GABAPENTIN 100MG CAPSULES
PL 20137/0001

GABAPENTIN 300MG CAPSULES
PL 20137/0002

GABAPENTIN 400MG CAPSULES
PL 20137/0003

UKPAR

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LAY SUMMARY

The MHRA today granted Clarendon Pharma Ltd Marketing Authorisations (licences) for the medicinal products Gabapentin 100mg Capsules (PL 20137/0001), Gabapentin 300mg Capsules (PL 20137/0002) and Gabapentin 400mg Capsules (PL 20137/0003). These are prescription only medicines (POM) for the treatment of neuropathic pain and epilepsy.

Gabapentin Capsules contain the active ingredient gabapentin, which mimics the neurotransmitter gamma-aminobutyric acid (GABA).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Gabapentin Capsules outweigh the risks, hence Marketing Authorisations have been granted.

GABAPENTIN 100MG CAPSULES
PL 20137/0001

GABAPENTIN 300MG CAPSULES
PL 20137/0002

GABAPENTIN 400MG CAPSULES
PL 20137/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Gabapentin 100mg Capsules (PL 20137/0001), Gabapentin 300mg Capsules (PL 20137/0002) and Gabapentin 400mg Capsules (PL 20137/0003) on 14th March 2006. The products are prescription only medicines.

These are abridged national applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Neurontin Capsules (Parke Davis, UK).

The products contain the active ingredient gabapentin, which belongs to a pharmacotherapeutic group that is structurally related to the neurotransmitter gamma-aminobutyric acid (GAMA).

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Gabapentin

Gabapentin is a white or almost white powder, which is freely soluble in water, soluble in methanol and practically insoluble in acetone.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

There is no Ph Eur monograph for gabapentin, however, an appropriate in-house specification is 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.

Appropriate stability data have been generated supporting a retest period of 36 months.

DRUG PRODUCT

Other ingredients

Other ingredients include the pharmaceutical excipients, lactose monohydrate, maize starch, talc, titanium dioxide (E171), yellow iron oxide (E172 – 300mg and 400mg capsules only), red iron oxide (E172 – 400mg capsules only) and gelatin. These all comply with their respective current Ph.Eur/USP monograph requirements, as appropriate. The capsule shells are printed and satisfactory details on the qualitative composition and specifications of ingredients used in the printing ink are also provided.

With the exception of lactose monohydrate and gelatin, none of the excipients used are of animal or human origin. Satisfactory current EDQM TSE Certificates of Suitability have been provided for the gelatine used in the manufacture of capsule shells. Assurances have been provided that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as milk collected for human consumption and the calf rennet used in the production of whey is manufactured in accordance with EMEA/CPMP/571/02 Public statement.

Dissolution

Dissolution profiles for all strengths of drug product were found to be similar to the originator products.

Manufacture

Copies of relevant certificates for all companies involved in the manufacture, packaging, storage, distribution and batch release of the finished product have been provided and are satisfactory.

A description and flow-chart of the manufacturing method has been provided and is satisfactory. In-process controls are satisfactory and supported by in-process data. Process validation has been carried out on three pilot-scale batches of each strength (including the biobatch). The results appear satisfactory.

Finished product specification
The finished product specifications are satisfactory and are supported by batch analytical, stability and biobatch data. Test methods have been described and have been adequately validated as appropriate. Certificates of analysis have been provided for any working standards used.

Container Closure System
The capsules are packaged in transparent PVC /aluminium blisters. Specifications and routine tests are provided and are satisfactory. The transparent PVC, aluminium and the lacquer used to coat the aluminium all comply with relevant guidelines concerning contact with food materials and EEC requirements.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set, which is satisfactory. The storage precautions 'Store in the original packaging' and 'Do not store above 25°C' have been included.

Bioequivalence
Bioequivalence studies have been performed comparing the applicant's 400mg capsules with the reference product Neurontin 400mg capsules. Satisfactory batch data and comparative dissolution data are provided for test and reference products used in the biostudy.

No bioequivalence studies have been performed for the 100mg and 300mg capsules and have been satisfactorily justified in line with guideline requirements.

Expert Report
A satisfactory Pharmaceutical Expert Report has been submitted with appropriate CV.

Summary of Product Characteristics
Pharmaceutical aspects of the SPC are satisfactory and supported by data submitted.

Patient Information Leaflet
This is satisfactory.

Labelling
This is satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

These applications for generic products claim essential similarity to Neurontin Capsules (Parke Davis, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

INDICATIONS

Neuropathic Pain

Gabapentin capsules are indicated for the treatment of neuropathic pain.

Epilepsy

Adults and children over 12 years of age

Gabapentin capsules are an anti-epileptic drug indicated as add-on therapy for partial seizures and partial seizures with secondary generalisation in patients who have not achieved satisfactory control with or who are intolerant to standard anticonvulsants used alone or in combination.

Children 6-12 years of age

Gabapentin capsules may be used as add-on therapy for partial seizures and partial seizures with secondary generalisation, in children aged between 6-12 years, who have not achieved satisfactory control with, or who are intolerant to, standard anticonvulsants used alone or in combination, if the benefit: risk is considered favourable. Gabapentin capsules should be initiated and supervised by a neurological specialist.

Children under 6 years of age

There are inadequate data in this age group and therefore the use of Gabapentin capsules is not recommended.

These indications are consistent with those of the cross-referenced product licences.

DOSE & DOSE SCHEDULE

These are in line with those of the cross referenced product licence.

TOXICOLOGY

No new data are submitted or required.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but its mechanism of action is different from that of several drugs that interact with GABA synapses. The identification and function of the gabapentin binding site remains to be elucidated and the relevance of its various actions to the anticonvulsant effect to be established. Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.

Pharmacokinetic properties

Mean plasma gabapentin concentrations (C_{max}) occurred approximately 3 hours (T_{max}) following single oral doses of Gabapentin regardless of dose size or formulation. Mean T_{max} values following multiple dose administration were approximately 1 hour shorter than the values following single-dose administration.

Mean C_{max} and AUC values increased with increasing dose; however, the increase was less than dose proportional. Deviation from linearity is very slight up to 600mg

for both parameters and thus should be minimal at doses of 300mg to 400mg three times daily where the antiepileptic effect generally occurs.

Following repeated Gabapentin administration, steady state is achieved within 1 to 2 days after the start of the multiple dosing and is maintained throughout the dosing regime. Absolute bioavailability of a 300mg oral dose of Gabapentin was approximately 60%. At doses of 300mg and 400mg, Gabapentin bioavailability is unchanged following multiple-dose administration.

The presence of food did not influence the bioavailability of Gabapentin. Gabapentin is not metabolised in humans and does not induce hepatic mixed function oxidase enzymes.

Gabapentin elimination from plasma following IV administration was best described by linear pharmacokinetics. Elimination half-life (T½) of gabapentin ranged from 5 to 7 hours. Gabapentin elimination parameters, apparent plasma T½ and renal clearance (CL_R) were independent of dose and remained unchanged following repeated administration. Renal clearance was the sole elimination pathway for gabapentin. Since gabapentin is not metabolised in humans, the amount of drug recovered in urine is indicative of gabapentin bioavailability. Following a single 200mg oral dose of [C_{14}]gabapentin recovery of radioactivity was essentially complete with approximately 80% and 20% of the dose recovered in urine and faeces, respectively.

As renal function (as determined by creatinine clearance) decreases with increasing age, gabapentin oral clearance, renal clearance and elimination-rate constant decrease proportionally.

Gabapentin pharmacokinetics were determined in 24 healthy paediatric subjects between the ages of 4 and 12 years. In one single dose study, pharmacokinetic parameters were similar in children weighing 26-50 kg, but not in children weighing 17-25 kg. No multiple dose studies have been conducted in children.

Bioequivalence

The applicant has submitted an open-label, single dose, randomised, two-period cross-over study which compared the test product, Gabapentin 400mg rapid release capsules with the reference product, Neurontin® 400mg rapid release capsules. The study was performed in healthy volunteers.

The test product was compared to the reference product with respect to the pharmacokinetic variables C_{max}, C_{max}/AUC (0-∞), $t_{½.z}$, AUC (0-t_{last}) and AUC (0-∞) using an analysis of variance with sequence, subject (sequence), product and period effects after a logarithmic transformation of the data. Parametric point estimates and 90% confidence intervals for the 'test/reference' mean ratios of those variable were calculated and presented graphically. In addition, a non-parametric point estimate and 90% confidence interval for the 'test-reference' median difference of T_{max} was calculated. Bioequivalence of the test and reference product was assessed on the basis of the confidence intervals for the primary variables AUC (0-∞) and C_{max} in relation to the bioequivalence range of 80% to 125%.

The main pharmakonetic findings are summarised in the table below.

SUMMARY OF PHARMACOKINETIC DATA FOR GABAPENTIN
[n=36; Dose: 1 x 400mg gabapentin rapid release capsule]

		Neurontin ® (Reference)		**Gabapentin (Test)**			
VARIABLE	**UNIT**	**GEOMETRIC**		**GEOMETRIC**		**MEAN RATIO**	**90% CONFIDENCE INTERVAL**
		Mean	**SD**	**Mean**	**SD**	**(%) ***	**(%) ****
C_{max}	(ng/ml)	**3387**	1.38	**3393**	1.34	**100**	92.5 ; 109
T_{max}#	(h)	**3.25**		**3.50**		**0.25**	0.00 ; 0.50
AUC (0-t_{last})	(ng.h/ml)	**32418**	1.32	**33468**	1.32	**103**	96.5 ; 111
AUC (0-∞)	(ng.h/ml)	**33302**	1.32	**34362**	1.31	**103**	96.7 ; 110
C_{max}/AUC (0-∞)	(l/h)	**0.10**	1.15	**0.10**	1.18	**97.1**	92.7 ; 102
$T_{½.z}$	(h)	**6.57**	1.21	**6.51**	1.18	**99.2**	94.7 ; 104
MT_{vsys}	(h)	**9.81**	1.12	**9.82**	1.10		

* Point estimate of 'test/reference' mean ratio from analysis of log-transformed data.
**90% Conventional confidence interval for the 'test/reference' mean ratio from analysis of variance of log-transformed data.
Medians, ranges, non-parametric point estimate of 'test/reference' median difference and corresponding confidence interval.

The results of the study show that the 90% Confidence Intervals for the log-transformed parameters $AUC_{(o-t)}$ and $AUC_{(o-\infty)}$ for Gabapentin were all within the 80-125% acceptable range. These results therefore demonstrate that the test product, Gabapentin 400mg capsules is bioequivalent to the reference product, Neurontin® 400mg rapid release capsules.

The essentially linear pharmacokinetics of Gabapentin, particulary at this relatively dose range, makes it likely that the lower-doses of Gabapentin formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

A total of seven adverse events were reported during the study. These included headaches (four events), in three subjects and nausea (two events) in one subject and a bee sting which was not related to study medication. All were assessed as mild or moderate in intensity. No serious adverse event was reported.

The study design, analytical methodology and statistical evaluation of the presented bioequivalent trial are in accordance with the recommendations of the relevant CPMP guidelines: 'Investigation of bioavailability and bioequivalence.' Therefore, the bioequivalence of the generic product with the referenced innovator product has been proven.

EFFICACY

No new efficacy data are presented for this application and none is required. However the applicant has provided a critical and extensive review of clinical trials published in the literature regarding the efficacy and safety of Gabapentin in patients with epilepsy and neuropathic pain.

SAFETY

No new safety data are provided or needed. But the applicant has provided a brief safety review of Gabapentin. No new safety issues have been identified.

EXPERT REPORT

A satisfactory Clinical Expert Report has been submitted with appropriate CV.

SUMMARY OF PRODUCT CHARACTERISTICS

The text of the proposed SPC is essentially the same as that of the cross-reference product licence.

PATIENT INFORMATION LEAFLET

This is satisfactory.

LABELLING

This is satisfactory.

DISCUSSION

Drugs structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) such as Gabapentin, have been available in the UK for over 10 years. The use of Gabapentin is well established. It has recognised efficacy and acceptable safety.

With regards to the current application, sufficient clinical information has been submitted. When used as indicated, Gabapentin has a favourable benefit-to-risk ratio. The hazard associated with Gabapentin appears to be low and acceptable when considered in relation to its therapeutic benefits.

CONCLUSION

Marketing authorisations may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Gabapentin 100mg, 300mg and 400mg Capsules 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Gabapentin 400mg Capsules and Neurontin 400mg Capsules (Parke Davis, UK). Given that linear kinetics apply over the therapeutic dose range, products are manufactured by the same manufacturer and process, that proportional formulae for the capsules have been used and that similar dissolution profiles have been shown for the 100mg capsules, 200mg capsules and biobatch, a separate bioequivalence study using the 100mg or 200mg capsules is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Neurontin Capsules.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with gabapentin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

GABAPENTIN 100MG CAPSULES
PL 20137/0001

GABAPENTIN 300MG CAPSULES
PL 20137/0002

GABAPENTIN 400MG CAPSULES
PL 20137/0003

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 26th March 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 25th April 2003
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 27th June 2003 and further information relating to the quality dossiers on 31st July 2003, 26th February 2004, 25th April 2005 and 10th January 2006.
4	The applicant responded to the MHRA's requests, providing further information on 2nd July 2003 and on 17th December 2003, 12th November 2004, 31st May 2005, 11th August 2005, 12th October 2005 and 16th January 2006 for the quality sections.
5	The applications were determined on 14th March 2006

GABAPENTIN 100MG CAPSULES
PL 20137/0001

GABAPENTIN 300MG CAPSULES
PL 20137/0002

GABAPENTIN 400MG CAPSULES
PL 20137/0003

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gabapentin 100mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains gabapentin 100mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

A two-piece, white opaque hard gelatin capsule, marked GA100 with company logo, containing a white to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic Pain

Gabapentin is indicated for the treatment of neuropathic pain.

Epilepsy

Adults and children over 12 years of age

Gabapentin is an anti-epileptic drug indicated as add-on therapy for partial seizures and partial seizures with secondary generalisation in patients who have not achieved satisfactory control with or who are intolerant to standard anticonvulsants used alone or in combination.

Children 6-12 years of age

Gabapentin may be used as add-on therapy for partial seizures and partial seizures with secondary generalisation, in children aged between 6-12 years, who have not achieved satisfactory control with, or who are intolerant to, standard anticonvulsants used alone or in combination, if the benefit : risk is considered favourable. Gabapentin should be initiated and supervised by a neurological specialist.

Children under 6 years of age

There are inadequate data in this age group and therefore the use of gabapentin is not recommended.

4.2 Posology and method of administration

Neuropathic Pain

Adults (over the age of 18)

Gabapentin should be titrated to a maximum dose of 1800 mg per day.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg three times a day on day 3, as described in Table 1.

Table 1: Dosing Chart – Initial Titration

Dose	Day 1	Day 2	Day 3
900mg	300mg QD [a]	300mg BID [b]	300mg TID [c]

a QD = once a day
[b] BID = two times a day
[c] TID = three times a day

Thereafter, the dose can be increased using increments of 300mg per day given in three divided doses to a maximum of 1800mg per day. It is not necessary to divide the doses equally when titrating gabapentin.

It is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

Elderly
Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2).

Epilepsy
Adults and Children aged over 12
The anti-epileptic effect of gabapentin generally occurs at 900 to 1200mg/day.

It is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg three times a day on day 3, as described in Table 1. Thereafter, the dose can be increased using increments of 300mg per day given in three equally divided doses to a maximum dose of 2400mg per day.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of one week.

Elderly
Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2).

Children 6-12 years of age
The recommended dose of gabapentin is 25 to 35 mg/kg/day given in divided doses (3 times a day). Titration to an effective dose can take place over 3 days

by giving 10 mg/kg/day on Day 1, 20 mg/kg/day on Day 2 and 25 to 35 mg/kg/day on Day 3.

The following maintenance dosing schedule is suggested:

Weight Range (kg)	Total mg Dose/Day
26-36	900
37-50	1200

Dosage Adjustment in Patients with Compromised Renal Function or those Undergoing Haemodialysis
Dosage adjustment is recommended in patients with compromised renal function as described in Table 2, or those undergoing haemodialysis.

Patients with Compromised Renal Function:

Table 2: Maintenance Dosage of Gabapentin in Adults with Reduced Renal Function

Renal function Creatinine Clearance (ml/minute)	Total Daily Dose[a] mg/day		
	Normal Dosage		
≥ 80	**900**	**1200**	**2400**
50-79	600	600	1200
30-49	300	300	600
15-29	150[b]	300	300
<15	150[b]	150[b]	150[b]

[a] Total daily dose should be administered as a tid regimen. Doses used to treat patients with normal renal function (creatinine clearance >80 ml/min) range from 900 to 2400 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79 ml/min).
[b] To be administered as 300 mg every other day.

Patients Undergoing Haemodialysis:
For patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400mg is recommended then 200 to 300mg of gabapentin following each 4 hours of haemodialysis.

4.3 Contraindications

Gabapentin is contra-indicated in patients who are hypersensitive to gabapentin or to the product's components.

4.4 Special warnings and precautions for use

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, there is a need for dose reduction, discontinuation or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Gabapentin is not generally considered effective in the treatment of absence seizures.

Patients taking gabapentin can be the subject of mood and behavioural disturbances. Such reports have been noted in patients on gabapentin although a causal link has not been established.

Caution is recommended in patients with a history of psychotic illness. On commencing gabapentin therapy, psychotic episodes have been reported in some patients with, and rarely without, a history of psychotic illness. Most of these events resolved when gabapentin was discontinued or the dosage was reduced.

Gabapentin Capsules contain lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Gabapentin may be used in combination with other anti-epileptic drugs without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other anti-epileptic drugs.

There is no interaction between gabapentin and phenytoin, valproic acid, carbamazepine or phenobarbitone. Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving anti-epileptic agents.

Co-administration of gabapentin with oral contraceptives including norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either component.

In a clinical study where gabapentin and an aluminium and magnesium containing antacid when given at the same time, gabapentin's bioavailability was reduced by up to 24%. It is recommended that gabapentin is taken about two hours following any such antacid administration. The slight decrease in renal excretion of gabapentin observed when co-administered with cimetidine is not expected to be of clinical importance.

Renal excretion of gabapentin is unaltered by probenecid.

Food has no effect on gabapentin pharmacokinetics.

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test when gabapentin was added to other anticonvulsant drugs, the more specific sulphosalicylic acid precipitation procedure is recommended to determine urinary protein.

4.6 Pregnancy and lactation

Safe use in human pregnancy has not been established. Reproduction studies in mice, rats or rabbits at doses up to 50, 30 and 25 times respectively, the

daily human dose of 3600mg revealed no evidence of impaired fertility or harm to the foetus due to gabapentin administration. However, because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Gabapentin is excreted in human milk but the effect on the nursing infant is unknown. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from gabapentin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Gabapentin acts on the central nervous system and may produce drowsiness, dizziness, or other related symptoms. These otherwise mild or moderate adverse events could be potentially dangerous in patients driving or operating machinery, particularly until such time as the individual patient's experience with the drug is established.

4.8 Undesirable effects

Neuropathic Pain

Based on placebo-controlled studies, the most common possible side-effects >1/10) associated with treating neuropathic pain with gabapentin are: dizziness and somnolence.

Common possible side-effects (between 1/10 and 1/100) are: diarrhoea, dry mouth, peripheral edema, weight gain, abnormal gait, amnesia, ataxia, abnormal thinking, rash and amblyopia.

Uncommon possible side-effects (between 1/100 and 1/1000) are: accidental injury, asthenia, back pain, constipation, flatulence, nausea, confusion, hypesthesia, vertigo, dyspnea and pharyngitis.

Epilepsy (Adults)

Since gabapentin has most often been administered in combination with other anti-epileptic agents, it is not possible to determine which agents, if any are associated with adverse events. However, based on placebo-controlled, double blind studies, the most common possible side-effects >1/10) are: somnolence and dizziness.

Common possible side-effects (between 1/10 and 1/100) are: ataxia, fatigue, nystagmus, tremor, diplopia, amblyopia, dysarthria, amnesia, asthenia, paraesthesia, arthralgia, purpura, dyspepsia, anxiety, weight increase, urinary tract infection and pharyngitis.

Uncommon possible side-effects (between 1/100 and 1/1000) are: leucopenia, nervousness, rhinitis and male sexual dysfunction (impotence).

As with the other AEDs there have been rare reports of urinary incontinence, pancreatitis, elevated liver function tests, erythema multiforme and Stevens Johnson Syndrome where a causal relationship to treatment has not been

established. Rarely confusion, depression, emotional lability, hostility, abnormal thinking and psychoses/hallucinations have been reported. Blood glucose fluctuations in patients with diabetes, myalgia, headache, nausea and/or vomiting have also been reported.

Epilepsy (Children)
In children aged 3-12 years in placebo controlled and long term trials, the most common >10%) side-effects were emotional lability, nervousness and thinking abnormally. All reports of these events were rated as mild or moderate and discontinuation or dose reduction were infrequent.

In children aged 3-12 years in controlled add-on trials, side-effects that occurred with an incidence of 2% or greater than placebo were: somnolence, fatigue, weight increase, hostility, emotional lability, dizziness, hyperkinesia, nausea/vomiting, viral infection, fever, bronchitis, respiratory infection. Some of these side-effects could be attributed to common viral childhood illness.

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49grams. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise toxicity from overdoses.

Although gabapentin can be removed by haemodialysis it is not usually required. However, in patients with renal impairment, haemodialysis may be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics
ATC code: N03AX

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but its mechanism of action is different from that of several drugs that interact with GABA synapses. The identification and function of the gabapentin binding site remains to be elucidated and the relevance of its various actions to the anticonvulsant effect to be established. Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.

5.2 Pharmacokinetic properties

Mean plasma gabapentin concentrations (Cmax) occurred approximately 3 hours (Tmax) following single oral doses of gabapentin regardless of dose size or formulation. Mean Tmax values following multiple dose administration were approximately 1 hour shorter than the values following single-dose administration.

Mean Cmax and AUC values increased with increasing dose; however, the increase was less than dose proportional. Deviation from linearity was very slight up to 600mg for both parameters and thus should be minimal at doses of 300mg to 400mg three times daily where the anti-epileptic effect generally occurs.

Following repeated gabapentin administration, steady state was achieved within 1 to 2 days after the start of the multiple dosing and was maintained throughout the dosing regime.

Plasma gabapentin concentration-time profiles were similar between gabapentin solution and capsule formulations following single doses of 300 and 400mg. Absolute bioavailability of a 300mg oral dose of gabapentin was approximately 60%. At doses of 300mg and 400mg, gabapentin bioavailability was unchanged following multiple-dose administration.

The presence of food does not influence the bioavailability of gabapentin.

Gabapentin is not metabolised in humans and does not induce hepatic mixed function oxidase enzymes.

Gabapentin elimination from plasma following IV administration was best described by linear pharmacokinetics. Elimination half-life (T½) of gabapentin ranged from 5 to 7 hours. Gabapentin elimination parameters, apparent plasma T½ and renal clearance (CL_R) were independent of dose and remained unchanged following repeated administration. Renal clearance was the sole elimination pathway for gabapentin. Since gabapentin is not metabolised in humans, the amount of drug recovered in urine is indicative of gabapentin bioavailability. Following a single 200mg oral dose of [C_{14}]gabapentin recovery of radioactivity was essentially complete with approximately 80% and 20% of the dose recovered in urine and faeces, respectively.

As renal function (as determined by creatinine clearance) decreases with increasing age, gabapentin oral clearance, renal clearance and elimination-rate constant decrease proportionally.

Gabapentin pharmacokinetics were determined in 24 healthy paediatric subjects between the ages of 4 and 12 years. In one single dose study, pharmacokinetic parameters were similar in children weighing 26-50kg, but not in children weighing 17-25 kg. No multiple dose studies have been conducted in children.

5.3 Preclinical safety data

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose. Peak plasma drug concentrations and areas under the concentration time curve in rats at 2000 mg/kg is 10 times higher than plasma concentrations in humans given 3600 mg/day.

The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not affect survival, did not metastasise or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is therefore of uncertain significance.

Gabapentin has no genotoxic potential. It was not mutagenic in the Ames bacterial plate incorporation assay or at the HGPRT locus in mammalian cells in the presence or absence of metabolic activation. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Fill: Lactose monohydrate
Maize starch
Talc

Capsule Shell: Titanium dioxide (E 171)
Gelatin

Printing Ink: Shellac
Titanium dioxide (E171)
FD&C Blue 1/Brilliant Blue FCF Lake (E133)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

The capsules are packed in blister strips of aluminium foil and transparent PVC. Each blister strip contains 10 capsules. The blisters are then packed into cartons containing 20, 50, 100 or 200 capsules. Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

No additional information.

7. MARKETING AUTHORISATION HOLDER

Clarendon Pharma Limited
19 King Street
Seagrave
Leicestershire
LE12 7LY

8. MARKETING AUTHORISATION NUMBER
PL 20137/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/03/2006

10 DATE OF REVISION OF THE TEXT
14/03/2006

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gabapentin 300mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains gabapentin 300mg.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

A two-piece, yellow opaque hard gelatin capsule, marked GA300 with company logo, containing a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic Pain

Gabapentin is indicated for the treatment of neuropathic pain.

Epilepsy

Adults and children over 12 years of age

Gabapentin is an anti-epileptic drug indicated as add-on therapy for partial seizures and partial seizures with secondary generalisation in patients who have not achieved satisfactory control with or who are intolerant to standard anticonvulsants used alone or in combination.

Children 6-12 years of age

Gabapentin may be used as add-on therapy for partial seizures and partial seizures with secondary generalisation, in children aged between 6-12 years, who have not achieved satisfactory control with, or who are intolerant to, standard anticonvulsants used alone or in combination, if the benefit : risk is considered favourable. Gabapentin should be initiated and supervised by a neurological specialist.

Children under 6 years of age

There are inadequate data in this age group and therefore the use of gabapentin is not recommended.

4.2. Posology and method of administration

Neuropathic Pain

Adults (over the age of 18)

Gabapentin should be titrated to a maximum dose of 1800 mg per day.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg three times a day on day 3, as described in Table 1.

Table 1: Dosing Chart – Initial Titration

Dose	Day 1	Day 2	Day 3
900mg	300mg QD [a]	300mg BID [b]	300mg TID [c]

a QD = once a day
[b] BID = two times a day
[c] TID = three times a day

Thereafter, the dose can be increased using increments of 300mg per day given in three divided doses to a maximum of 1800mg per day. It is not necessary to divide the doses equally when titrating gabapentin.

It is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

Elderly
Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2).

Epilepsy
Adults and Children aged over 12
The anti-epileptic effect of gabapentin generally occurs at 900 to 1200mg/day.

It is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg three times a day on day 3, as described in Table 1. Thereafter, the dose can be increased using increments of 300mg per day given in three equally divided doses to a maximum dose of 2400mg per day.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of one week.

Elderly
Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2).

Children 6-12 years of age
The recommended dose of gabapentin is 25 to 35 mg/kg/day given in divided doses (3 times a day). Titration to an effective dose can take place over 3 days

by giving 10 mg/kg/day on Day 1, 20 mg/kg/day on Day 2 and 25 to 35 mg/kg/day on Day 3.

The following maintenance dosing schedule is suggested:

Weight Range (kg)	Total mg Dose/Day
26-36	900
37-50	1200

Dosage Adjustment in Patients with Compromised Renal Function or those Undergoing Haemodialysis
Dosage adjustment is recommended in patients with compromised renal function as described in Table 2, or those undergoing haemodialysis.

Patients with Compromised Renal Function:

Table 2: Maintenance Dosage of Gabapentin in Adults with Reduced Renal Function

Renal function Creatinine Clearance (ml/minute)	Total Daily Dose[a] mg/day		
	Normal Dosage		
≥ 80	900	1200	2400
50-79	600	600	1200
30-49	300	300	600
15-29	150[b]	300	300
<15	150[b]	150[b]	150[b]

[a] Total daily dose should be administered as a tid regimen. Doses used to treat patients with normal renal function (creatinine clearance >80 ml/min) range from 900 to 2400 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79 ml/min).
[b] To be administered as 300 mg every other day.

Patients Undergoing Haemodialysis:
For patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400mg is recommended then 200 to 300mg of gabapentin following each 4 hours of haemodialysis.

4.3. Contraindications

Gabapentin is contra-indicated in patients who are hypersensitive to gabapentin or to the product's components.

4.4. Special warnings and precautions for use

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, there is a need for dose reduction, discontinuation or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Gabapentin is not generally considered effective in the treatment of absence seizures.

Patients taking gabapentin can be the subject of mood and behavioural disturbances. Such reports have been noted in patients on gabapentin although a causal link has not been established.

Caution is recommended in patients with a history of psychotic illness. On commencing gabapentin therapy, psychotic episodes have been reported in some patients with, and rarely without, a history of psychotic illness. Most of these events resolved when gabapentin was discontinued or the dosage was reduced.

Gabapentin Capsules contain lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Gabapentin may be used in combination with other anti-epileptic drugs without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other anti-epileptic drugs.

There is no interaction between gabapentin and phenytoin, valproic acid, carbamazepine or phenobarbitone. Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving anti-epileptic agents.

Co-administration of gabapentin with oral contraceptives including norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either component.

In a clinical study where gabapentin and an aluminium and magnesium containing antacid when given at the same time, gabapentin's bioavailability was reduced by up to 24%. It is recommended that gabapentin is taken about two hours following any such antacid administration. The slight decrease in renal excretion of gabapentin observed when co-administered with cimetidine is not expected to be of clinical importance.

Renal excretion of gabapentin is unaltered by probenecid.

Food has no effect on gabapentin pharmacokinetics.

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test when gabapentin was added to other anticonvulsant drugs, the more specific sulphosalicylic acid precipitation procedure is recommended to determine urinary protein.

4.6. Pregnancy and lactation

Safe use in human pregnancy has not been established. Reproduction studies in mice, rats or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600mg revealed no evidence of impaired fertility or harm to the foetus due to gabapentin administration. However, because

animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Gabapentin is excreted in human milk but the effect on the nursing infant is unknown. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from gabapentin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7. Effects on ability to drive and use machines

Gabapentin acts on the central nervous system and may produce drowsiness, dizziness, or other related symptoms. These otherwise mild or moderate adverse events could be potentially dangerous in patients driving or operating machinery, particularly until such time as the individual patient's experience with the drug is established.

4.8. Undesirable effects

Neuropathic Pain

Based on placebo-controlled studies, the most common possible side-effects >1/10) associated with treating neuropathic pain with gabapentin are: dizziness and somnolence.

Common possible side-effects (between 1/10 and 1/100) are: diarrhoea, dry mouth, peripheral edema, weight gain, abnormal gait, amnesia, ataxia, abnormal thinking, rash and amblyopia.

Uncommon possible side-effects (between 1/100 and 1/1000) are: accidental injury, asthenia, back pain, constipation, flatulence, nausea, confusion, hypesthesia, vertigo, dyspnea and pharyngitis.

Epilepsy (Adults)

Since gabapentin has most often been administered in combination with other anti-epileptic agents, it is not possible to determine which agents, if any are associated with adverse events. However, based on placebo-controlled, double blind studies, the most common possible side-effects >1/10) are: somnolence and dizziness.

Common possible side-effects (between 1/10 and 1/100) are: ataxia, fatigue, nystagmus, tremor, diplopia, amblyopia, dysarthria, amnesia, asthenia, paraesthesia, arthralgia, purpura, dyspepsia, anxiety, weight increase, urinary tract infection and pharyngitis.

Uncommon possible side-effects (between 1/100 and 1/1000) are: leucopenia, nervousness, rhinitis and male sexual dysfunction (impotence).

As with the other AEDs there have been rare reports of urinary incontinence, pancreatitis, elevated liver function tests, erythema multiforme and Stevens Johnson Syndrome where a causal relationship to treatment has not been established. Rarely confusion, depression, emotional lability, hostility, abnormal thinking and psychoses/hallucinations have been reported. Blood

glucose fluctuations in patients with diabetes, myalgia, headache, nausea and/or vomiting have also been reported.

Epilepsy (Children)
In children aged 3-12 years in placebo controlled and long term trials, the most common >10%) side-effects were emotional lability, nervousness and thinking abnormally. All reports of these events were rated as mild or moderate and discontinuation or dose reduction were infrequent.

In children aged 3-12 years in controlled add-on trials, side-effects that occurred with an incidence of 2% or greater than placebo were: somnolence, fatigue, weight increase, hostility, emotional lability, dizziness, hyperkinesia, nausea/vomiting, viral infection, fever, bronchitis, respiratory infection. Some of these side-effects could be attributed to common viral childhood illness.

4.9. Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49grams. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise toxicity from overdoses.

Although gabapentin can be removed by haemodialysis it is not usually required. However, in patients with renal impairment, haemodialysis may be indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics
ATC code: N03AX

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but its mechanism of action is different from that of several drugs that interact with GABA synapses. The identification and function of the gabapentin binding site remains to be elucidated and the relevance of its various actions to the anticonvulsant effect to be established. Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.

5.2. Pharmacokinetic properties

Mean plasma gabapentin concentrations (Cmax) occurred approximately 3 hours (Tmax) following single oral doses of gabapentin regardless of dose size or formulation. Mean Tmax values following multiple dose administration were approximately 1 hour shorter than the values following single-dose administration.

Mean Cmax and AUC values increased with increasing dose; however, the increase was less than dose proportional. Deviation from linearity was very slight up to 600mg for both parameters and thus should be minimal at doses of

300mg to 400mg three times daily where the anti-epileptic effect generally occurs.

Following repeated gabapentin administration, steady state was achieved within 1 to 2 days after the start of the multiple dosing and was maintained throughout the dosing regime.

Plasma gabapentin concentration-time profiles were similar between gabapentin solution and capsule formulations following single doses of 300 and 400mg. Absolute bioavailability of a 300mg oral dose of gabapentin was approximately 60%. At doses of 300mg and 400mg, gabapentin bioavailability was unchanged following multiple-dose administration.

The presence of food does not influence the bioavailability of gabapentin.

Gabapentin is not metabolised in humans and does not induce hepatic mixed function oxidase enzymes.

Gabapentin elimination from plasma following IV administration was best described by linear pharmacokinetics. Elimination half-life (T½) of gabapentin ranged from 5 to 7 hours. Gabapentin elimination parameters, apparent plasma T½ and renal clearance (CL_R) were independent of dose and remained unchanged following repeated administration. Renal clearance was the sole elimination pathway for gabapentin. Since gabapentin is not metabolised in humans, the amount of drug recovered in urine is indicative of gabapentin bioavailability. Following a single 200mg oral dose of [C_{14}]gabapentin recovery of radioactivity was essentially complete with approximately 80% and 20% of the dose recovered in urine and faeces, respectively.

As renal function (as determined by creatinine clearance) decreases with increasing age, gabapentin oral clearance, renal clearance and elimination-rate constant decrease proportionally.

Gabapentin pharmacokinetics were determined in 24 healthy paediatric subjects between the ages of 4 and 12 years. In one single dose study, pharmacokinetic parameters were similar in children weighing 26-50kg, but not in children weighing 17-25 kg. No multiple dose studies have been conducted in children.

5.3. Preclinical safety data

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose. Peak plasma drug concentrations and areas under the concentration time curve in rats at 2000 mg/kg is 10 times higher than plasma concentrations in humans given 3600 mg/day.

The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not affect survival, did not metastasise or invade surrounding tissue, and

were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is therefore of uncertain significance.

Gabapentin has no genotoxic potential. It was not mutagenic in the Ames bacterial plate incorporation assay or at the HGPRT locus in mammalian cells in the presence or absence of metabolic activation. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule Fill: Lactose monohydrate
Maize starch
Talc
Capsule Shell: Titanium dioxide (E 171)
Yellow iron oxide (E172)
Gelatin
Printing Ink: Shellac
Titanium dioxide (E171)
FD&C Blue 1/Brilliant Blue FCF Lake (E133)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

18 months

6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

The capsules are packed in blister strips of aluminium foil and transparent PVC. Each blister strip contains 10 capsules. The blisters are then packed into cartons containing 20, 50, 100 or 200 capsules. Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

No additional information.

7. MARKETING AUTHORISATION HOLDER

Clarendon Pharma Limited
19 King Street
Seagrave
Leicestershire
LE12 7LY

8. MARKETING AUTHORISATION NUMBER

PL 20137/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/03/2006

10 DATE OF REVISION OF THE TEXT

14/03/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gabapentin 400mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains gabapentin 400mg.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

A two-piece, orange opaque hard gelatin capsule marked GA400 with company logo, containing a white to off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Neuropathic Pain

Gabapentin is indicated for the treatment of neuropathic pain.

Epilepsy

Adults and children over 12 years of age

Gabapentin is an anti-epileptic drug indicated as add-on therapy for partial seizures and partial seizures with secondary generalisation in patients who have not achieved satisfactory control with or who are intolerant to standard anticonvulsants used alone or in combination.

Children 6-12 years of age

Gabapentin may be used as add-on therapy for partial seizures and partial seizures with secondary generalisation, in children aged between 6-12 years, who have not achieved satisfactory control with, or who are intolerant to, standard anticonvulsants used alone or in combination, if the benefit : risk is considered favourable. Gabapentin should be initiated and supervised by a neurological specialist.

Children under 6 years of age

There are inadequate data in this age group and therefore the use of gabapentin is not recommended.

4.2. Posology and method of administration

Neuropathic Pain

Adults (over the age of 18)

Gabapentin should be titrated to a maximum dose of 1800 mg per day.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg three times a day on day 3, as described in Table 1.

Table 1: Dosing Chart – Initial Titration

Dose	Day 1	Day 2	Day 3
900mg	300mg QD [a]	300mg BID [b]	300mg TID [c]

a QD = once a day

[b] BID = two times a day

[c] TID = three times a day

Thereafter, the dose can be increased using increments of 300mg per day given in three divided doses to a maximum of 1800mg per day. It is not necessary to divide the doses equally when titrating gabapentin.

It is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

Elderly
Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2).

Epilepsy
Adults and Children aged over 12
The anti-epileptic effect of gabapentin generally occurs at 900 to 1200mg/day.

It is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg three times a day on day 3, as described in Table 1. Thereafter, the dose can be increased using increments of 300mg per day given in three equally divided doses to a maximum dose of 2400mg per day.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of one week.

Elderly
Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2).

Children 6-12 years of age
The recommended dose of gabapentin is 25 to 35 mg/kg/day given in divided doses (3 times a day). Titration to an effective dose can take place over 3 days

by giving 10 mg/kg/day on Day 1, 20 mg/kg/day on Day 2 and 25 to 35 mg/kg/day on Day 3.

The following maintenance dosing schedule is suggested:

Weight Range (kg)	Total mg Dose/Day
26-36	900
37-50	1200

Dosage Adjustment in Patients with Compromised Renal Function or those Undergoing Haemodialysis
Dosage adjustment is recommended in patients with compromised renal function as described in Table 2, or those undergoing haemodialysis.

Patients with Compromised Renal Function:

Table 2: Maintenance Dosage of Gabapentin in Adults with Reduced Renal Function

Renal function **Creatinine Clearance (ml/minute)**	**Total Daily Dose[a]** **mg/day**		
	Normal Dosage		
≥ 80	**900**	**1200**	**2400**
50-79	600	600	1200
30-49	300	300	600
15-29	150[b]	300	300
<15	150[b]	150[b]	150[b]

[a] Total daily dose should be administered as a tid regimen. Doses used to treat patients with normal renal function (creatinine clearance >80 ml/min) range from 900 to 2400 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79 ml/min).
[b] To be administered as 300 mg every other day.

Patients Undergoing Haemodialysis:
For patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400mg is recommended then 200 to 300mg of gabapentin following each 4 hours of haemodialysis.

4.3. Contraindications

Gabapentin is contra-indicated in patients who are hypersensitive to gabapentin or to the product's components

4.4. Special warnings and precautions for use

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsant agents in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, there is a need for dose

reduction, discontinuation or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Gabapentin is not generally considered effective in the treatment of absence seizures.

Patients taking gabapentin can be the subject of mood and behavioural disturbances. Such reports have been noted in patients on gabapentin although a causal link has not been established.

Caution is recommended in patients with a history of psychotic illness. On commencing gabapentin therapy, psychotic episodes have been reported in some patients with, and rarely without, a history of psychotic illness. Most of these events resolved when gabapentin was discontinued or the dosage was reduced.

Gabapentin Capsules contain lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction

Gabapentin may be used in combination with other anti-epileptic drugs without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other anti-epileptic drugs.

There is no interaction between gabapentin and phenytoin, valproic acid, carbamazepine or phenobarbitone. Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving anti-epileptic agents.

Co-administration of gabapentin with oral contraceptives including norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either component.

In a clinical study where gabapentin and an aluminium and magnesium containing antacid when given at the same time, gabapentin's bioavailability was reduced by up to 24%. It is recommended that gabapentin is taken about two hours following any such antacid administration. The slight decrease in renal excretion of gabapentin observed when co-administered with cimetidine is not expected to be of clinical importance.

Renal excretion of gabapentin is unaltered by probenecid.

Food has no effect on gabapentin pharmacokinetics.

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test when gabapentin was added to other anticonvulsant drugs, the more specific sulphosalicylic acid precipitation procedure is recommended to determine urinary protein.

4.6. Pregnancy and lactation

Safe use in human pregnancy has not been established. Reproduction studies in mice, rats or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600mg revealed no evidence of impaired fertility or harm to the foetus due to gabapentin administration. However, because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Gabapentin is excreted in human milk but the effect on the nursing infant is unknown. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from gabapentin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7. Effects on ability to drive and use machines

Gabapentin acts on the central nervous system and may produce drowsiness, dizziness, or other related symptoms. These otherwise mild or moderate adverse events could be potentially dangerous in patients driving or operating machinery, particularly until such time as the individual patient's experience with the drug is established.

4.8. Undesirable effects

Neuropathic Pain

Based on placebo-controlled studies, the most common possible side-effects >1/10) associated with treating neuropathic pain with gabapentin are: dizziness and somnolence.

Common possible side-effects (between 1/10 and 1/100) are: diarrhoea, dry mouth, peripheral edema, weight gain, abnormal gait, amnesia, ataxia, abnormal thinking, rash and amblyopia.

Uncommon possible side-effects (between 1/100 and 1/1000) are: accidental injury, asthenia, back pain, constipation, flatulence, nausea, confusion, hypesthesia, vertigo, dyspnea and pharyngitis.

Epilepsy (Adults)

Since gabapentin has most often been administered in combination with other anti-epileptic agents, it is not possible to determine which agents, if any are associated with adverse events. However, based on placebo-controlled, double blind studies, the most common possible side-effects >1/10) are: somnolence and dizziness.

Common possible side-effects (between 1/10 and 1/100) are: ataxia, fatigue, nystagmus, tremor, diplopia, amblyopia, dysarthria, amnesia, asthenia, paraesthesia, arthralgia, purpura, dyspepsia, anxiety, weight increase, urinary tract infection and pharyngitis.

Uncommon possible side-effects (between 1/100 and 1/1000) are: leucopenia, nervousness, rhinitis and male sexual dysfunction (impotence).

As with the other AEDs there have been rare reports of urinary incontinence, pancreatitis, elevated liver function tests, erythema multiforme and Stevens Johnson Syndrome where a causal relationship to treatment has not been established. Rarely confusion, depression, emotional lability, hostility, abnormal thinking and psychoses/hallucinations have been reported. Blood glucose fluctuations in patients with diabetes, myalgia, headache, nausea and/or vomiting have also been reported.

Epilepsy (Children)

In children aged 3-12 years in placebo controlled and long term trials, the most common >10%) side-effects were emotional lability, nervousness and thinking abnormally. All reports of these events were rated as mild or moderate and discontinuation or dose reduction were infrequent.

In children aged 3-12 years in controlled add-on trials, side-effects that occurred with an incidence of 2% or greater than placebo were: somnolence, fatigue, weight increase, hostility, emotional lability, dizziness, hyperkinesia, nausea/vomiting, viral infection, fever, bronchitis, respiratory infection. Some of these side-effects could be attributed to common viral childhood illness.

4.9. Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49grams. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise toxicity from overdoses.

Although gabapentin can be removed by haemodialysis it is not usually required. However, in patients with renal impairment, haemodialysis may be indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics
ATC code: N03AX

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but its mechanism of action is different from that of several drugs that interact with GABA synapses. The identification and function of the gabapentin binding site remains to be elucidated and the relevance of its various actions to the anticonvulsant effect to be established. Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.

5.2. Pharmacokinetic properties

Mean plasma gabapentin concentrations (C_{max}) occurred approximately 3 hours (T_{max}) following single oral doses of gabapentin regardless of dose size or formulation. Mean T_{max} values following multiple dose administration were approximately 1 hour shorter than the values following single-dose administration.

Mean C_{max} and AUC values increased with increasing dose; however, the increase was less than dose proportional. Deviation from linearity was very slight up to 600mg for both parameters and thus should be minimal at doses of 300mg to 400mg three times daily where the anti-epileptic effect generally occurs.

Following repeated gabapentin administration, steady state was achieved within 1 to 2 days after the start of the multiple dosing and was maintained throughout the dosing regime.

Plasma gabapentin concentration-time profiles were similar between gabapentin solution and capsule formulations following single doses of 300 and 400mg. Absolute bioavailability of a 300mg oral dose of gabapentin was approximately 60%. At doses of 300mg and 400mg, gabapentin bioavailability was unchanged following multiple-dose administration.

The presence of food does not influence the bioavailability of gabapentin.

Gabapentin is not metabolised in humans and does not induce hepatic mixed function oxidase enzymes.

Gabapentin elimination from plasma following IV administration was best described by linear pharmacokinetics. Elimination half-life (T½) of gabapentin ranged from 5 to 7 hours. Gabapentin elimination parameters, apparent plasma T½ and renal clearance (CL_R) were independent of dose and remained unchanged following repeated administration. Renal clearance was the sole elimination pathway for gabapentin. Since gabapentin is not metabolised in humans, the amount of drug recovered in urine is indicative of gabapentin bioavailability. Following a single 200mg oral dose of [C_{14}]gabapentin recovery of radioactivity was essentially complete with approximately 80% and 20% of the dose recovered in urine and faeces, respectively.

As renal function (as determined by creatinine clearance) decreases with increasing age, gabapentin oral clearance, renal clearance and elimination-rate constant decrease proportionally.

Gabapentin pharmacokinetics were determined in 24 healthy paediatric subjects between the ages of 4 and 12 years. In one single dose study, pharmacokinetic parameters were similar in children weighing 26-50kg, but not in children weighing 17-25 kg. No multiple dose studies have been conducted in children.

5.3. Preclinical safety data

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose. Peak plasma drug concentrations

and areas under the concentration time curve in rats at 2000 mg/kg is 10 times higher than plasma concentrations in humans given 3600 mg/day.

The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not affect survival, did not metastasise or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is therefore of uncertain significance.

Gabapentin has no genotoxic potential. It was not mutagenic in the Ames bacterial plate incorporation assay or at the HGPRT locus in mammalian cells in the presence or absence of metabolic activation. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule Fill: Lactose monohydrate
Maize starch
Talc

Capsule Shell: Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Gelatin

Printing Ink: Shellac
Titanium dioxide (E171)
FD&C Blue 1/Brilliant Blue FCF Lake (E133)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

18 months

6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

The capsules are packed in blister strips of aluminium foil and transparent PVC. Each blister strip contains 10 capsules. The blisters are then packed into cartons containing 20, 50, 100 or 200 capsules. Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

No additional information.

7. MARKETING AUTHORISATION HOLDER

Clarendon Pharma Limited
19 King Street
Seagrave
Leicestershire
LE12 7LY

8. MARKETING AUTHORISATION NUMBER

PL 20137/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/03/2006

10 DATE OF REVISION OF THE TEXT

14/03/2006

PATIENT INFORMATION LEAFLET

Gabapentin 100mg, 300mg and 400mg Capsules

Read this leaflet carefully before you start taking this medicine. This leaflet contains a summary of information about your medicine. Read this leaflet before taking your capsules, even if you have only collected a repeat prescription. You may wish to keep this leaflet as you may want to read it again. If you have further questions, please ask your doctor or your pharmacist.

Marketing Authorisation Holder: Clarendon Pharma Limited
19 King Street, Seagrave, Leicestershire, LE12 7LY

Manufacturer: Arrow Generics Limited
Unit 2, Eastman Way, Stevenage, Herts SG1 4SZ

WHAT IS YOUR MEDICINE?
Your medicine is in the form of a hard capsule. Each capsule contains the active ingredient gabapentin. The capsules are available in three strengths containing 100mg, 300mg and 400mg of gabapentin.

The 100mg capsules are white gelatin capsules marked with GA100 and a company logo in blue ink.
The 300mg capsules are yellow gelatin capsules marked with GA300 and a company logo in blue ink.
The 400mg capsules are orange gelatin capsules marked with GA400 and a company logo in blue ink.

Each capsule contains:
In the capsule contents: lactose monohydrate, talc and maize starch.
In the capsule shell: gelatin and titanium dioxide (E171). The colorants used in the different strengths of capsule are as follows: the 300mg capsules contain yellow iron oxide (E172) and the 400mg capsules contain red iron oxide (E172).
In the printing ink: shellac, titanium dioxide (E171) and FD&C Blue 1/Brilliant Blue FCF Lake (E133).

Gabapentin Capsules are available in transparent blister packs of 20, 50, 100 and 200 capsules, although not all pack sizes may be marketed.

WHAT IS YOUR MEDICINE USED FOR?
Gabapentin belongs to a group of medicines used to treat neuropathic pain (pain caused by damage to the nerves) and epilepsy.

You have been prescribed Gabapentin Capsules for the following reasons, which your doctor will explain to you:

- You have chronic (long-lasting) neuropathic pain. This may be caused by a number of diseases such as diabetes, shingles, trauma (an injury or wound) and diseases of the nervous system. The pain sensation may feel: hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, pins and needles etc.
- Your current treatment for epilepsy is not fully controlling your condition or is causing problems such as side effects. Unless your doctor tells you otherwise, you should take Gabapentin Capsules in addition to your current treatment.

DO NOT TAKE GABAPENTIN CAPSULES IF:
- You have ever had an allergic reaction to gabapentin or any of the other ingredients.
- You are pregnant, planning to become pregnant or breastfeeding
- You have a history of psychosis (hallucinations or abnormal thinking)
- You have kidney problems
- You are taking any other medicines apart from your current epilepsy or pain medication

Gabapentin Capsules should not be taken by children under the age of 6 years.

Gabapentin Capsules contain lactose, if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

If you think any of these conditions apply to you, tell your doctor and follow the advice given.

CAN YOU TAKE GABAPENTIN CAPSULES WITH OTHER MEDICINES?
Gabapentin can be taken with other anti-epileptic drugs and the oral contraceptive pill. If you take gabapentin at the same time as antacids containing aluminium or magnesium (e.g. for indigestion), the absorption of gabapentin may be reduced. It is therefore recommended that you take Gabapentin Capsules about 2 hours after the antacid.

If you buy 'over-the-counter' medicines at a chemist, you should tell the pharmacist that you are taking gabapentin.
If you visit your dentist or need an operation, you should tell the dentist or doctor that you are taking gabapentin.

HOW TO TAKE YOUR MEDICINE
Gabapentin Capsules should be taken as your doctor has prescribed and as stated on the pharmacy label on your medicine.

Neuropathic Pain:
Adults (over 18 years):
Your doctor will start your treatment by giving you a low dose of 300mg gabapentin on the first day, the dose will increase to 600mg on the second day and 900mg on the third day. The dose may then continue to be increased to a maximum of 1800mg per day. This will be taken divided between 3 doses i.e. in the morning, at midday and in the evening.

Epilepsy:
Adults and children over 12 years:
The usual dose is 900mg to 2400mg each day divided between 3 doses i.e. in the morning, at midday and in the evening.

Elderly:
Elderly patients may have their dose adjusted by the doctor.

Children 6-12 years:
The dose for children is based on their weight and will be calculated by your doctor. The dose is usually divided between 3 doses i.e. in the morning, at midday and in the evening.

Always take the capsules with a glass of water. You can take the capsules with or without food, but should take them 2 hours after any antacid medication.

Do not take more than the dose prescribed by the doctor. Keep taking the capsules for as long as the doctor has asked you to. Do not stop taking Gabapentin Capsules without consulting your doctor.

If you forget to take your medicine:
If you forget to take your capsules at the correct time, just take them when you remember unless it is time for your next dose. Do not take 2 doses at the same time.

If you take too many capsules:
If you take too many capsules you should contact your doctor immediately or go to the nearest hospital casualty department. Remember to take the pack and any remaining capsules with you so that the doctor will know what you have taken.

WHAT UNDESIRABLE EFFECTS DOES YOUR MEDICINE HAVE?
Most people take gabapentin without any problems. However, sometimes side effects may occur.

Neuropathic Pain
In neuropathic pain, the most common side effects are dizziness and drowsiness, diarrhoea, dry mouth, swelling of the hands and feet, weight gain, staggering walk, memory loss, abnormal thinking, rash and double or blurred vision. Uncommon side effects include: accidental injury, weakness, back pain, constipation, flatulence ('wind'), feeling sick, confusion, reduced sensation to touch, pain, heat or cold, vertigo, shortness of breath and sore throat.

If you become dizzy or drowsy, or your sight is affected you should avoid driving and operating machinery.

Epilepsy
In epilepsy, the most common side effects in adults include: drowsiness and dizziness, staggering walk, tiredness, unusual eye movements, tremor, double or blurred vision, stammering, memory loss, weakness, pins and needles or numbness, joint pain, bruising, indigestion, anxiety, weight gain, urinary infection and sore throat. Uncommon side effects include: nervousness, unusual sensations in the nose and impotence.

Serious side effects with gabapentin are rare. The following side effects have been seen with other anti-epileptic medication but a definite link with gabapentin has not been established: incontinence, pancreatitis (inflammation of the pancreas leading to stomach pain), increases in liver function blood tests, rashes with an associated general illness, depression, confusion, mood and behaviour changes, hallucinations or abnormal thoughts. Changes in blood sugar levels have been seen in patients with diabetes. Muscle pain, headache, feeling or being sick have also been reported.

If you become dizzy or drowsy, or your sight is affected you should avoid driving and operating machinery.

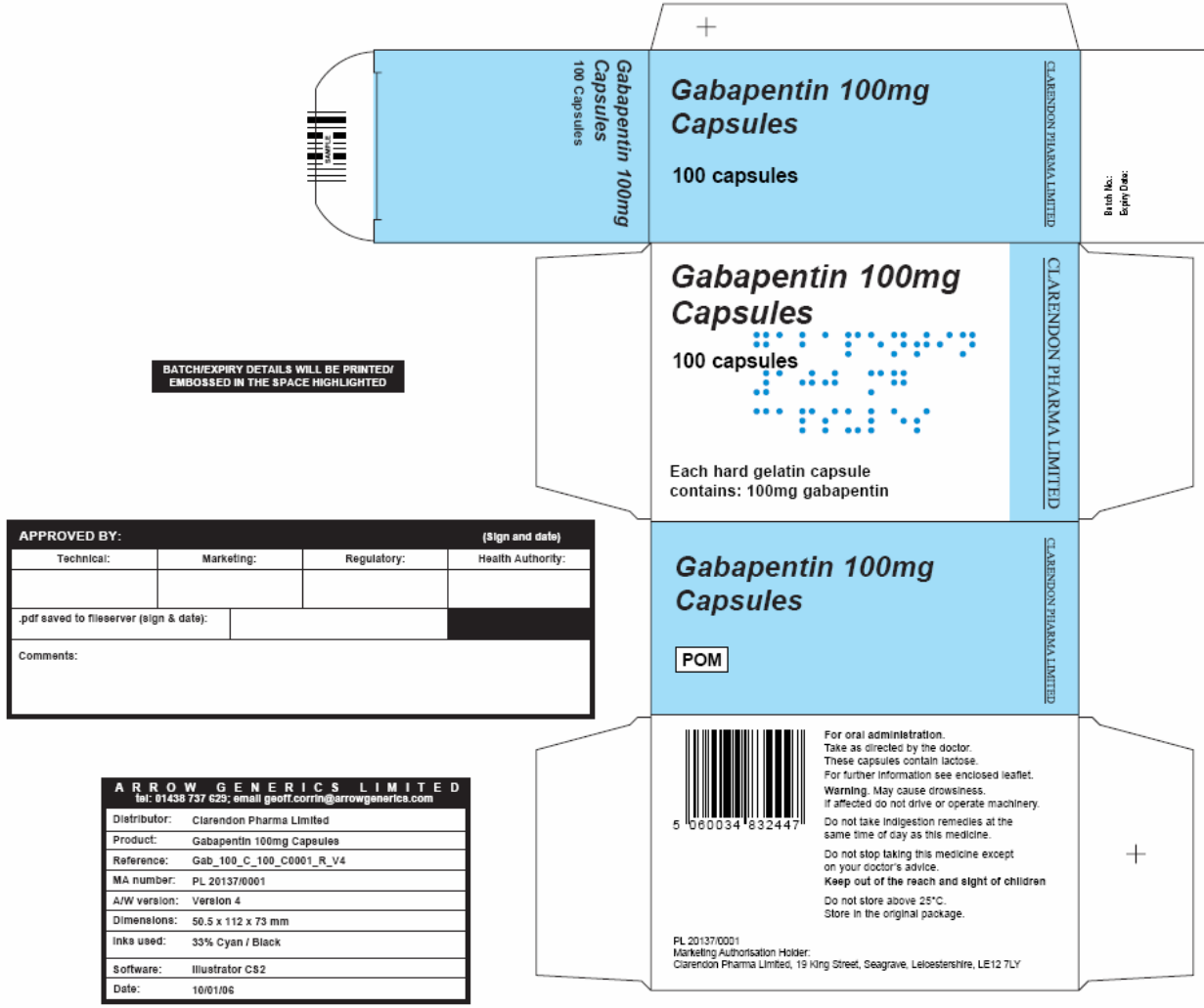
Children are most likely to have the following side effects: mood and behaviour changes, nervousness and abnormal thinking. Occasionally the following have been reported: tiredness, weight gain, dizziness, decreased attention span, feeling or being sick, fever, viral infection, chest and/or throat infection. Some of these are often seen in childhood viral infections.

If you suffer from any of these unwanted side effects, or effects not specified in this information leaflet, please inform your doctor or pharmacist.

WHERE TO KEEP YOUR MEDICINE
Keep all medicines out of the reach and sight of children. Do not store Gabapentin Capsules above 25°C. Store in the original package.

Do not use after the expiry date stated on the carton.

This medicine has been prescribed for you personally and you should **NOT** pass it on to others. It my harm them, even if their symptoms are the same as yours.
Date of preparation of this leaflet: April 2005



BATCH/EXPIRY DETAILS WILL BE PRINTED/ EMBOSSED IN THE SPACE HIGHLIGHTED

APPROVED BY:			(Sign and date)
Technical:	Marketing:	Regulatory:	Health Authority:
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Comments:			

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Distributor:	Clarendon Pharma Limited
Product:	Gabapentin 100mg Capsules
Reference:	Gab_100_C_100_C0001_R_V4
MA number:	PL 20137/0001
A/W version:	Version 4
Dimensions:	50.5 x 112 x 73 mm
Inks used:	33% Cyan / Black
Software:	Illustrator CS2
Date:	10/01/06

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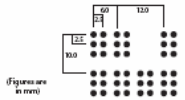

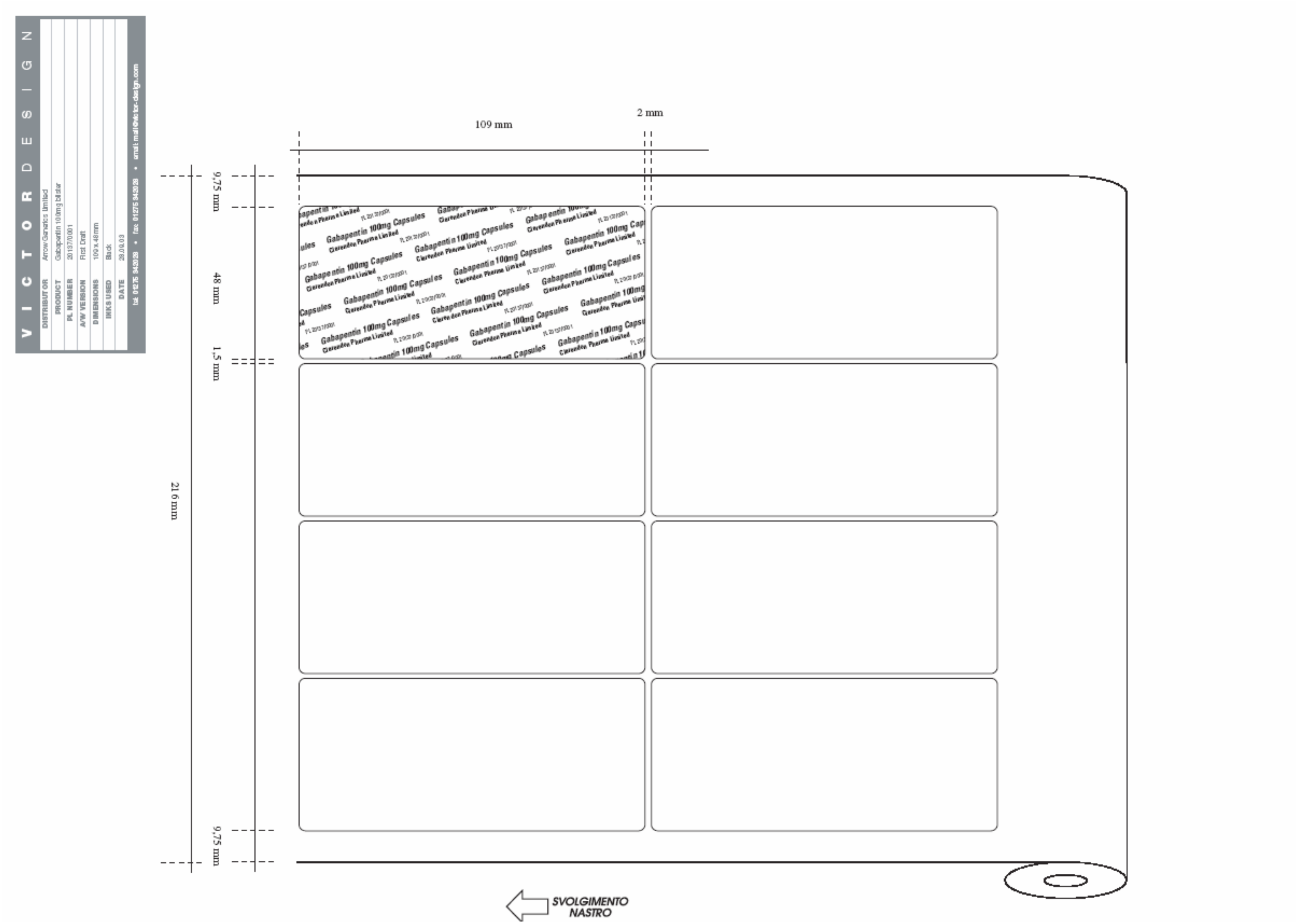
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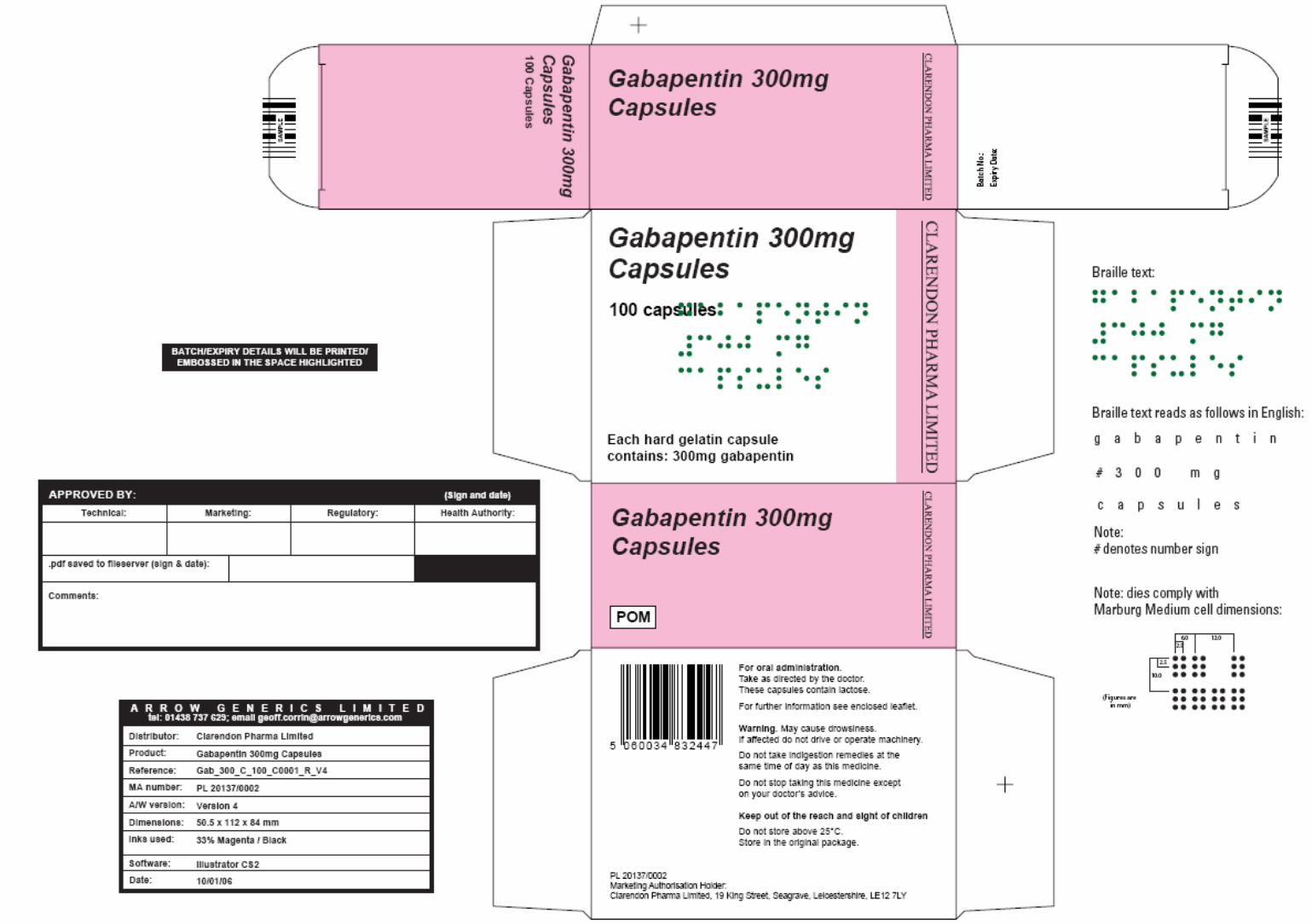
Gabapentin 100mg Capsules
Clarendon Pharma Limited
SVOLGIMENTO NASTRO


Gabapentin 300mg Capsules
100 Capsules
CLARENDON PHARMA LIMITED
Batch No.:
Expiry Date:
Gabapentin 300mg Capsules
100 capsules
CLARENDON PHARMA LIMITED
Each hard gelatin capsule contains: 300mg gabapentin
Gabapentin 300mg Capsules
CLARENDON PHARMA LIMITED
POM
5 060034 832447
For oral administration.
Take as directed by the doctor.
These capsules contain lactose.
For further information see enclosed leaflet.
Warning. May cause drowsiness.
If affected do not drive or operate machinery.
Do not take indigestion remedies at the same time of day as this medicine.
Do not stop taking this medicine except on your doctor's advice.
Keep out of the reach and sight of children
Do not store above 25°C.
Store in the original package.
PL 20137/0002
Marketing Authorisation Holder:
Clarendon Pharma Limited, 19 King Street, Seagrave, Leicestershire, LE12 7LY
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MA number: PL 20137/0002
A/W version: Version 4
Dimensions: 50.5 x 112 x 84 mm
Inks used: 33% Magenta / Black
Software: Illustrator CS2
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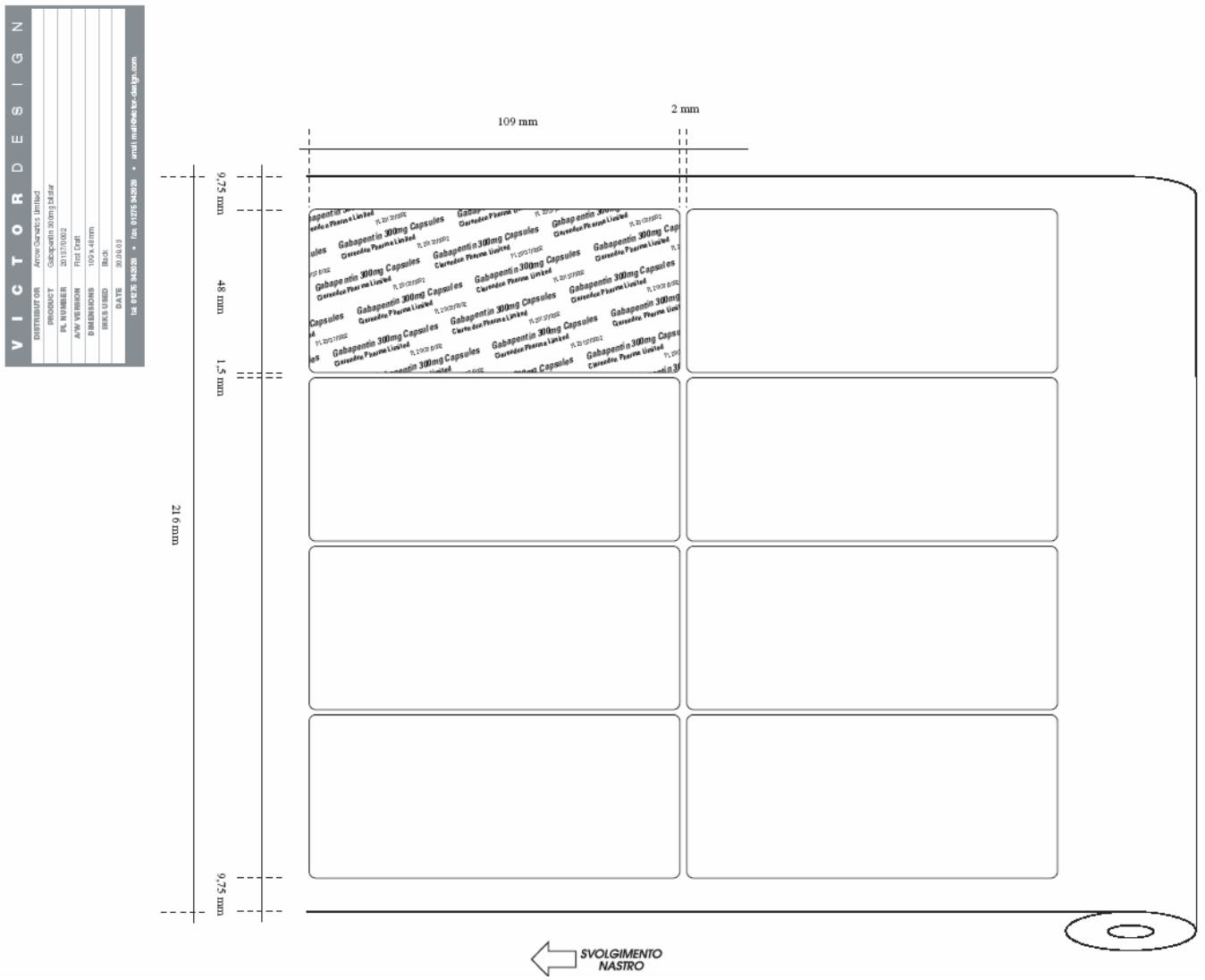
(Figures are in mm)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PRODUCT Gabapentin 300mg blister
PL NUMBER 20137/0002
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DATE 30.09.09
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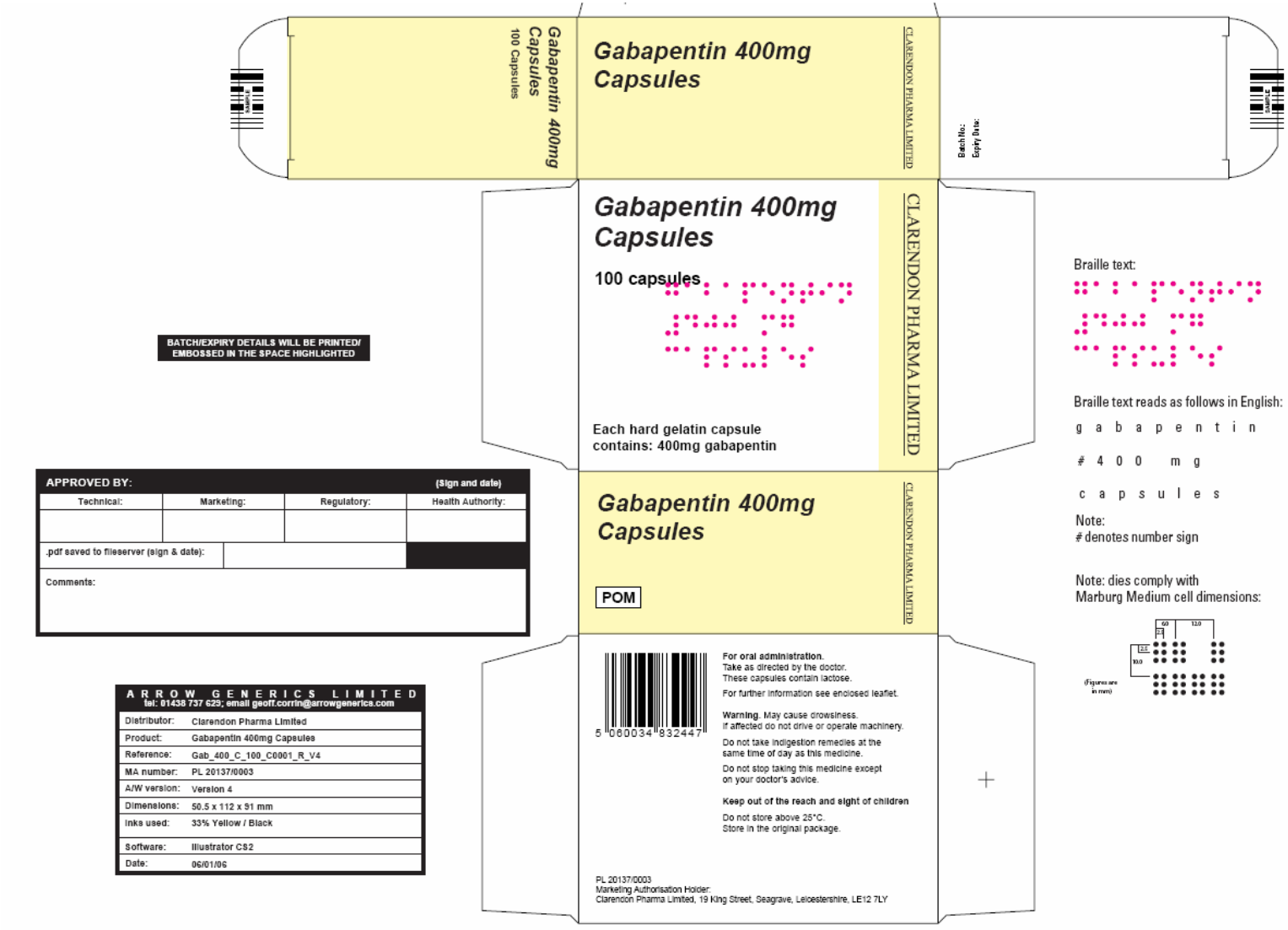
Gabapentin 300mg Capsules
Clarendon Pharma Limited
SVOLGIMENTO NASTRO


Gabapentin 400mg Capsules
100 Capsules
CLARENDON PHARMA LIMITED
Batch No.:
Expiry Date:
Gabapentin 400mg Capsules
100 capsules
Each hard gelatin capsule contains: 400mg gabapentin
CLARENDON PHARMA LIMITED
Gabapentin 400mg Capsules
POM
CLARENDON PHARMA LIMITED
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For oral administration.
Take as directed by the doctor.
These capsules contain lactose.
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If affected do not drive or operate machinery.
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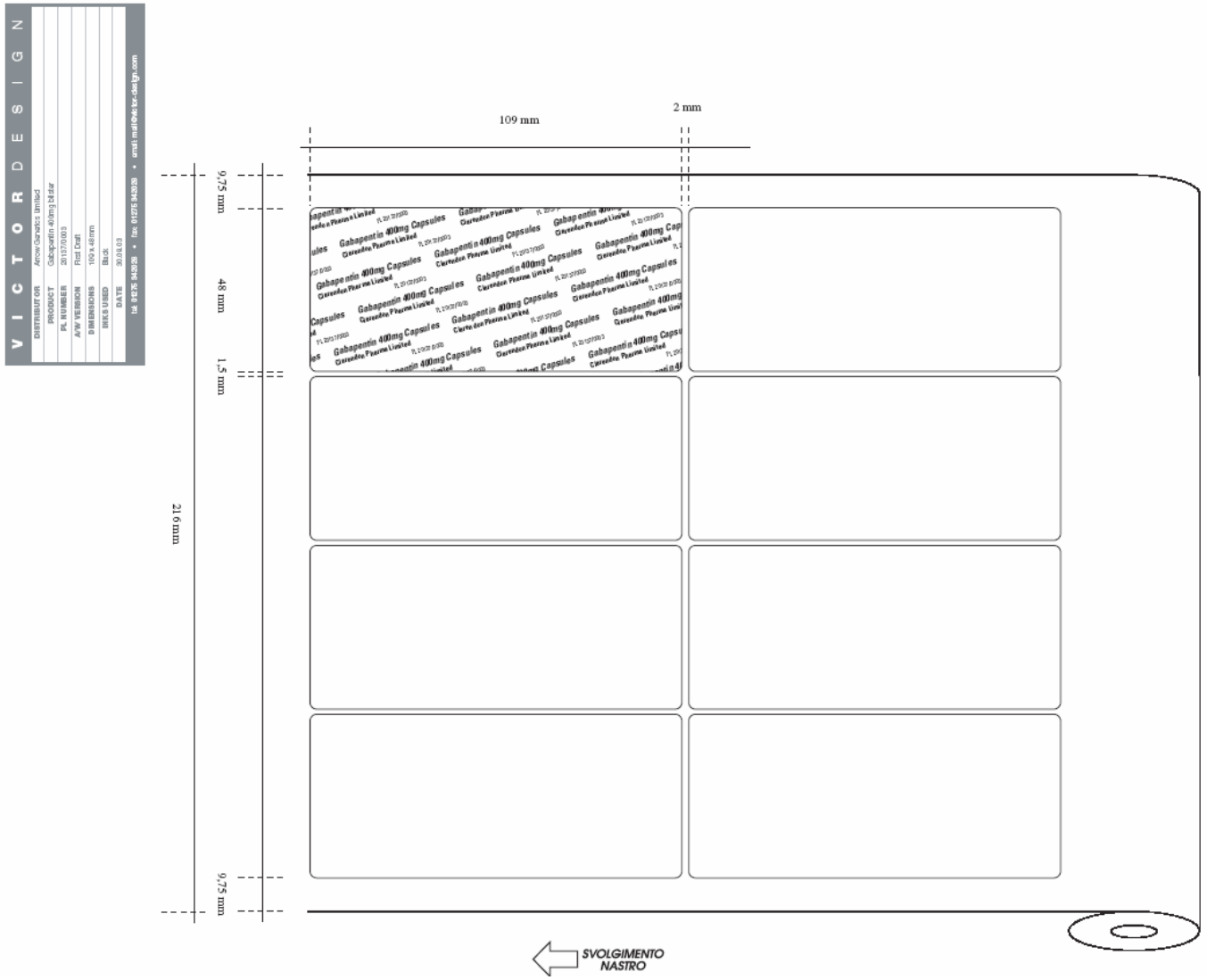
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