CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Natriumvalproaat Sandoz Chrono 300 mg, prolonged release tablets
Natriumvalproaat Sandoz Chrono 500 mg, prolonged release tablets

Sandoz B.V, The Netherlands

Sodium valproate and valproic acid

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/736/01-02/MR
Registration number in the Netherlands: RVG 33299, 33300

19 May 2009

Pharmacotherapeutic group:	Antiepileptics, Fatty acid derivatives
ATC code:	N03AG01
Route of administration:	oral
Therapeutic indication:	treatment of primary and secondary forms of generalized epilepsy and partial epilepsy
Prescription status:	prescription only
Date of authorisation in NL:	12 December 2005
Concerned Member States:	BE, CZ, DE, DK, EE, FI, LT, LV, PL, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) and Article 10(3) (SK)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Natriumvalproaat Sandoz Chrono 300 and 500 mg prolonged release tablets, from Sandoz B.V, the Netherlands. The date of authorisation was on 12 December 2005 in the Netherlands.

The product is indicated for:
Primary form of generalized epilepsy
- typical and atypical absences (petit mal)
- myoclonic seizures
- tonic-clonic seizures (grand mal)
- mixed forms of tonic-clonic seizures and absences
- atonic seizures

May also be used for manifestations of epilepsy that do not adequately respond to other antiepileptic agents, such as:
Secondary form of generalized epilepsy
- especially akinetic and atonic seizures,

Partial epilepsy
- both with elemental (focal) and complex (psychomotor) symptoms.

A comprehensive description of the indications and posology is given in the SPC.

Valproic acid, like its salt sodium valproate, is an antiepileptic agent.
The mechanism of action is not yet fully understood. On the basis of animal studies, it is widely believed that part of the effect can be attributed to an increase in the levels of the neurotransmitter gamma amino butyric acid (GABA) in cerebrum and cerebellum as a result of inhibition of its metabolism. It is possible that the GABA receptor is then influenced. The therapeutic effect appears a few days to more than one week after initiation of treatment

This mutual recognition procedure concerns a generic application claiming essential similarity with the Dutch innovator product Depakine Chrono 300 and 500 mg prolonged release tablets, which have been registered in the Netherlands by Sanofi-Synthelabo B.V. since 1989 (300 mg, RVG 13157) and 1988 (500 mg, RVG 11775). In addition, reference is made to Depakine authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC in all member states excluding the Slovak Republic. In the Slovak Republic the marketing authorisation is granted for the 300 mg formulation based on article 10(3) of Directive 2001/83/EC. This deviation is made because of the absence of the 300 mg strength for the innovator in the Slovak Republic. As the new legislation has not yet been implemented nationally, the use of the European Reference Product cannot be accepted by the Slovak authorities. The documentation submitted by the applicant covers both legal bases.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted four bioequivalence studies. In one study the pharmacokinetic profile of the product Natriumvalproaat Sandoz Chrono 300 mg, is compared with the pharmacokinetic profile of the reference product Ergenyl Chrono 300, registered in Germany. Ergenyl is the German name for the reference product. In the other three bioequivalence studies the pharmacokinetic profile of the product Natriumvalproaat Sandoz Chrono 500 mg, is compared with the pharmacokinetic profile of the reference

product Dépakine chrono 500 mg, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substances as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances

The active substances are sodium valproate and valproic acid, established active substances described in the European Pharmacopoeia. Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Sodium valproate is provided by manufacturers which used the CEP procedure. Valproic acid is provided by manufacturers using the CEP procedure or the Active Substance Master File (ASMF) procedure.

Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance use in the medicinal product.

Sodium valproate
Sodium valproate is a crystalline powder which is hygroscopic. It is very soluble in water. The active substance specification of sodium valproate is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Depending on the CEP, the substance is additionally tested for residual solvents and/or other specific impurities. Batch analytical data demonstrating compliance with this specification have been provided for each supplier.
Assessment of the retest period was part of granting the CEP. An adequate re-test period for the different supplier of at least 2 years has been defined based on the conducted stability studies.

Valproic acid
Valproic acid is a colourless or very slightly yellow, clear liquid, which is slightly viscous. The active substance specification of valproic acid is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Depending on the ASM, the substance is additionally tested for residual solvents and/or other specific impurities. Batch analytical data demonstrating compliance with this specification have been provided for each supplier.
Assessment of the retest period was part of granting the CEP. The manufacturers using the ASM procedure, stability data are provided demonstrating the stability of the active substance over 3 years. Adequate re-test periods have been defined for the different suppliers based on conducted stability studies.

Medicinal Product

Composition
Natriumvalproaat Sandoz Chrono 300 and 500 mg prolonged release tablets contain as active ingredient sodium valproate (200 mg and 333 mg respectively) and valproic acid 87 mg and 145 mg, corresponding to 100 mg and 167 mg of sodium valproate, respectively.
Natriumvalproaat Sandoz Chrono 300 and 500 mg prolonged release tablets are white, oblong tablets with a score line. The tablets are packed in aluminium/aluminium blisters and inserted into a carton.

The excipients for both strengths are colloidal hydrated silica, ethylcellulose (E 462), colloidal anhydrous silica, hypromellose, macrogol 6000, methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%, saccharin sodium, talc and titanium dioxide (E 171). The two strengths are dose-proportional.
The used excipients are well known and safe in proposed concentrations. The excipients comply with the relevant Ph.Eur. monographs and are compatible with the active ingredient as demonstrated in the stability testing.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packaging is common and suitable for the product.
The purpose was to develop tables that would be bio-equivalent with the innovator product by Sanofi-Synthelabo B.V.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. For one manufacturer, process validation data on the product have been presented in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification for the tablets includes tests for identification and assay of sodium valproate, identification of titanium oxide, uniformity of dosage units, resistance to crushing, dissolution, impurities, microbiological impurity, appearance, width, length and mean weight. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided from 5 batches of both strengths in accordance with applicable European guidelines demonstrating the stability of the product over 36 months without any special storage conditions. On the basis of the data submitted, a shelf life was granted of 36 months, in aluminium/aluminium blisters inserted into a carton without specific storage condition. The MAH will submit the stability results of the studies that will be continued to support the complete shelf life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Depakine, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of sodium valproate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Sodium valproate and valproic acid are well-known active substances with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with the approved SPC of the innovator product Depakine Chrono 300 and 500 mg prolonged release tablets, marketed by Sanofi-Synthelabo.

For this generic application, the MAH has submitted four bioequivalence studies:
- One single-dose study compared the pharmacokinetic profile of the test product Natriumvalproaat Sandoz Chrono 300 mg with the reference product Ergenyl Chrono 300 mg under fasted conditions.
- Two single-dose studies compare the pharmacokinetic profile of the test product Natriumvalproaat Sandoz Chrono 500 mg with the reference product Dépakine Chrono 500 mg under either fasted or fed conditions.
- One multiple-dose study compared the pharmacokinetic profile of the test product Natriumvalproaat Sandoz Chrono 500 mg x 2 with the reference product Dépakine Chrono 500 mg x 2 under fasted conditions.

The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Study 1, single-dose study with 300 mg under fasted conditions

A two-treatment, two-period, two-sequence randomised crossover, single-dose study was carried out in fasted conditions in 16 healthy male subjects, aged 22-45 years. The reference product is Ergenyl® Chrono 300, modified release tablet, marketed in Germany. Each subject received a single dose (300 mg) of one of the two sodium valproate formulations after 10 hours fasting. For each subject there were two dosing periods, separated by a washout period of 16 days. The tablets were administered with 240 ml water. Blood samples were taken at predose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 16, 18, 21, 24, 36, 48, 72 and 84 hours after administration of the single dose. All 16 subjects completed the study and were eligible for pharmacokinetic and statistical evaluation. For one subject, $AUC_{0-\infty}$ was not calculated because of a poor fit of the terminal linear part of the concentration-time curve on a semi-logarithmic scale.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} as median (range)) of valproic acid following single-dose administration of 300 mg tablet under fasted conditions.

Treatment N = 16	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	356.8 ± 139.5	376.8 ± 121.4	11.5 ± 2.8	8.5 (4.5-16)	13.5 ± 3.3
Reference	332.1 ± 139.1	332.5 ± 125.3	12.9 ± 2.2	6.75 (4-12)	12.7 ± 3.1
***Ratio (90% CI)**	1.08 (1.00-1.18)	1.10 (1.03-1.18)	0.89 (0.84-0.95)	-	-
CV (%)	11%	10%	10%	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals (CI) of the ratio's calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate.

Study 2, single-dose study with 500 mg under fasted conditions

A two-treatment, two-period, two-sequence randomised crossover, single-dose study was carried out in fasted conditions in 18 healthy male subjects, aged 20-38 years. The reference product is Dépakine® chrono 500 mg, marketed in France. Each subject received a single dose (500 mg) of one of the two sodium valproate formulations after 10 hours fasting. For each subject there were two dosing periods, separated by a washout period of 16 days. The tablets were administered with 240 ml water. Blood samples were taken at predose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 15, 24, 36, 48, 72 and 84 hours after administration of the single dose. All subjects completed the study and were eligible for pharmacokinetic and statistical evaluation.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} as median (range)) of valproic acid following single-dose administration of 500 mg tablet under fasted conditions

Treatment N =18	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	550.3 ± 191.0	573.7 ± 195.4	18.6 ± 4.0	12 (3-24)	14.1 ± 2.6
Reference	603.4 ± 147.9	625.6 ± 161.9	19.1 ± 3.2	9 (4-15)	14.6 ± 3.0
***Ratio (90% CI)**	0.88 (0.77-1.01)	0.88 (0.79-1.00)	0.92 (0.86-0.99)	-	-
CV (%)	24%	22%	13%	-	-

The 90% confidence intervals of the ratio's calculated for C_{max} are within the bioequivalance acceptance range of 0.80 – 1.25. The 90% CI of the ratio's for AUC_{0-t} and $AUC_{0-\infty}$ were below the lower limit of acceptance of 0.80. The statistical analysis of the pharmacokinetic data was adequate.

Study 3, single-dose study with 500 mg under fed conditions

A two-treatment, two-period, two-sequence randomised crossover, single dose study was carried out in fed conditions in 16 healthy male subjects, aged 22-45 years. The reference product is Dépakine® Chrono 500 mg, marketed in France. Each subject received a single dose (500 mg) of one of the two formulations of sodium valproate, five minutes after a standardised high-fat meal (1048 kcal, fat contributed for 60% to the total energy content). For each subject there were two dosing periods, separated by a washout period of 1 week. The tablets were administered with 240 ml water. Blood samples were taken at predose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 15, 24, 36, 48, 72 and 84 hours after administration of the single dose. All subjects completed the study and were eligible for pharmacokinetic and statistical evaluation.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} as median (range)) of valproic acid following single-dose administration of 500 mg tablet under fed conditions

Treatment N = 16	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	627.1 ± 140.6	648.2 ± 143.3	21.4 ± 4.0	12 (7-18)	13.4 ± 1.7
Reference	637.0 ± 155.7	661.0 ± 168.6	21.5 ± 2.3	10 (6.5-14)	13.4 ± 2.8
***Ratio (90% CI)**	0.99 (0.93-1.05)	0.99 (0.92-1.06)	0.98 (0.93-1.05)	-	-
CV (%)	11%	12%	10%	-	-

After a high fat meal, the 90% confidence intervals of the test/reference ratio's calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate.

Food effect

After administration of a single oral dose of 500 mg sodium valproate modified release tablet, C_{max} was 11-17% lower under fed conditions compared to fasting conditions (Study 2), for both the test and the reference product. The AUC levels were not statistically significantly changed after food intake.

Study 4, multiple-dose study with 2 x 500 mg under fasted conditions

A two-treatment, two-period, two-sequence randomised crossover, multiple-dose study carried out in 24 healthy male subjects. During six consecutive days, each subject received once daily two tablets of 500 mg sodium valproate, of either the test or reference formulation. The reference product is Dépakine® Chrono 500 mg, marketed in France. For each subject there were two dosing periods, separated by a washout period of 16 days. The tablets were administered with 240 ml water. A pre-dose sample was drawn every day to assess trough values (C_{min}). After the last dose, blood samples were taken at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 9, 10, 12, 14, 16, 18, 21 and 24 hours after administration of the dose.
Four subjects dropped out of the study: two because of vomiting within 12 hours after administration of the study medication and two on their own request. The results of the remaining 20 subjects were used for pharmacokinetic and statistical analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of valproic acid following multiple-dose administration of 2 x 500 mg tablets under fasted conditions

Treatment	**AUC_{0-24}** µg/ml/h	**C_{max}** µg/ml	**C_{min}** µg/ml	**PTF%** %
Test	1517.5 ± 406.8	73.3 ± 20.4	51.4 ± 14.7	46.5 ± 18.2
Reference	1517.3 ± 408.7	75.1 ± 19.1	47.8 ± 15.8	50.4 ± 10.9
***Ratio (90% CI)**	1.00 (0.95-1.04)	0.98 (0.93-1.02)	1.08 (0.99-1.17)	0.88 (0.77-1.01)
CV (%)	8%	8%	15%	25%

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

At steady state, the 90% confidence intervals of the test/reference ratio's calculated for AUC_{0-24}, C_{min} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The test product had a lower %PTF, as indicated by the 90% CI of 0.77-1.01. The statistical analysis of the pharmacokinetic data was adequate.

Conclusions

Based on the pharmacokinetic parameters of valproic acid, bioequivalence was demonstrated in a single-dose study of the 300 mg tablets under fasted conditions, and in a single-dose study of the 500 mg tablets under fed conditions. The 90% confidence intervals calculated for $AUC_{0-\infty}$ AUC_{0-t} and C_{max} were within the bioequivalence acceptance range of 0.80 – 1.25. Bioequivalence was also demonstrated for AUC_{0-24}, C_{max} and C_{min} in the 500 mg multiple-dose study under fasted state. The test product had a lower peak trough fluctuation as indicated by the 90% CI of 0.77-1.01.

Bioequivalence was not fully demonstrated in the 500 mg single-dose study under fasted conditions. The 90% CI for $AUC_{0-\infty}$ varied between 0.77-1.01. The 90% CI for C_{max} in this study fell however within the bioequivalence acceptance range of 0.80-1.25 (0.86-0.99).
In the SPC of the innovator product it is mentioned, that the intra-individual and inter-individual variance of the valproic acid plasma concentrations is large after an established dose. According to the EMEA guidelines CPMP/EWP/QWP/1401/98, a 90% CI acceptance interval of 0.75-1.33 might be acceptable in drugs with high variability. On this account, bioequivalence could be demonstrated in the 500 mg single-dose study under fasted conditions. Moreover, it is explicitly mentioned in the SPC and PIL of both the innovator product and the products at issue that the tablets should be taken together with food.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan
Sodium valproate and valproic acid were first approved in the Netherlands in 1971, and there is now more than 10 years post-authorisation experience with these active substances. The safety profiles of sodium valproate and valproic acid can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.
PSURs will be submitted every three years.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Natriumvalproaat Sandoz Chrono 300 and 500 mg prolonged release tablets have a proven chemical-pharmaceutical quality and are generic forms of Depakine Chrono 300 and 500 mg prolonged release tablets. Depakine is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. During the MRP procedure, updating took place of several sections of the SPC, especially the sections 4.2, 4.4, 4.5 and 4.8.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The board followed the advice of the assessors. No discussion in the Board meeting was deemed necessary.

On the basis of the data submitted, the MEB considered that the bioequivalence for Natriumvalproaat Sandoz Chrono 300 and 500 mg, prolonged release tablets, with the reference products has been demonstrated and has therefore granted a marketing authorisation on 12 December 2005.

The member states mutually recognised the Dutch evaluation of the marketing authorisation. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 5 May 2006.

The following post-approval commitments have been made during the procedure:

Quality – medicinal product
- The MAH will supply validation data of the manufacturing process at the upper side of production scale for one of the production sites.
- The MAH will submit the stability results of the studies that will be continued to support the complete shelf life. Furthermore, the first 3 production scale batches will be placed into a stability study as well.

Patient leaflet (only EE)

- The MAH will add the following sentences in the 'blue box section' of the national patient leaflet in order to ensure compliance in cases of off-label use:
  'Note that the doctor may have prescribed this medicine for a different purpose and/or at a different dosage from that given in the package leaflet. You must always follow the doctor's prescription and the instructions given on the label of the pack.'

PSURs will be submitted every three years. The first PSUR will cover the period from December 2005 till December 2008.

The date for the first renewal will be: 12 December 2010.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name and/or address of a manufacturer of the finished product.	NL/H/0736/ 001/IA/001	IA	19/6/2006	3/7/2006	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0736/ 001/IA/002	IA	19/6/2006	3/7/2006	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Not including batch control/testing.	NL/H/0736/ 001/IA/003	IA	19/6/2006	3/7/2006	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0736/ 001/IA/004	IA	19/6/2006	3/7/2006	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Not including batch control/testing.	NL/H/0736/ 001/IA/005	IA	19/6/2006	3/7/2006	Approval	N
Minor change in the manufacture of the finished product	NL/H/0736/ 001/IB/006	IB	26/6/2006	14/7/2006	Approval	N
Harmonisation between PIL and SPC. Harmonisation within PIL	NL/H/0736/ 001/II/007	II	4/1/2007	1/6/2007	Approval	Y, Annex I
Change in the name and/or address of a manufacturer of the finished product.	NL/H/0736/ 001/IA/008	IA	27/4/2007	11/5/2007	Approval	N
Change in the name and/or address of a manufacturer of the finished product.	NL/H/0736/ 001/IA/009	IA	5/9/2007	19/9/2007	Approval	N
Change in the name and/or address of a manufacturer of the finished product.	NL/H/0736/ 001/IA/010	IA	29/5/2008	12/6/2008	Approval	N
Amendments of SPC and PIL due to a general safety warning on antiepileptics issued by PhVWP July 2008	NL/H/0736/ 001/II/011	II	15/10/2008	15/10/2008	Approval	Y, Annex II

Annex I - Variation Assessment report, NL/H/0736/001/II/007

The MAH recognised differences between the PIL and the SPC and within the PIL and proposed changes to the PIL. The variation procedure started 4 January 2007.

The changes made to the PIL:
In section 1 a description of atonic seizures has been added to the indications.
In section 2 – taking other medicines – a statement that possible dose adjustment can be necessary has been included in the first general lines. Furthermore, warnings regarding the interaction with phenytoin and clonazepam have been added.
In section 3 the information on the method of administration has been brought in line with the SPC

Annex II - Variation Assessment report, NL/H/0736/001/II/011

According to the decision of PhVWP in July 2008, the MAH submitted a type II variation application. The PhVWP decision is based on a European review of antiepileptic medicines which concluded that any medicine in this class may be associated with a small risk of suicidal thoughts and behaviour. According to this decision the SPC and PIL were updated.

The following text was added to the SPC:

Risk of suicidal thoughts and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo controlled trials of anti-epileptic drugs has also 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 valproate.
Therefore patients should be monitored for signs of suicidal ideation and behaviours 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.

The following text was added to the PIL :

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