. Therapy is initiated at a low dose followed by gradual titration to an effective dose. Dose and titration rate should be guided by clinical response.

The indications are consistent with those for the reference products and are satisfactory.

The posology is consistent with that for the reference products and is satisfactory.

The clinical pharmacology of topiramate is well known. A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

No new clinical toxicology data have been submitted and none are required for these types of application.

IV.2 Pharmacokinetics

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Topiramate 200 mg tablets (test) and Topamax 200 mg film-coated tablets (PL 00242/0304, Janssen-Cilag Limited; reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). The use of the 200 mg strength only for the bioequivalence study has been adequately justified.

This was a randomised, two-treatment, two-period, two sequence, single dose crossover bioavailability and bioequivalence study conducted in 26 (24 + 2 alternates) healthy adult male human subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 17 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 144.0 hours after administration of test or reference product. The drug concentration levels in plasma were determined by a validated LC/MS/MS method.

The primary pharmacokinetic parameters for this study were C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Results:

Twenty-five subjects completed the study and 24 were used in the statistical analysis. There were no deaths or serious adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for a randomised, two-treatment, two-period, single dose crossover study between the test and reference products. n=24 healthy subjects, dosed fasted; t=144 hours. Wash-out period: 17 days

Parameters (Units)	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Reference Product-A	Test Product-B	Ratio (B / A)%	
C_{max} (ng/ml)	5163.077	5130.845	99.4%	95.90-102.98%
AUC_{0-t} (ng.h/ml)	179193.662	177215.978	98.9%	96.69-101.15%
$AUC_{0-\infty}$ (ng.h/ml)	186692.315	185359.908	99.3%	97.04-101.59%

Conclusion on Bioequivalence
The results of the bioequivalence study show that the test product and reference product are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Topiramate 25 mg, 50 mg, and 100 mg tablets. Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. As Topiramate 25 mg, 50 mg, 100 mg, and 200 mg tablets meet the criteria specified in the *Note for Guidance on the investigation of bioavailability and bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200 mg strength were extrapolated to the 25 mg, 50 mg, and 100 mg strength products.

IV.3 Pharmacodynamics
No novel pharmacodynamic data are supplied or required for this application.

IV.4 Clinical efficacy
No new data have been submitted and none are required. Efficacy is reviewed in the clinical overview. The efficacy of topiramate is well established from its extensive use in clinical practice.

IV.5 Clinical safety
No new data have been submitted and none are required for applications of this type. Safety is reviewed in the clinical overview. The safety profile of topiramate is well-known.

IV.6 Risk Management Plan (RMP)
This application was submitted, and approved, before implementation of the Pharmacovigilance legislation on 21 July 2012 and, therefore, preceded the mandatory requirement of an RMP for a new Marketing Authorisation. A suitable justification for not submitting a Risk Management Plan was provided and this was considered satisfactory.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

IV.7 Discussion on the clinical aspects
All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Topiramate 200 mg tablets, Accord Healthcare Limited) and reference (Topamax 200 mg film-coated tablets; PL 00242/0304, Janssen-Cilag Limited) products within acceptance limits. Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. The results and conclusions of the bioequivalence study on the 200 mg strength were extrapolated to the 25 mg, 50 mg, and 100 mg strength products.

The approved SmPCs are consistent with those for the reference products, and are acceptable.

The final PIL is in line with the approved SmPCs and is satisfactory.

The labelling is satisfactory.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.

V User consultation

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

VI Overall conclusion, benefit/risk assessment and recommendation

Quality

The important quality characteristics of Topiramate 25 mg, 50 mg, 100 mg, and 200 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Non-clinical

No new non-clinical data were submitted and none are required for applications of this type.

Efficacy

Bioequivalence has been demonstrated between the applicant’s Topiramate 200 mg tablets, and the reference product, Topamax 200 mg film-coated tablets (PL 00242/0304, Janssen-Cilag Limited).

Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. As Topiramate 25 mg, 50 mg, 100 mg, and 200 mg tablets were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200 mg strength were extrapolated to the 25 mg, 50 mg, and 100 mg strength products, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

Product literature

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

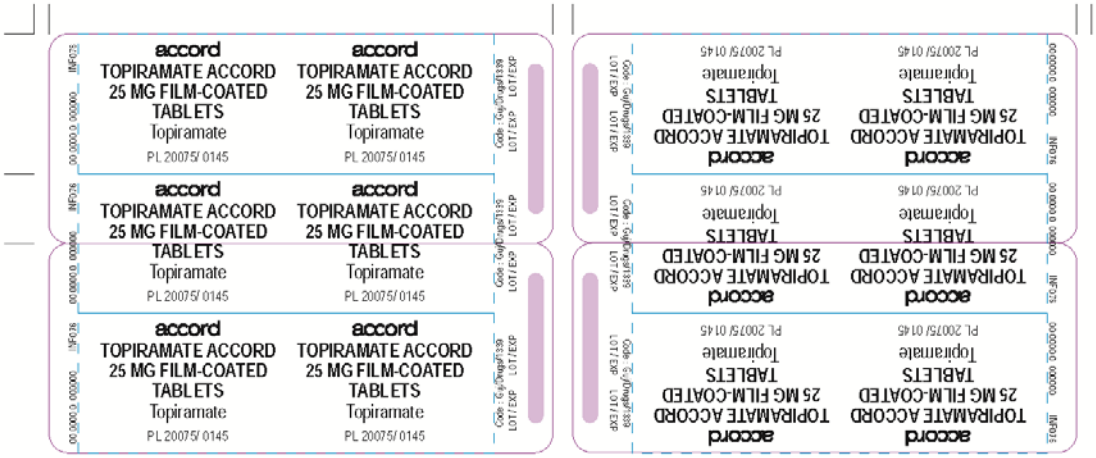
Benefit/risk assessment

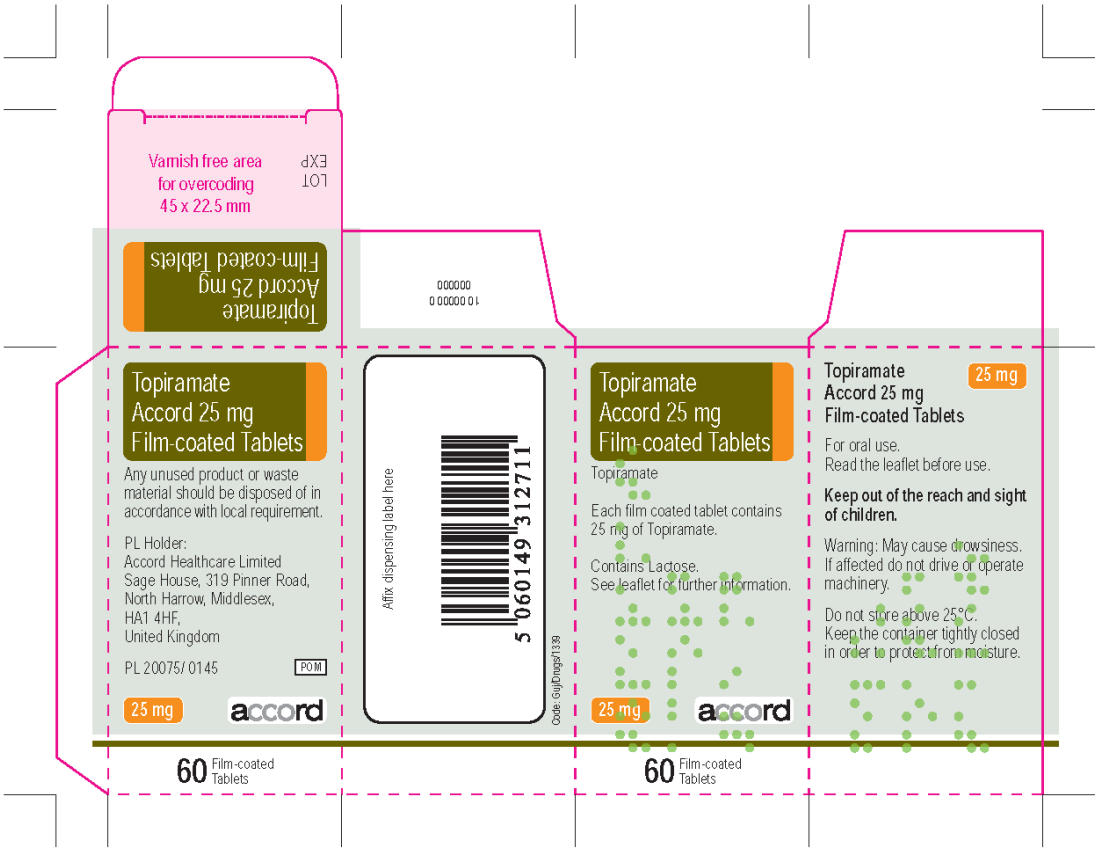
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with topiramate is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), package leaflet text and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference products. In accordance with Directive 2012/84/EU, as amended, the current approved UK versions of the SmPCs and package leaflet text for these products are available on the Medicines and Healthcare products Regulatory Agency website.

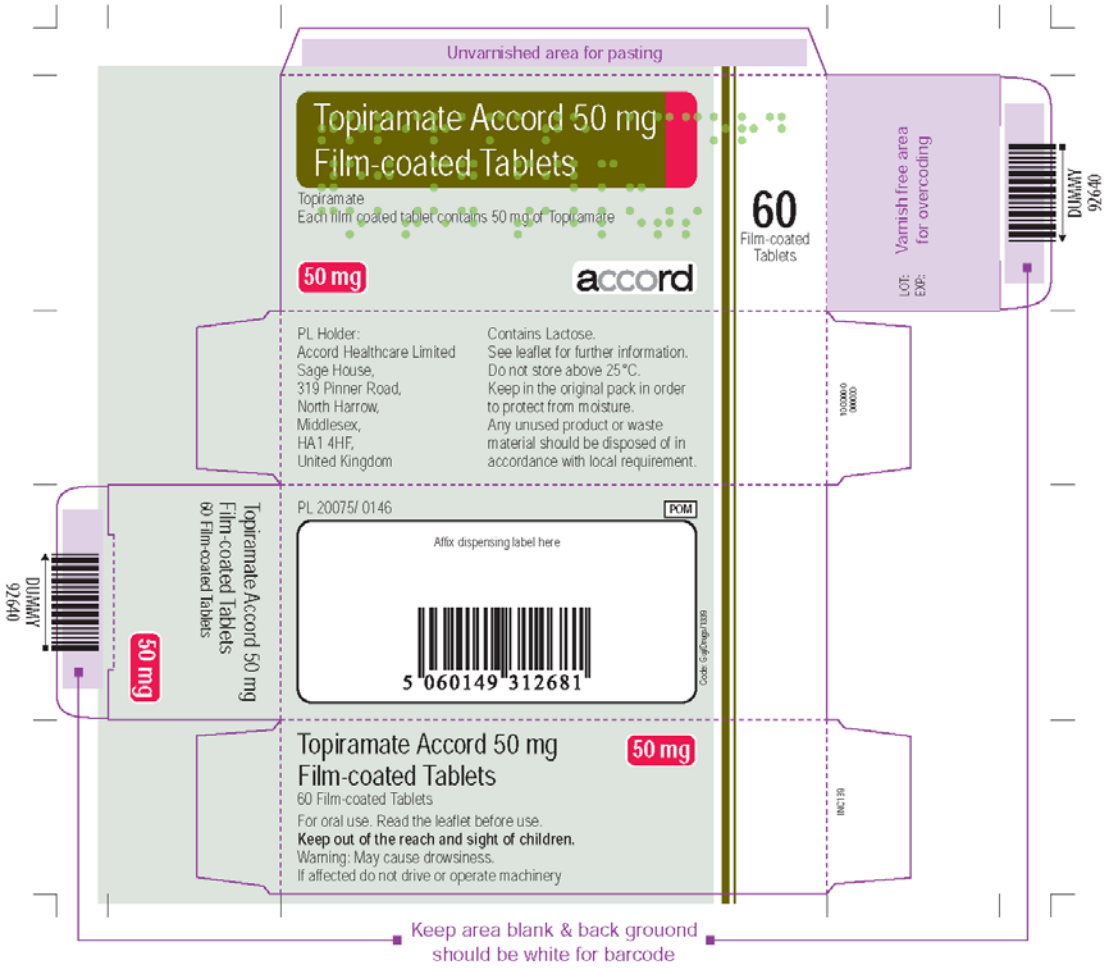
The currently approved labelling text is listed below:

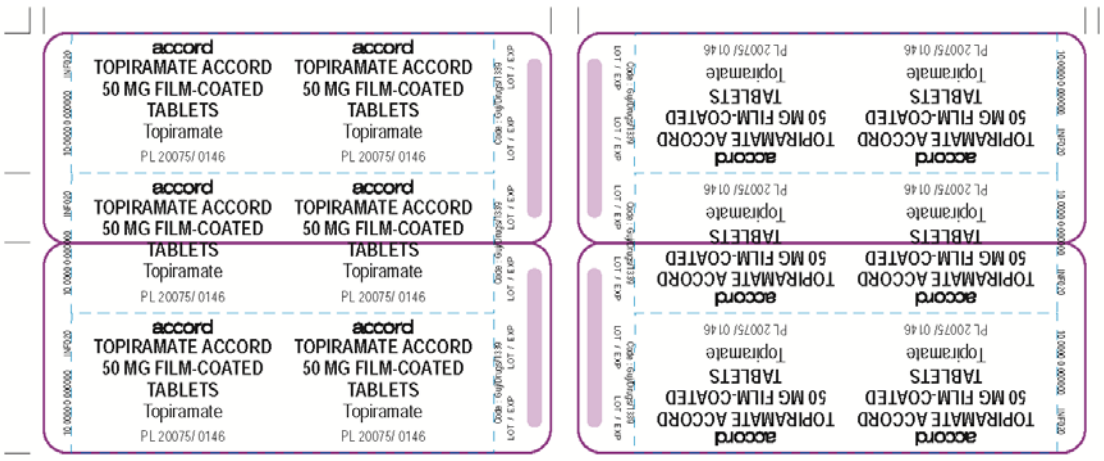

Unvarnished area for pasting
Topiramate Accord 25 mg
Film-coated Tablets
Topiramate
Each film coated tablet contains 25 mg of Topiramate
25 mg
accord
60
Film-coated
Tablets
Keep area blank &
Varnish free
for overcoding
LOT:
EXP.:
DUMMY
92640
PL Holder:
Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex,
HA1 4HF,
United Kingdom
Contains Lactose.
See leaflet for further information.
Do not store above 25°C.
Keep in the original pack in order to
protect from moisture.
Any unused product or waste material
should be disposed of in accordance
with local requirement.
PL 20075/0145
POM
Affix dispensing label here
5 060149 312674
Topiramate Accord 25 mg
Film-coated Tablets
60 Film-coated Tablets
25 mg
DUMMY
92640
Topiramate Accord 25 mg
Film-coated Tablets
60 Film-coated Tablets
For oral use. Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery
25 mg
Keep area blank & back grouond
should be white for barcode

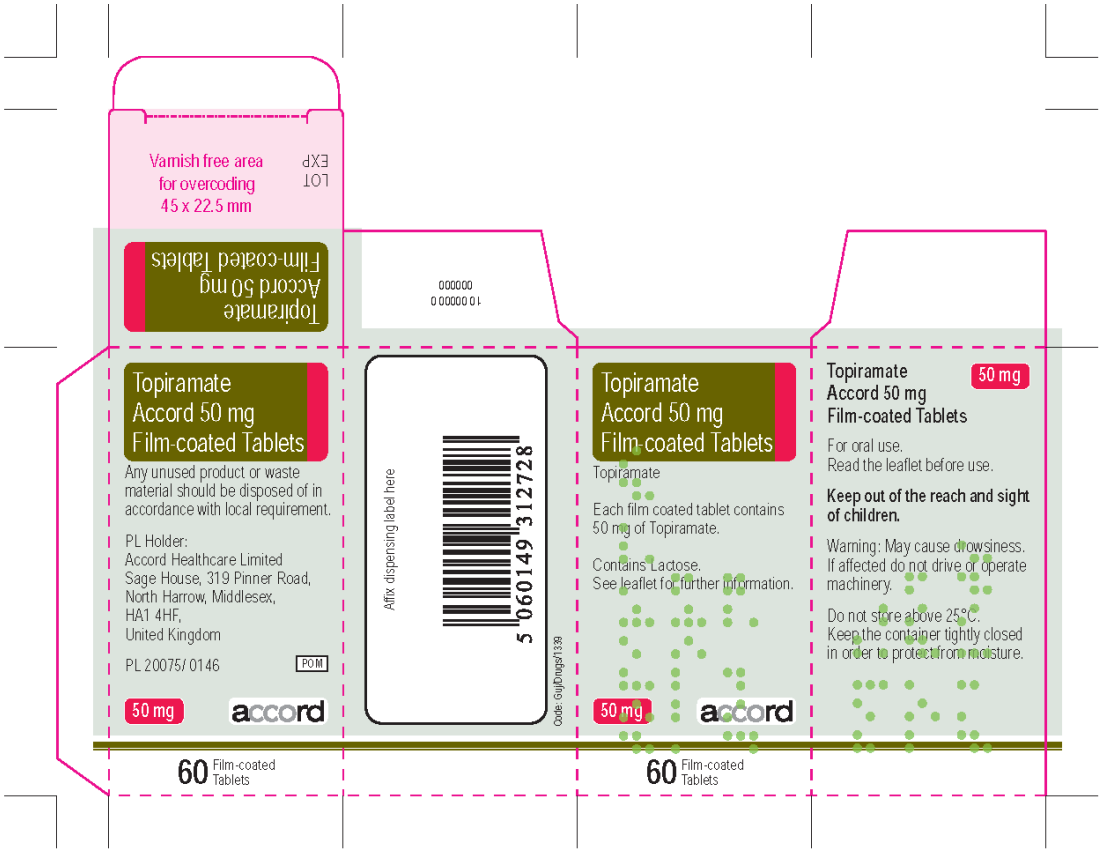

accord
TOPIRAMATE ACCORD
25 MG FILM-COATED
TABLETS
Topiramate
PL 20075/0145


Varnish free area
for overcoding
45 x 22.5 mm
EXP
LOT
Topiramate
Accord 25 mg
Film-coated Tablets
Topiramate
Accord 25 mg
Film-coated Tablets
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF,
United Kingdom
PL 20075/ 0145
POM
25 mg
accord
60 Film-coated Tablets
Affix dispensing label here
5 060149 312711
Topiramate
Accord 25 mg
Film-coated Tablets
Topiramate
Each film coated tablet contains 25 mg of Topiramate.
Contains Lactose.
See leaflet for further information.
25 mg
accord
60 Film-coated Tablets
Topiramate
Accord 25 mg
Film-coated Tablets
25 mg
For oral use.
Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery.
Do not store above 25°C.
Keep the container tightly closed in order to protect from moisture.

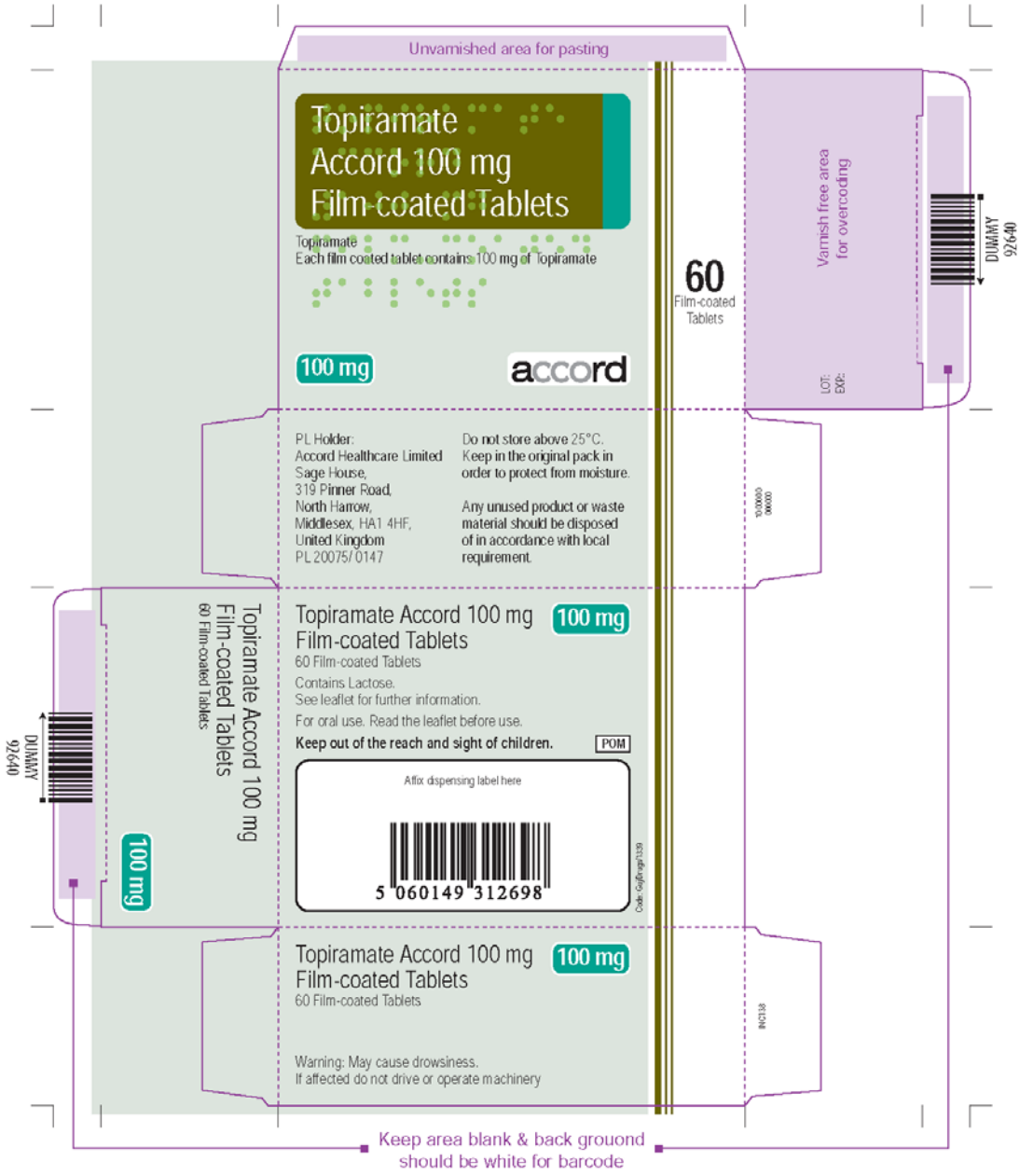

Topiramate Accord 25 mg Film-coated Tablets
Topiramate
Each film coated tablet contains 25 mg of Topiramate.
Contains Lactose. See leaflet for further information.
For oral use. Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery
25 mg
PL 20075/ 0145
Do not store above 25°C. Keep the container tightly closed in order to protect from moisture.
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder: Accord Healthcare Limited
Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom
POM
accord
60 Film-coated Tablets
Varnish free area
9 mm x 20 mm
EXP
LOT

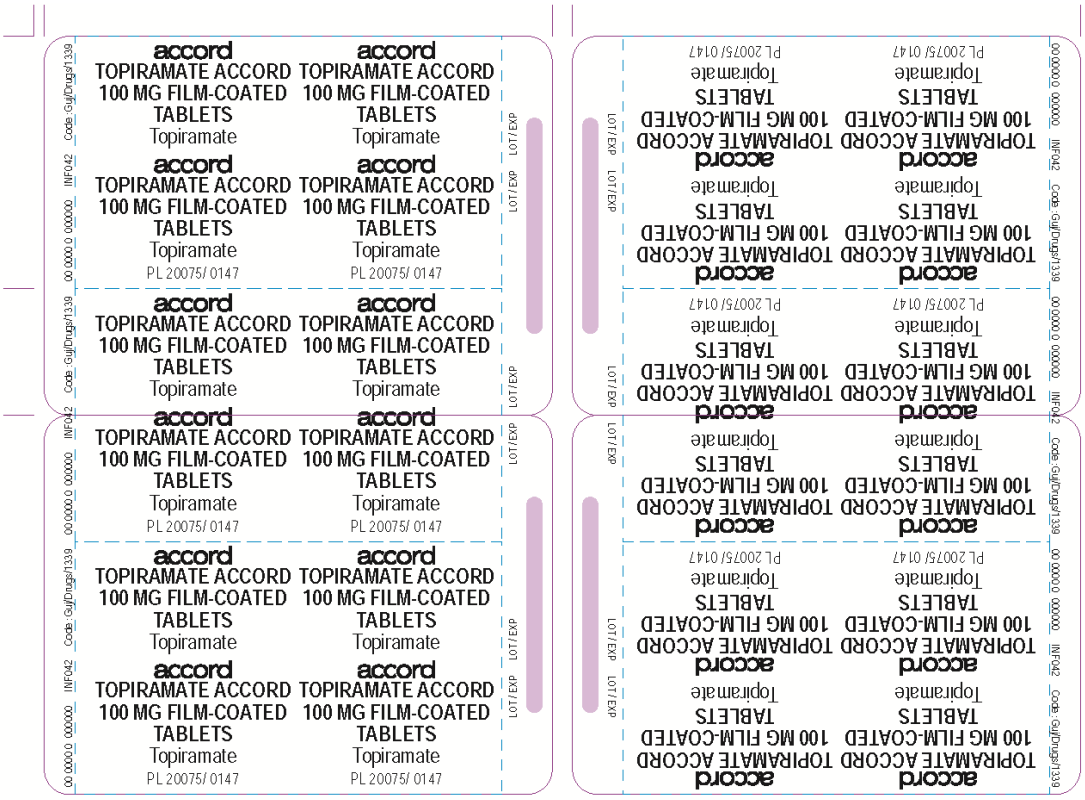

Unvarnished area for pasting
Topiramate Accord 50 mg
Film-coated Tablets
Topiramate
Each film coated tablet contains 50 mg of Topiramate
50 mg
accord
60
Film-coated
Tablets
Varnish free area
for overcoding
LOT:
EXP:
DUMMY
92640
PL Holder:
Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex,
HA1 4HF,
United Kingdom
Contains Lactose.
See leaflet for further information.
Do not store above 25°C.
Keep in the original pack in order
to protect from moisture.
Any unused product or waste
material should be disposed of in
accordance with local requirement.
PL 20075/ 0146
POM
Affix dispensing label here
5 060149 312681
Topiramate Accord 50 mg
Film-coated Tablets
60 Film-coated Tablets
50 mg
Topiramate Accord 50 mg
Film-coated Tablets
60 Film-coated Tablets
For oral use. Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery
Keep area blank & back grouond
should be white for barcode

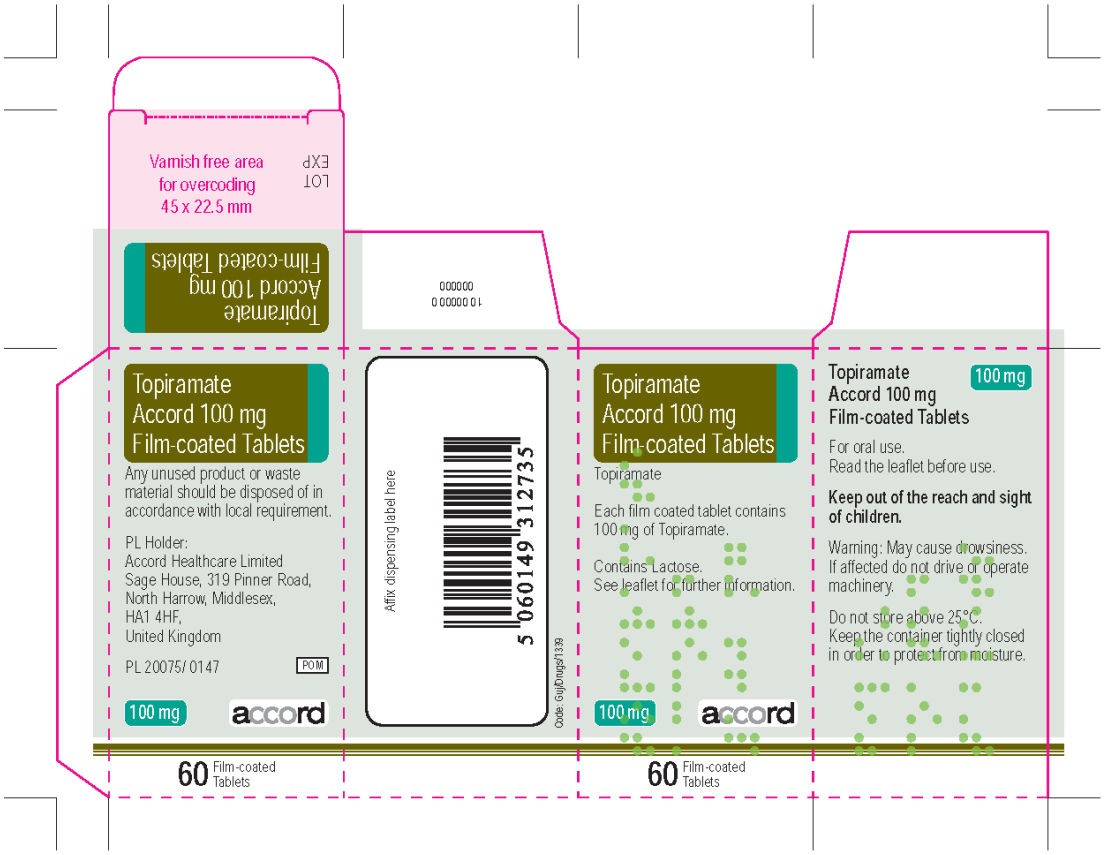

accord
TOPIRAMATE ACCORD
50 MG FILM-COATED
TABLETS
Topiramate
PL 20075/ 0146


Varnish free area
for overcoding
45 x 22.5 mm
EXP
LOT
Topiramate
Accord 50 mg
Film-coated Tablets
Topiramate
Accord 50 mg
Film-coated Tablets
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF,
United Kingdom
PL 20075/ 0146
POM
50 mg
accord
60 Film-coated Tablets
Affix dispensing label here
5 060149 312728
Code: GrpDrugs*1339
Topiramate
Accord 50 mg
Film-coated Tablets
Topiramate
Each film coated tablet contains 50 mg of Topiramate.
Contains Lactose.
See leaflet for further information.
50 mg
accord
60 Film-coated Tablets
Topiramate
Accord 50 mg
Film-coated Tablets
50 mg
For oral use.
Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery.
Do not store above 25°C.
Keep the container tightly closed in order to protect from moisture.

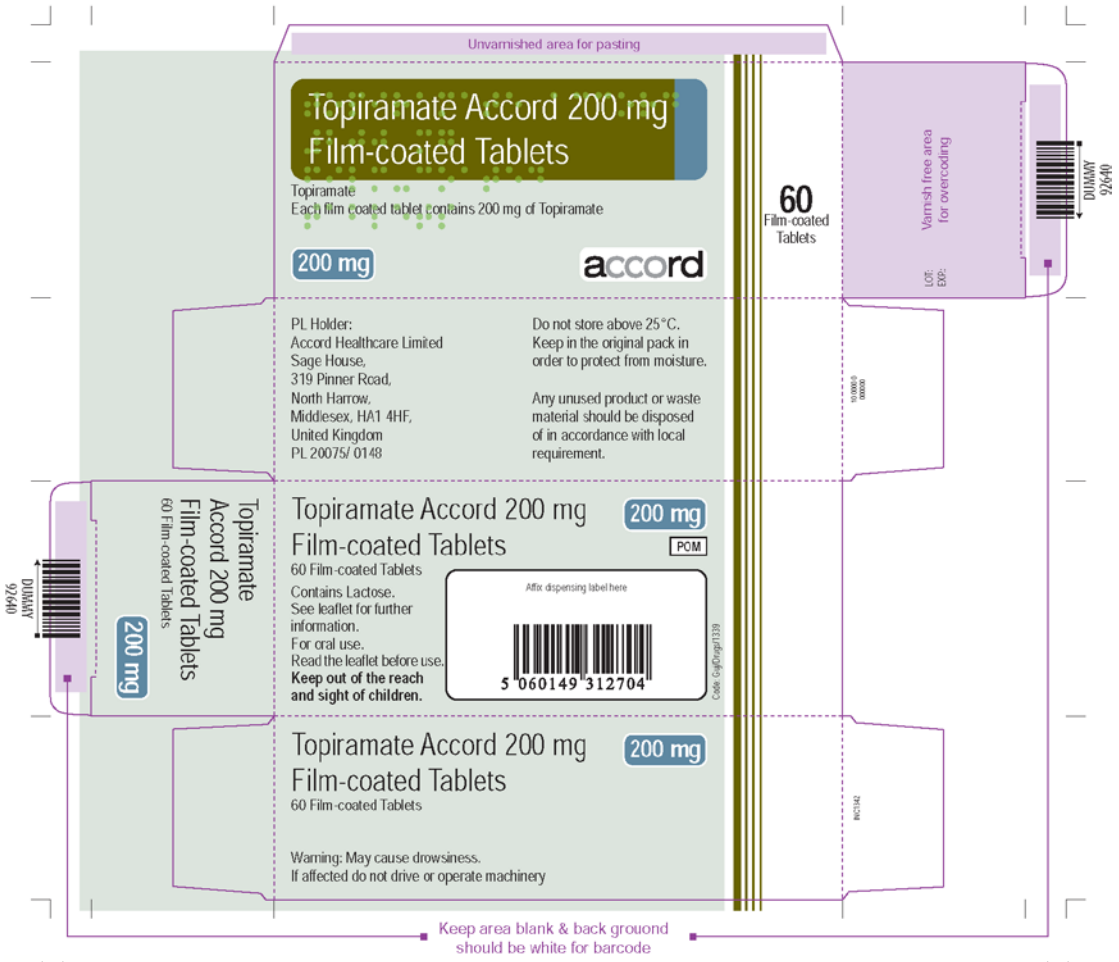

Topiramate Accord 50 mg Film-coated Tablets
Topiramate
Each film coated tablet contains 50 mg of Topiramate.
Contains Lactose. See leaflet for further information.
For oral use. Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery
50 mg
PL 20075/ 0146
Do not store above 25 °C. Keep the container tightly closed in order to protect from moisture.
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder: Accord Healthcare Limited
Sage House, 319 Pinner Road, North Harrow,
Middlesex, HA1 4HF, United Kingdom
POM
accord
60
Film-coated Tablets
Code: GrpDrugs*1339
xx.xxxx.x.xxxxx
Varnish free area
9 mm x 20 mm
EXP
LOT

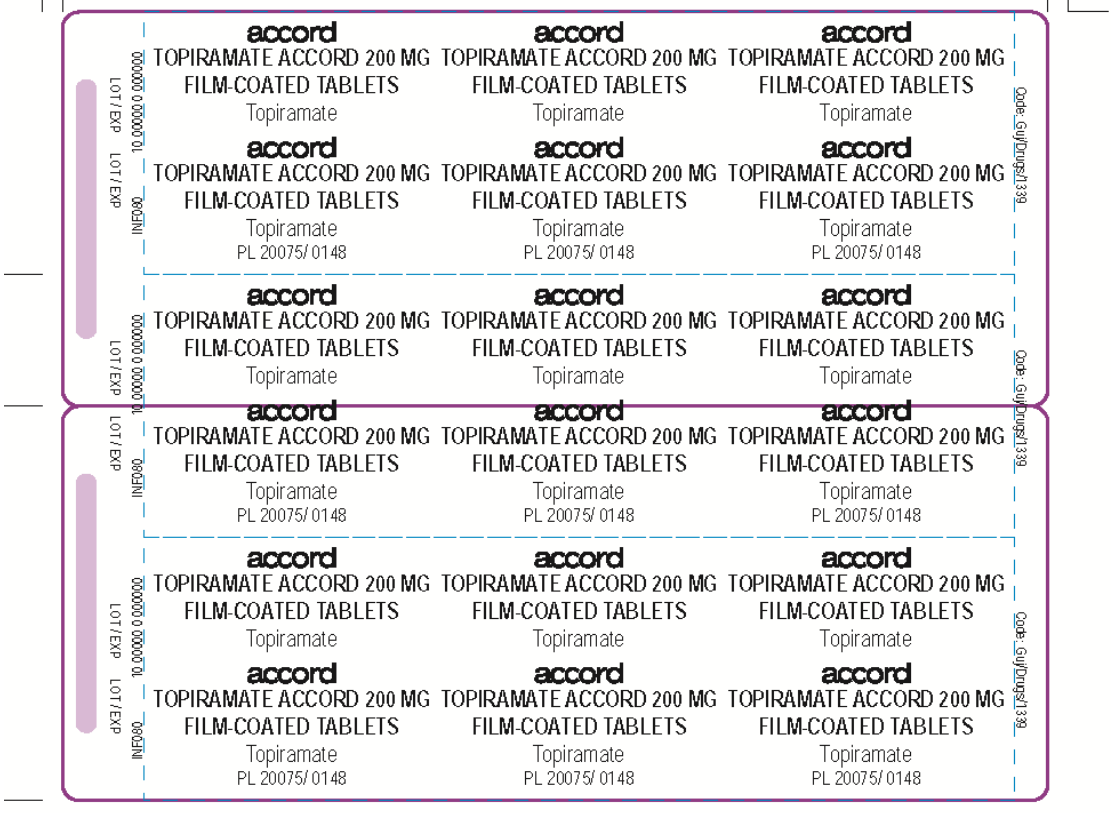

Unvarnished area for pasting
Topiramate Accord 100 mg Film-coated Tablets
Topiramate
Each film coated tablet contains 100 mg of Topiramate
100 mg
accord
60 Film-coated Tablets
Varnish free area for overcoding
LOT:
EXP:
DUMMY 92640
PL Holder:
Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom
PL 20075/0147
Do not store above 25°C.
Keep in the original pack in order to protect from moisture.
Any unused product or waste material should be disposed of in accordance with local requirement.
Topiramate Accord 100 mg Film-coated Tablets
100 mg
60 Film-coated Tablets
Contains Lactose.
See leaflet for further information.
For oral use. Read the leaflet before use.
Keep out of the reach and sight of children.
POM
Affix dispensing label here
5 060149 312698
Topiramate Accord 100 mg Film-coated Tablets
60 Film-coated Tablets
100 mg
DUMMY 92640
Topiramate Accord 100 mg Film-coated Tablets
100 mg
60 Film-coated Tablets
Warning: May cause drowsiness.
If affected do not drive or operate machinery
Keep area blank & back grouond should be white for barcode

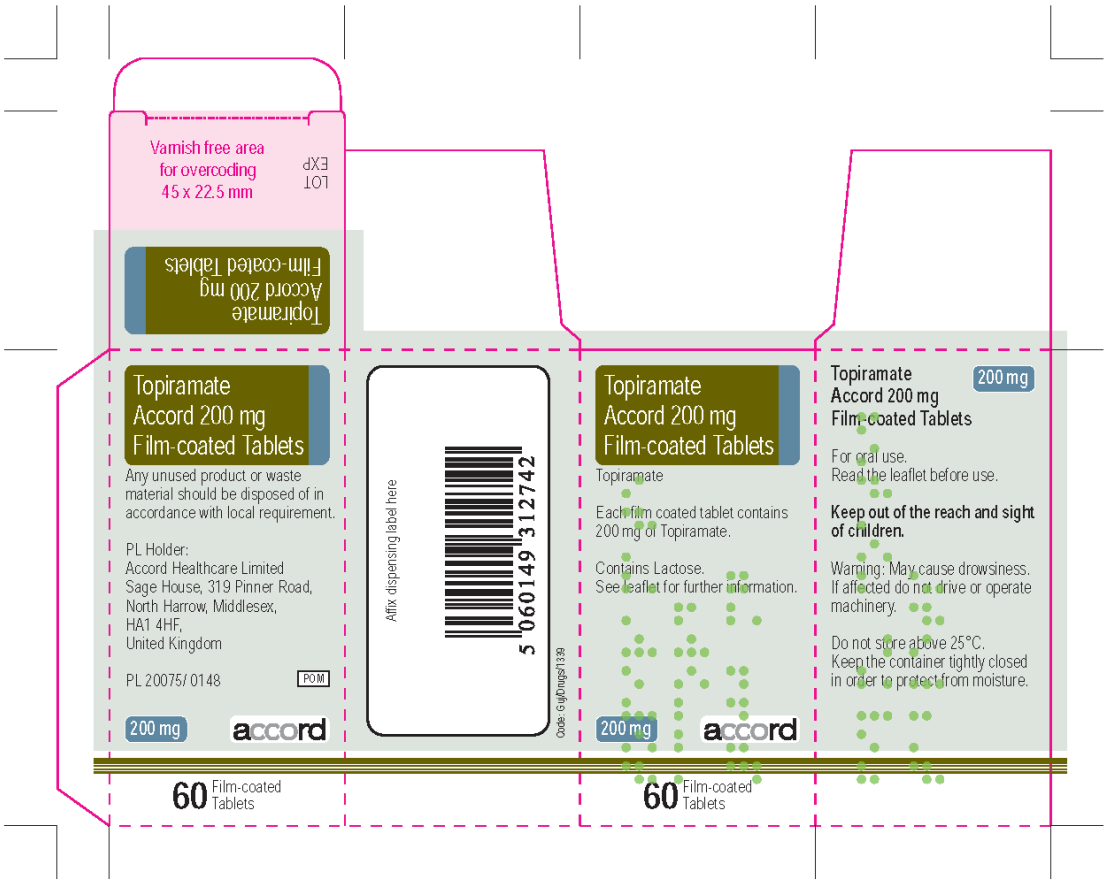

accord
TOPIRAMATE ACCORD
100 MG FILM-COATED
TABLETS
Topiramate
PL 20075/ 0147
LOT/EXP
Code: GulfDrugs*1339
INF042
00 00000 000000

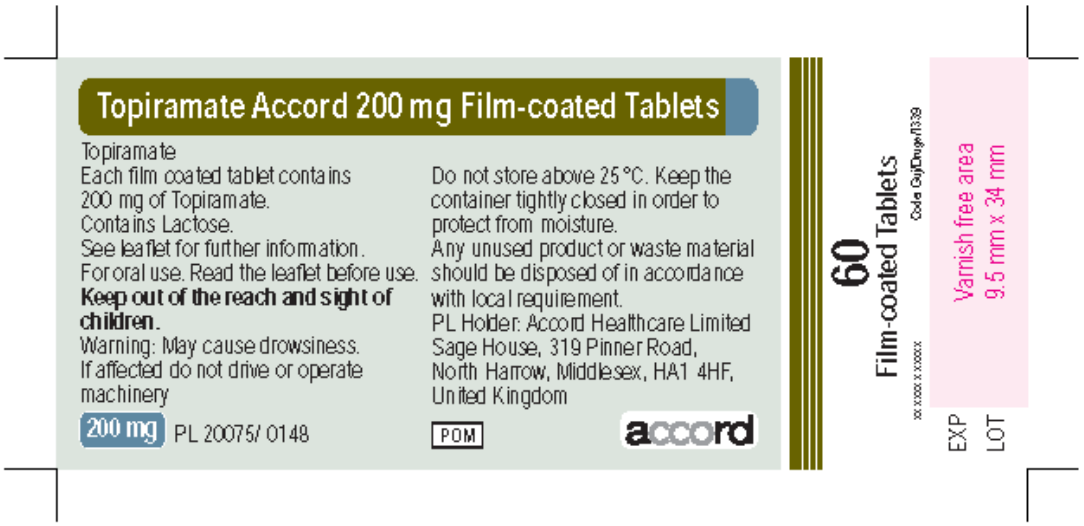

Varnish free area
for overcoding
45 x 22.5 mm
EXP
LOT
Topiramate
Accord 100 mg
Film-coated Tablets
Topiramate
Accord 100 mg
Film-coated Tablets
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF,
United Kingdom
PL 20075/ 0147
POM
100 mg
accord
60 Film-coated Tablets
Affix dispensing label here
5 060149 312735
Code: GuyDrugs#1339
Topiramate
Accord 100 mg
Film-coated Tablets
Topiramate
Each film coated tablet contains 100 mg of Topiramate.
Contains Lactose.
See leaflet for further information.
100 mg
accord
60 Film-coated Tablets
Topiramate
Accord 100 mg
Film-coated Tablets
100 mg
For oral use.
Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery.
Do not store above 25°C.
Keep the container tightly closed in order to protect from moisture.


Topiramate Accord 100 mg Film-coated Tablets
Topiramate
Each film coated tablet contains 100 mg of Topiramate.
Contains Lactose. See leaflet for further information.
For oral use. Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery
100 mg
PL 20075/ 0147
POM
accord
Do not store above 25 °C. Keep the container tightly closed in order to protect from moisture.
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder: Accord Healthcare Limited
Sage House, 319 Pinner Road, North Harrow,
Middlesex, HA1 4HF, United Kingdom
60 Film-coated Tablets
xx xxxx x xxxxx
Code: GuyDrugs#1339
Varnish free area
9 mm x 20 mm
EXP
LOT


Unvarnished area for pasting
Topiramate Accord 200 mg Film-coated Tablets
Topiramate
Each film coated tablet contains 200 mg of Topiramate
200 mg
accord
60 Film-coated Tablets
Varnish free area for overcoding
LOT:
EXP:
DUMMY 92640
PL Holder:
Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom
PL 20075/ 0148
Do not store above 25°C.
Keep in the original pack in order to protect from moisture.
Any unused product or waste material should be disposed of in accordance with local requirement.
Topiramate Accord 200 mg Film-coated Tablets
60 Film-coated Tablets
200 mg
POM
Contains Lactose.
See leaflet for further information.
For oral use.
Read the leaflet before use.
Keep out of the reach and sight of children.
Affix dispensing label here
5 060149 312704
Topiramate Accord 200 mg Film-coated Tablets
60 Film-coated Tablets
200 mg
Warning: May cause drowsiness.
If affected do not drive or operate machinery
Keep area blank & back grouond should be white for barcode


accord
TOPIRAMATE ACCORD 200 MG FILM-COATED TABLETS
Topiramate
PL 20075/ 0148
LOT/EXP
EXPIRY


Varnish free area
for overcoding
45 x 22.5 mm
EXP
LOT
Topiramate
Accord 200 mg
Film-coated Tablets
Topiramate
Accord 200 mg
Film-coated Tablets
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF,
United Kingdom
PL 20075/ 0148
POM
200 mg
accord
Affix dispensing label here
5 060149 312742
Code: GuyDrugs1339
Topiramate
Accord 200 mg
Film-coated Tablets
Topiramate
Each film coated tablet contains 200 mg of Topiramate.
Contains Lactose.
See leaflet for further information.
200 mg
accord
60 Film-coated Tablets
Topiramate
Accord 200 mg
Film-coated Tablets
200 mg
For oral use.
Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery.
Do not store above 25°C.
Keep the container tightly closed in order to protect from moisture.
60 Film-coated Tablets


Topiramate Accord 200 mg Film-coated Tablets
Topiramate
Each film coated tablet contains 200 mg of Topiramate.
Contains Lactose.
See leaflet for further information.
For oral use. Read the leaflet before use.
Keep out of the reach and sight of children.
Warning: May cause drowsiness.
If affected do not drive or operate machinery
200 mg
PL 20075/ 0148
Do not store above 25 °C. Keep the container tightly closed in order to protect from moisture.
Any unused product or waste material should be disposed of in accordance with local requirement.
PL Holder: Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom
POM
accord
60
Film-coated Tablets
Code GuyDrugs1339
xx xxxx x xxxxx
EXP
LOT
Varnish free area
9.5 mm x 34 mm

Annex - Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**
To update section 4.6 (pregnancy and lactation) and 4.7 (driving and machines) of the SmPC in line with the reference product, Topamax 25 mg, 50 mg, 100 mg, 200 mg tablets. Consequential updates are made to the PIL.	UK/H/1438/001-004 /IB/001/G	Y	11 April 2011	28 October 2011	Approval	N
To update SmPC and PIL of Topiramate 25/50/100/200 mg Tablets following publication of Paediatric Assessment Report for a EU WorkSharing (WS) procedure on 11 March 2011.	UK/H/1438/001-004/1B/003	Y	18 August 2011	27 October 2011	Approved	N
To update the section 1 (name of the medicinal product) of the SmPC in line with the advice to include the MAH name, which was issued by the Commission on Human Medicines (CHM) about prescribing and dispensing of Anti-epileptic Drug (AED) products.	National Type IB Variation	Y	03 December 2013	12 February 2014	Approved	Y – Annex 1
To submit a new bioequivalence study.	UK/H/1438/001-004/II/014	N	23 April 2015	25 September 2015	Approved	Y – Annex 2
To introduce the Risk Management Plan (RMP).	UK/H/1438/001-004/II/015	N	25 June 2015	22 September 2015	Approved	N

Annex 1

Our Reference:	PL 20075/0145 - 0016
Product:	PL 20075/0145 Topiramate Accord 25 mg film-coated tablets
Marketing Authorisation Holder:	Accord Healthcare Limited
Active Ingredient(s):	Topiramate
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	

Reason:
To update the section 1 (name of the medicinal product) in line with the advice to include the MAH name, which was issued by the Commission on Human Medicines (CHM) about prescribing and dispensing of Anti-epileptic Drug (AED) products.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 146494 and covers the following submissions PL 20075/0147 - 0016, PL 20075/0148 - 0017, PL 20075/0146 - 0017.

Supporting Evidence
Amended SmPC, labelling and PIL were provided.

Evaluation
This is a type IB variation number A.2.b to update the section 1 (name of the medicinal product) in line with the advice to include the MAH name, which was issued by the Commission on Human Medicines (CHM) about prescribing and dispensing of AED products.

Conclusion
The proposed changes are acceptable.

In accordance with Directive 2010/84/EU, the Summary of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Approved
Date: 12 February 2014

Annex 2

Our Reference:	PL 20075/0145 - 0025
Product:	Topiramate Accord 25 mg film-coated tablets
Marketing Authorisation Holder:	Accord Healthcare Limited
Active Ingredient(s):	Topiramate
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Complex
EU Procedure Number (if applicable):	UK/H/1438/001-004/II/014

Reason:
To submit a new bioequivalence study.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 162608 and covers the following submissions PL 20075/0147 - 0025, PL 20075/0146 - 0026, PL 20075/0148 - 0026.

Supporting Evidence
The Applicant wishes to file a Type II variation (C.I.4) to submit the new bioequivalence (BE) study for the current product to meet the new BE guideline.

A complete BE study report has been enclosed in Module 5 of the Common Technical Dossier (CTD).

No change to product information is part of this variation. No change in risk/benefit balance has been proposed.

Evaluation
Pharmacokinetic study
An open label, balanced, randomised, two-treatment, two sequence, two-period, single oral dose, crossover, bioequivalence study of Topiramate Accord 200 mg film-coated tablets (test product) versus Topamax 200 mg film-coated tablets (reference product) in healthy, adult, male human subjects under fasting conditions.

After an overnight fast of at least 10 hours a single oral dose (200 mg) of either the test or the reference product was administered with 240 ml of drinking water at ambient temperature with the subjects in sitting posture. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post-dose. The two treatment periods were separated by a 24-day washout period.

Design of the study was standard and acceptable. The blood sampling schedule was appropriate to describe the selected PK parameters. The sampling was extended to 72 hours post dose. The washout period was sufficient in view of the half-life.

The main pharmacokinetic results are presented below:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%		
$\ln C_{max}$	5273.644	5239.099	100.7	97.26 – 104.18	100.0
$\ln AUC_{0-72}$	150662.313	151059.247	99.7	98.36 – 101.13	100.0

The 90% confidence intervals for the primary variables AUC_{0-72} and C_{max} are well within the acceptance range of 80.00-125.00%. Based on the submitted bioequivalence studies bioequivalence to the reference product may be concluded.

Conclusion
The results of the study can be accepted as valid. The bioequivalence has been shown. There are no new safety signals emerging as the results of the study.

Decision: Approved
Date: 25 September 2015