GaPP2 Protocol

A multi-centre, double blind randomised controlled trial of the efficacy and mechanism of action of gabapentin for the management of chronic pelvic pain in women

Study Protocol

GaPP2

A multi-centre, double blind randomised controlled trial of the efficacy and mechanism of action of gabapentin for the management of chronic pelvic pain in women

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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Amendment details

Version No./ Date	Amendment Type	Summary of Changes Made
01_20th June 2015 Protocol v2	Substantial – Ethics and MHRA	Update of contact details Clarification of terms Change of FSS to BFI and addition of PUF Addition of pharmacogenetic sub-study
02_11th November 2015	Substantial – Ethics only	Change of PI in Aberdeen, Leicester and Birmingham Women's
03_11th January 2016	Substantial – Ethics only	Addition of Birmingham QE as a site
04_4th February 2016 Protocol v3	Substantial – MHRA only	Update of SmPC **Reasons for adding or updating:** Change to section 4.4 - Special warnings and precautions for use Change to section 4.8 - Undesirable effects Change to section 10 - Date of revision of the text Description - To update sections 4.4 and 4.8 of the SPC in line with the Final Assessment report (PhV-20150203) dated 11.02.2015 with consequential updates to the PIL. SmPC sections update – 4.4, 4.8 and 10
05_5th February 2016 Protocol v4	Substantial – Ethics only	Insertion of ISCTRN and funding references Clarification of unblinding procedures Update of contact details Removal of analgesic use while in study details to reflect the analgesic use may reduce. Removal of heat stimulus from fMRI process Change of fMRI PIS to remove thermal stimuli v4 Addition of pt emergency card.v1
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02_17th November 2015	Non-substantial	Update of questionnaires v3.2 Update of text working v 1.2
03_16th December 2015	Non-substantial	Update of questionnaires v3.3

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PROTOCOL APPROVAL

GaPP2: A multi-centre, double blind randomised controlled trial of the efficacy and mechanism of action of gabapentin for the management of chronic pelvic pain in women

EudraCT number 2014-005035-13

Signatures

Chief Investigator	Signature	Date
Trial Statistician	Signature	Date
Sponsor(s) Representative	Signature	Date
Principal Investigator	Signature	Date

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
CPP	Chronic pelvic pain
CRF	Case Report Form
CRIC	Clinical Research Imaging Centre
CTIMP	Clinical Trial of Investigational Medicinal Products
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
GHQ	General Health Questionnaire
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IUS	Intrauterine system
MTD	Maximum tolerated dose
NHS	National Health Service
NRS	Numerical Rating Scale
PUF	Pelvic Pain and Urinary/Frequency Patient Symptom Scale
QoL	Quality of Life
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SF12	Short Form
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UAR	Unexpected Adverse Reaction
WPAIQ	Work and Productivity Activity Impairment Questionnaire

SUMMARY

LAY SUMMARY

Chronic pelvic pain (CPP) affects >1 million UK women. It accounts for 20% of gynaecological consultations and was highlighted in the Chief Medical Officer's Annual Report in 2009 as a key area of unmet need. Evidence-based treatments for CPP are limited, and management is often unsatisfactory. If no pathology is identified, the pain is much more difficult to treat and a drug called gabapentin, which has been used safely and successfully to treat other chronic pain conditions is being increasingly prescribed. There is currently no evidence to show whether it is effective or not for CPP.

We will investigate the effectiveness of gabapentin in women with CPP. In addition, we want to understand whether changes in the central nervous system of women with CPP are responsible for their symptoms and whether these can predict response to gabapentin. The main aim of the study is to demonstrate whether a reduction in daily pain can be achieved with the treatment of gabapentin.

We will randomise 300 women with CPP where no cause has been found, to participate in a clinical trial where they are allocated at random to gabapentin or placebo (dummy capsules). We will collect information on pain, physical and emotional wellbeing at the beginning of the study and then weekly between weeks 13 and 16 post-randomisation.We will ask a subset of 50 women (from Scottish sites) to undergo a functional magnetic resonance imaging (fMRI) scan to look at brain activity before and during treatment.

TRIAL SUMMARY

DESIGN:	A multi-centre, double blind randomised controlled trial of the efficacy and mechanism of action of gabapentin for the management of chronic pelvic pain in women.
SETTING:	At least 8 NHS hospitals within the United Kingdom
TARGET POPULATION:	300 women with a history of pelvic pain in whom a laparoscopy reveals no obvious pelvic pathology. 150 will be randomised to gabapentin and 150 to placebo. 50 participating women in Scotland will be recruited to fMRI sub study. **INCLUSION CRITERIA** • Women aged between 18-50 years • Chronic pelvic pain (non-cyclical with or without dysmenorrhoea or dyspareunia) of >3 months duration • Pain located within the true pelvis or between and below anterior iliac crests • No obvious pelvic pathology at laparoscopy (laparoscopy must have taken place at least 2 weeks ago, but no more than 36 months prior to screening • Using or willing to use effective contraception if necessary to avoid pregnancy • Able to give written informed consent. • For both the worst and average pre-randomisation Numerical Rating Scale (NRS) questions will be asked via text/telephone, at least three of the four weekly scores need to be returned to the trials office and least two of the worst pain scores should be ≥4. **EXCLUSION CRITERIA** ▪ Known pelvic pathology: o Endometriosis (macroscopic lesions) o complex or >5cm ovarian cyst o fibroid >3cm o dense adhesions ▪ Current malignancy under treatment ▪ Current use of gabapentin/pregabalin ▪ Taking GnRH agonists and unable/unwilling to stop ▪ Surgery planned in next 6 months ▪ History of significant renal impairment ▪ Previous reaction to gabapentin ▪ Breast feeding ▪ Pregnant ▪ Planned pregnancy in next 6 months ▪ Pain suspected to be of gastrointestinal origin (positive Rome III Diagnostic Criteria) ▪ Prohibited medication (see SmPC) ▪ Co-enrolment in another CTIMP ▪ Metal implant / pacemaker / claustrophobia (fMRI subgroup only)

HEALTH TECHNOLOGIES ASSESSED:	Blinded allocation to either gabapentin or placebo. Drugs will be titrated as per a set schedule over 4 weeks with optimal dose maintained until the end of week 16 before unblinding and titration down if necessary.
OUTCOME MEASURES:	**Primary Outcome:** Dual measures of worst and average pelvic pain scores assessed weekly by a numerical rating scale (NRS) during the final 4 weeks of treatment (weeks 13-16 post-randomisation). **Secondary Outcomes:** Physical/emotional functioning assessed using: NRS, SF-12 quality of life, Brief Pain Inventory, Brief Fatigue Inventory, General Health Questionnaire, Work and Productivity Activity Impairment, Pain Catastrophizing and Sexual Activity Questionnaires, PainDETECT™. These outcomes will be assessed at the end of the treatment period prior to unblinding (16 weeks post-randomisation). The Pelvic Pain and Urinary/Frequency (PUF) Patient Symptom Scale will be completed at baseline as a predictor of treatment success according to these symptoms. The use of rescue analgesics and attendance with healthcare professionals for CPP use will be assessed in treatment diaries and in data capture during each visit
SUBSTUDY OBJECTIVES	**Mechanistic clinical (sub-study) objectives:** To assess brain activity (fMRI) at rest and in response to noxious stimuli at baseline and before unblinding. **Pharmacogenetic sub-study objectives:** To assess if drug efficacy and potential side effect profiles can determined by genetic influences and if these influences are detectable.
ANALYSIS:	The analysis will be by intention to treat. Point estimates, 95% confidence intervals and p-values from two-sided tests will be calculated for all main outcome measures. A Statistical Analysis Plan will be drawn up prior to any analysis. We will use a linear regression model to estimate differences in the primary outcomes between groups, including baseline score and the minimisation variables as covariates. A Bonferroni correction will be applied to the corresponding p-value as there are two primary outcomes. Further analysis using a repeated measures (multi-level) model will be also be performed incorporating all eight recorded scores. Data from the other continuous measures (e.g. questionnaire scores) will be analysed in a similar fashion. Other outcome measures (use of permitted analgesic medication, satisfaction) will be analysed using standard methods (tests for trend, absolute and relative risks). The fMRI data will be analysed using a voxelwise approach and using a hierarchical linear model. Analysis of variance will be performed to identify the extent of drug effect and to confirm the brain areas on which gabapentin acts in women with CPP. In the gabapentin cohort, univariable and multivariable linear regression will be performed to examine whether baseline scan data can predict response to treatment (NRS). In addition, genome-wide genetic information related to pharmacogenetics of gabapentin will be analysed in saliva in order to obtain a better understanding if there are any genetic reasons differentiating responders from non-responders and possibly enhancing our ability to predict intolerance to that drug.

SAMPLE SIZE:	We have based our sample size on being able to detect a minimally important difference of 1 point in NRS scores with high levels of power. Our pilot study showed worst and average pain scores to have standard deviations between 2 and 2.5. If the SD is at the higher end of these estimates (2.5), we can detect a difference of 1 point with 80% power (p=0.05) with 100 patients in each group. To account for any increase in the risk of type I error that may be associated with having co-primary outcome measures we have applied a Bonferonni correction (alpha reduced to 0.025 from 0.05) which increases the sample size to 120 per group. Furthermore, to account for an expected average 20% lost to follow-up we will randomise 150 per group, 300 patients in total. Based on previous studies and statistical techniques used to analyse the data (www.fmrib.ox.ac.uk/fsl), we estimate that we will need to recruit 50 women (25 per group) for the fMRI sub-study to identify significant differences using mixed effect analyses.

1 INTRODUCTION

1.1 BACKGROUND

Chronic pelvic pain (CPP) affects over 1 million women in the UK (BMC Public Health 2006 6:177),

The pathogenesis of the painful symptoms experienced by women with CPP is poorly understood. They are associated with specific pathological processes, such as endometriosis, but up to 55% of women with CPP appear to have no obvious underlying pathology (BMJ. 2010 341:c4834).

Chronic pelvic pain is the reason for 20% of gynaecological consultations and causes a 45% reduction in work productivity. The annual cost for caring for UK women with CPP has been estimated at £154 million (Best Pract Res Clin Obstet Gynaecol. 2006 20(5):695-711).

The management of CPP is difficult (Cochrane Database Syst Rev 2000;(4):CD000387) because in the absence of underlying pathology, no established gynaecological treatments are available.

1.2 RATIONALE FOR STUDY

We carried out a pilot feasibility randomised controlled trial (BMJ Open 2012 2[3] pii: e001297) to which we recruited 47 participants in two centres over a period of 12 months. Analysis showed that a full study was feasible and that patients randomised to gabapentin may perform better than those randomised to placebo. We found one other study that attempted to determine the efficacy of gabapentin against amitriptyline and showed that gabapentin had a great efficacy (80% v 70% improvement in pain scores at 12 months) but did not examine effect on QoL in 49 women. This therefore shows a need for this definitive trial to determine the true efficacy and mechanism of action of gabapentin in the management of women with CPP.

Current understanding of the mechanism of action of gabapentin has relied on studies in non-specific disease models and animals using functional magnetic resonance imaging (fMRI) of the brain. This modality has been successfully employed to investigate nocioceptive processing in humans and has shown that gabapentin is effective in modulating nocioceptive transmission when central sensitisation is present (Proc Natl Acad Sci U S A 2005 102(50):18195). In anaesthetised rats, fMRI has shown that gabapentin produces significant and discrete changes in brain activation (Br J Pharmacol 2008 153(7):1558). However, a recent review has highlighted the need for studies of nocioceptive processing, using fMRI, to further understanding of CPP (BJOG 2009 116(2):240). We believe that fMRI could also be used to investigate the mechanism of action of gabapentin in CPP, leading to further understanding of the pathophysiology of painful symptoms of CPP and the identification of novel treatment strategies.

Furthermore, it is increasingly clear that drug efficacy, as well as potential side effect profiles, can be strongly determined by genetic influences. We will investigate 1) the influence of genetic variation on gabapentin efficacy and potential intolerance, and 2)

the potential for stratification of patients with likely drug response based on genetic profiles.

Risks and benefits

Gabapentin (a GABA analogue) is being increasingly prescribed in general practice for CPP. It is also recommended by some practitioners as a treatment of choice for CPP in a multi-disciplinary setting, despite no evidence on which to base this recommendation, and no clear mechanism of action.

Side effects may be experienced but gabapentin is usually well tolerated and side effects are often short lived and will stop on dose reduction or stopping of the medication. Patients may benefit from effective pain relief while in the study.

As detailed in the SmPC (Appendix 2), there is a small increased risk of suicidal ideation and behaviour with gabapentin. Therefore, the response to the question regarding mood within the GHQ questionnaire will be monitored carefully by the research nurses. In addition, at each visit open-ended questions will be asked to determine if the participants are experiencing any change in mood which may indicate suicidal ideation or behaviour. If suicidal ideation is suspected then the participant will be withdrawn from treatment then referred to and followed up by their clinical care team.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

- To test the hypothesis that treatment with gabapentin has the potential to provide a safe, effective and convenient oral treatment and to prove if it can alleviate pain in women with chronic pelvic pain (CPP) in the absence of any obvious pelvic pathology.

2.1.2 Secondary Objectives

- To test the hypothesis that treatment with gabapentin has the potential to improve physical and emotional functioning in women with chronic pelvic pain (CPP) in the absence of any obvious pelvic pathology.

2.1.3 Mechanistic fMRI sub-study

- Determine the presence of central changes in women with CPP and no obvious underlying pathology
- Determine the effect of gabapentin on central pain processing in women with CPP and no underlying pathology
- Determine whether there are baseline fMRI measures that correlate with response to treatment
- Determine whether there are clinical measures that correlate with response to treatment

2.**1.4 Pharmacogenetic sub-study**

- Determine the influence of genetic variation on gabapentin efficacy and potential intolerance.
- Determine the stratification of patients with likely drug response based on genetic profiles.

2.2 OUTCOMES

2.2.1 Primary Outcome

We will employ co-primary outcome measures of average and worst pain scores recorded on a numerical rating scale (NRS).

Weekly pain scores (on a 0-10 scale) in the form of:

i) 'average pain this week' and

ii) 'worst pain this week'

These will be recorded during the final four weeks of treatment (weeks 13-16 post randomisation). Average pain score will be taken as the average of i) and worst pain score as the worst response from ii).

2.2.2 Secondary Outcomes

Physical/emotional functioning assessed using the following questionnaires:

- NRS: to include an examination of the proportion of women that have a 30% reduction in average and worst pain scores from baseline to end of treatment.
- Short Form-12 quality of life: Short Form Health Survey provides summary information on physical and mental health status.
- Brief Pain Inventory: a comprehensive instrument for pain assessment
- Brief Fatigue Inventory: to measure the severity of fatigue in adults
- General Health Questionnaire: to identify psychological distress
- Work and Productivity Activity Impairment: a valid questionnaire for assessing impairments in paid work and activities
- Pain catastrophizing scale: one of the most widely used instruments for measuring catastrophic thinking related to pain
- Sexual Activity Questionnaires: The sexual activity questionnaire is a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort
- PainDetect™: a new screening questionnaire to identify neuropathic components in patients
- Pelvic Pain and Urinary/Frequency Patient Symptom Scale (baseline only): a questionnaire that is predictive of treatment success.
- Number of attendances to healthcare professionals for CPP will be recorded in treatment diaries, at study visits and in questions at baseline and end of treatment.
- Use of concomitant medications will be recorded to identify any reductions in analgesic use.

All secondary outcomes will be assessed at the end of the treatment period prior to unblinding (16 weeks post-randomisation).

2.2.3 Mechanistic Sub-study Endpoints

Central pain processing: Brain activity (fMRI) at rest and in response to noxious stimuli.

2.2.4 Pharmacogenetic Sub-study Endpoints

Gabapentin efficacy and intolerance.

3 STUDY DESIGN

Double blind placebo controlled randomised multi-centre clinical trial with nested mechanistic fMRI brain study.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

300 women with a history of pelvic pain in whom a laparoscopy reveals no obvious pelvic pathology. Of these 300 participants, 50 (25 randomised to gabapentin and 25 randomised to placebo) will be recruited to take part in the mechanistic sub-study. Participants recruited from sites in Scotland will be invited to take part in the mechanistic sub-study. All fMRI scans and blood sampling undertaken as part of the sub-study will be conducted in Edinburgh.

4.2 INCLUSION CRITERIA

- Women aged between 18-50 years
- Chronic pelvic pain (non-cyclical with or without dysmenorrhoea or dyspareunia) of >3 months duration
- Pain located within the true pelvis or between and below anterior iliac crests
- No obvious pelvic pathology at laparoscopy (laparoscopy must have taken place at least 2 weeks ago, but no more than 36 months prior to screening)
- Using or willing to use effective contraception if necessary to avoid pregnancy
- Able to give informed consent
- For both the worst and average pre-randomisation Numerical Rating Scale (NRS) questions, at least three of the four weekly scores returned to the trials office. At least two of the worst pain scores should be ≥4.
-

4.3 EXCLUSION CRITERIA

- Known pelvic pathology:
    - Endometriosis (macroscopic lesions)
    - complex or >5cm ovarian cyst
    - fibroid >3cm
    - dense adhesions
- Current malignancy under treatment
- Current use of gabapentin/pregabalin.
- Taking GnRH agonists and unable/unwilling to stop

- Surgery planned in the next 6 months
- History of significant renal impairment
- Previous reaction to gabapentin
- Breast feeding
- Pregnant
- Planned pregnancy in next 6 months
- Pain suspected to be of gastrointestinal origin (positive Rome III Diagnostic Criteria)
- Prohibited medications (see SmPC – Appendix 2))
- Metal implant/pacemaker/claustrophobia (fMRI subgroup only).
- Co-enrolment in another CTIMP

4.4 CO-ENROLMENT

Participants will be permitted to take part in non-interventional studies (e.g. questionnaire studies). Participants will not be permitted to co-enrol in other drug (CTIMP) trials.

5 PARTICIPANT SELECTION AND ENROLMENT

The expected number of women randomised per year has been calculated as 33% of the predicted number of eligible women. The figure of 33% is based on the data from our pilot trial in Edinburgh and Aberdeen where we recruited 34% of the eligible women. We expect this figure to be higher in the full randomised controlled trial (RCT) because we have extended our inclusion criteria to include women who have had a laparoscopy with no obvious pelvic pathology <36 months ago (previously this was <6 months ago). Expected numbers from other participating sites has been assessed from figures recruited to similar studies from BCTU.

IDENTIFYING PARTICIPANTS

Women will be identified by their clinician and asked if they will talk to a member of the clinical research team. If they agree, they will then be given a patient information sheet and will be asked if they are happy to be contacted to get their decision on whether they wish to participate. This will give them ample time to read the patient information sheet, ask any questions and make an informed choice of whether to participate or not.

For the fMRI sub-study, participating women in Scotland will be asked if they are willing to undergo two fMRI scans and two blood tests. A separate patient information sheet and consent form will be given. The scans will take place in Edinburgh.

5.1 CONSENTING PARTICIPANTS

Informed consent will be sought from participants by a member of the Clinical Research Team prior to any study related procedures taking place.

5.2 SCREENING FOR ELIGIBILITY

If participants express an interest in the study, following informed consent, they will be assessed to determine whether they fulfil all the potential eligibility criteria. This will include a 4 week pre-trial eligibility period to determine baseline worst pain score.

5.3 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

The following anonymised information will be monitored and collected for all potential participants with verbal consent:

- Year of birth
- Date in clinic
- Reason for not participating if willing to give a reason
- Reason for not entering the randomisation phase if participant willing to give a reason

5.4 RANDOMISATION

5.4.1 Randomisation Procedures

Immediately after eligibility has been established, baseline questionnaires have been completed, and once written informed consent has been obtained, the women may be randomised into the trial. The Birmingham Clinical Trials Unit will provide third party web-based randomisation with telephone back-up. Patients are entered and randomised into the trial by logging into secure online randomisation available at https://www.trials.bham.ac.uk/GAPP2

Each centre and each randomiser will be provided with a unique log-in username and password in order to randomise a patient online. The online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems. Alternatively, investigators can make one Freephone telephone call (Tel - 0800 953 0274) to the randomisation service. Telephone randomisations are available Monday-Friday, 09:00-17:00. Randomisation Forms will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form will need to be answered before a trial number can be given. If some data items are missing, randomisation will be suspended but can be resumed once the information is available. Only when all eligibility criteria and baseline data items have been provided will a trial number and treatment allocation be given followed by a confirmatory email sent to the randomising investigator, local Principal Investigator and the research nurse.

A minimisation procedure using a computer based algorithm will be used to avoid chance imbalances in in treatment allocation and the following potentially important variables:

1. Presence or absence of dysmenorrhoea (a pain score of ≥4 will be considered significant as some women will have some discomfort/pain with their periods)
2. Psychological distress measured by the General Health Questionnaire (scored as 0-12 with a cut off of 0-1 and 2-12 for minimisation)
3. Use of sex hormonal treatments (combined oral contraceptive, progestogens, levonorgestrel IUS, etc): yes/no.
4. Centre

In addition, to avoid any possibility of the treatment allocation becoming too predictable, we will include a random factor within the algorithm in which for a

proportion of the allocations (1 in 5) true randomisation will be implemented rather than by using the minimised allocation.

5.4.2 Embedded functional magnetic resonance imaging (fMRI) study

Participants from Scottish centres who consent to take part in the fMRI sub-study will be included until the target number of participants is reached. Equal numbers of participants randomised to gabapentin or placebo will be accrued, with any withdrawals from the fMRI protocol being replaced. This will be managed using the trial database and will ensure that all trial team remain blinded to treatment.

5.4.3 Treatment Allocation

Participants will be randomised in an equal (1:1) ratio to either gabapentin or placebo. After randomisation, participants will be allocated an oral treatment pack containing either gabapentin or placebo, both of identical appearance. There will be a drug protocol to follow in their treatment diaries. The same protocol will be used for the placebo. The participants will be allowed to use other medication (including analgesics, see SmPC – Appendix 2) throughout the study period.

5.4.4 Emergency Unblinding Procedures

All participants will be given an emergency card to carry while participating in the study. This will contain contact numbers and drug information.

The blinding code will only be broken in emergency situations for reasons of patient safety, where knowledge of the treatment administered is necessary for the treatment of a serious adverse event, although treatment should always be initiated with the presumption that the woman is taking gabapentin.

The mechanism for code breaking will be:

- An online code break facility will be part of the BCTU randomisation database with access limited to those who can break the blind.

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- The Sponsor will have access to the randomisation database in case of potential SUSARs.

In the event of unblinding before the end of the treatment period, whether accidental or deliberate e.g. due to a serious adverse event, the investigator must document the reasons for unblinding, action taken in the participant's medical records and the Investigator Site File. The local Principal Investigator must promptly notify the BCTU, as participants whose randomisation codes are broken will cease treatment with the study drug, but will continue to be followed up. BCTU will report all instances of unblinding before the end of the treatment period to the Sponsor.

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5.4.5 Withdrawal of Study Participants

Participants may discontinue from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or sponsor for safety, behavioural or administrative reasons. Withdrawal may be from treatment or

from the whole trial. With permission, all data obtained up to point of withdrawal will be used. If a participant does not return for a scheduled visit, every effort will be made to contact the participant. In any circumstance, every effort will be made to document subject outcome, if possible. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational products, return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

If the participant withdraws from treatment then she may be unblinded and if on gabapentin she will be advised to reduce the dose according to a recognised dose reduction protocol.

If the participant discontinues from the trial and also withdraws consent for the disclosure of future information, no further evaluations will be performed and no additional data will be collected.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

Gabapentin 300 mgs hard capsule (over-encapsulated)
Placebo

6.1.2 Study Drug Manufacturer

Sharp (Europe) Ltd.
Waller House
Elvicta Business Park
Crickhowell Powys NP8 1DF
UK

6.1.3 Marketing Authorisation Holder

Actavis UK Ltd
Whiddon Valley
Barnstaple
Devon EX32 8NS

6.1.4 Labelling and Packaging

Packaging and labelling of the over-encapsulated gabapentin will be carried out by:

Sharp (Europe) Ltd.
Waller House
Elvicta Business Park
Crickhowell Powys NP8 1DF

6.1.5 Storage

The medicinal product should be stored at room temperature not above 25°C

6.1.6 Summary of Product Characteristics or Investigators Brochure

The manufacturer may change the SmPC for this study as new information becomes available. The study will use the same version of the SmPC for each reporting period.

The study team will monitor and review changes to the SmPC and consider the impact on the study and revise documents if required.

PLACEBO

The matched placebo will be manufactured, labelled and packed by Sharp (Europe) Ltd

6.2 DOSING REGIME

Participants will start on 1 capsule (300mgs) daily and will increase by 1 capsule (300 mgs) increments every three days until they perceive that they are gaining adequate pain relief, or report side effects (eg dizziness, somnolence, mood changes, appetite and poor concentration), precludes them from further increases, up to a maximum dose of 9 capsules (2700 mgs), as shown in Table 1. The titration phase will last a maximum of 4 weeks. If necessary they will be advised to titrate down to the last tolerated dose with minimal side effects. They will be asked to maintain their best tolerated dose until the end of week 16. Patients will be advised and given written instructions regarding their dosing regimen by a member of the research team (as per table below). It will be recommended that the drug should be taken in three equally divided doses daily. Participants will be advised to remain on the maximum tolerated dose until the end of week 16. The same protocol will be used for the placebo. If the participant wishes to stop treatment then the dose will be reduced according to a dose reduction chart and written instructions will be given.

Table 1 Dose escalation schedule for GaPP2

Day in study	Total number of capsules/day (maximum)	Dosing	Maximum daily dose of gabapentin
1	1	1 capsule night	300 mg
2	1	1 capsule night	300 mg
3	1	1 capsule night	300 mg
4	2	1 capsule twice daily	600 mg
5	2	1 capsule twice daily	600 mg
6	2	1 capsule twice daily	600 mg
7	3	1 capsule three times daily	900 mg
8	3	1 capsule three times daily	900 mg
9	3	1 capsule three times daily	900 mg
10	4	1 capsule twice + 2 capsules at night	1200 mg
11	4	1 capsule twice + 2 capsules at night	1200 mg
12	4	1 capsule twice + 2 capsules at night	1200 mg
13	5	2 capsules twice + 1 capsule once	1500 mg
14	5	2 capsules twice + 1 capsule once	1500 mg
15	5	2 capsules twice + 1 capsule once	1500 mg
16	6	2 capsules three times daily	1800 mg
17	6	2 capsules three times daily	1800 mg
18	6	2 capsules three times daily	1800 mg
19	7	2 capsules twice + 3 capsules night	2100 mg
20	7	2 capsules twice + 3 capsules night	2100 mg
21	7	2 capsules twice + 3 capsules night	2100 mg
22	8	3 capsules twice + 2 capsules once	2400 mg
23	8	3 capsules twice + 2 capsules once	2400 mg
24	8	3 capsules twice + 2 capsules once	2400 mg

25	9	3 capsules three times daily	2700 mg
26	9	3 capsules three times daily	2700 mg
27	9	3 capsules three times daily	2700 mg
28 - 112	Remain on maximum tolerate dose until the end of week 16. (not exceeding 2700mg or 9 capsules per day). Daily dose should be divided equally into 3 doses.		

6.3 DOSE CHANGES

See above.

6.4 PARTICIPANT COMPLIANCE

All participants will be given a diary at randomisation and asked to document daily pain relieving drug use (including self-medication and alternative treatments, e.g. acupuncture). The diary also includes specific healthcare resource use questions (e.g. attendance at GP, hospital).

(We have removed this to reflect real clinical practices)

OVERDOSE

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

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

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

OTHER MEDICATIONS

6.4.1 Permitted concomitant medications

Participants may take concomitant medications during the course of the study as per the SmPC – Appendix 2. We will record use of medications taken to treat pain at each visit . We will follow IMMPACT guidelines (17), and only allow patients to remain on analgesic medications if they have been used as part of a stable regimen for at least 4 weeks prior to screening. We will collect the indication for the medication. The following will be permitted:

- opioids (<90 mg per day of morphine equivalents, e.g. codeine, tramadol)
- combination opiate analgesics (e.g. codeine and paracetamol [<3 g per day])
- tricyclic antidepressants
- benzodiazepines
- aspirin at doses ≤300 mg/day
- topical analgesics
- atypical benzodiazepines if used at a stable bedtime dose for sleep.

- Selective serotonin reuptake inhibitors will be allowed if used as a stable regimen for at least 3 months prior to baseline for depression.
- Non-steroidal anti-inflammatory drugs (NSAIDS) will also be permitted as rescue analgesia if dosed in accordance to package labelling for short-term treatment of not more than 7 days in total duration.

We will allow paracetamol as rescue analgesia for breakthrough pain but participants will be instructed not to exceed 3 g per day.

This list is not exhaustive, refer to the SmPC – Appendix 2.

6.4.2 Prohibited Medications

A comprehensive list of contra-indicated medications can be found in the SmPC – Appendix 2. As per the eligibility criteria, participants will not be randomised if taking gabapentin or pregablin.

7 STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

- Medical history
- Pregnancy test
- Prior and concomitant medications
- Adverse events

7.2 STUDY ASSESSMENTS (see Table 2 and appendix 1)

Week -4 **Visit 1**

Informed consent

Pre-trial entry eligibility screening (safety assessments)

- Medical history
- Contact details
- Medications

Week -4 to -1 4 weekly worst and average NRS pain scores (via text/telephone)

Visit 1A (may be at the same time as visit 1) (fMRI Sub-study participants only)

Informed consent (fMRI)

Brain fMRI (before randomised to treatment)

- Safety assessments
- fMRI safety checklist
- Blood sample

Baseline Week 0*	**Visit 2** Eligibility confirmed Pregnancy test Discuss contraception Demographics Questionnaires Saliva collection Serious Adverse Events Randomisation to gabapentin or placebo Treatment diary given to patient Current analgesic use Healthcare professional visits
Week 1 – 4	Dose escalation o Treatment diary
Week 4/5	**Visit 3** Collect medication Discuss contraception Adverse events Analgesic use
Weeks 5 - 12	Maintain maximum tolerated dose o Treatment diary
Week 8 -10	**Visit 4**** Collect medication Discuss contraception Adverse events Analgesic use
Week 13 - 16	Weekly NRS pain scores (via text/telephone) **Visit 4A** Brain fMRI
Week 16	**Visit 5** Questionnaires Collection of treatment diary Collection of unused study medication Unblinding Adverse events Analgesic use Visits to healthcare professionals
Weeks 17 – 19	Down titration if necessary (remote consultation if req) o Adverse events

*This can be up to 2 weeks after the fourth weekly NRS is due, to accommodate patient ability to make appointments and to schedule in fMRI scans for patients participating in the sub-study in Edinburgh

** This can be a telephone visit if no medication needed.

7.2.1 Daily Treatment Diary

The following measures will be completed by the subject in a daily treatment diary beginning on day 1 of treatment until Visit 5.

- Dose of gabapentin taken
- Reason for any change in trial medication dose
- Alternative therapies used
- Any visits to a healthcare professional
-

Table 2 Schedule of outcome assessment for the clinical trial and mechanistic studies

Phase	Run-in	Baseline, randomisation & treatment dispensed	Titration	Treatment		End of study & unblinding	Taper
Duration (weeks)	-4 to -1	0	1-4	5-12	13-16		17-19
All participants							
Weekly worst and average NRS	**x x x x**				**x x x x**		
Saliva sample		**X**					
SF12		**X**				**X**	
BPI		**X**				**X**	
PCQ		**X**				**X**	
SAQ		**X**				**X**	
BFI		**X**				**X**	
GHQ-12		**X**				**X**	
WPAIQ		**X**				**X**	
PainDETECT™		**X**				**X**	
PUF		**X**					
Adverse events			**X**	**X**	**X**	**X**	**X**
Permitted / Concomitant medication	**X**		**X**	**X**	**X**		**X**
Adherence or discontinuation			**X**	**X**	**X**		**X**
fMRI Substudy (50 Scottish participants – fMRI carried out in Edinburgh)							
fMRI brain	**X**				**X***		
Blood sample	**X**				**X**		
***** **second fMRI should take place a minimum of 8 weeks following randomisation**							

7.2.2 Functional magnetic resonance imaging (fMRI)

50 participants from centres in Scotland who have provided informed consent and are eligible to participate in the substudy will undergo functional magnetic resonance imaging (fMRI) of the brain at baseline (0 weeks) and after at least 8 weeks of treatment but before end of treatment. All fMRI scans (3T Siemens MRI) will be performed at the CRIC (Clinical Research Imaging Centre) in Edinburgh using previously validated standardised sequences. fMRI is a safe, non-invasive, sensitive and reliable technique used to detect central changes in patients and to establish the effects of pain-relieving drugs. Each fMRI will last ~60 mins and include measurements of brain activity at rest and in response to noxious stimulation (using pin pricks) of both a control site and an area where the clinical pain is perceived). In our pilot study we carried out 12 fMRI scans and despite the small sample size, our results support an effect of gabapentin on brain activity in women with CPP. Furthermore, they suggest a central component to CPP that can be suppressed with gabapentin. Participants tolerated the fMRI and stimuli well. Pain levels vary according to the woman's menstrual cycle. We will carry out the fMRI at the same stage of each participant's cycle. We will take a 15 ml blood sample at each fMRI to measure estradiol and progesterone levels. The storage and analysis of the blood samples will take place in the Queen's Medical Research Institute, University of Edinburgh. After the study these will be stored, with consent for use in other related studies.

8 DATA COLLECTION

Screening: Following consent, a member of the research team will carry out a screening visit to assess eligibility. All data will be recorded on a CRF and transferred to a secure database.

Participant Log: The clinical research team will keep an anonymised electronic log of women who fulfil the eligibility criteria, women who are invited to participate in the study, women recruited and women who leave the trial early. Reasons for non-recruitment (eg non-eligibility, refusal to participate, administrative error) will also be recorded. We will attempt to collect reasons for non-participation from women who decline to take part after previously providing contact details. During the course of the study, we will document reasons for withdrawal from the study and loss to follow-up if available.

NRS will be collected in eligibility phase (weeks -1 - -4) and again between weeks 13 – 16 of treatment.

Treatment diaries: details are documented in Section 6.5.

Questionnaires: A questionnaire will be given to all participants before randomisation (Baseline) and at 16 weeks post randomisation. This will include questions to capture the baseline demographic and clinical characteristics of the participants and include the following validated tools:

1. SF12
2. BPI (Brief pain inventory)
3. PCQ (Pain catastrophizing questionnaire)
4. SAQ (Sexual activity questionnaire)
5. WPAIQ (Work and productivity Activity Impairment questionnaire)

6. GHQ (General health questionnaire)
7. BFI (Brief Fatigue Inventory)
8. PainDETECT™
9. PUF (Pelvic Pain and Urinary/Frequency (PUF) Patient Symptom Scale) (baseline only)

All questionnaires will be anonymised and completed in private.

Source data for this trial will be defined as:

- Participant answered questionnaires
- Researcher completed CRFs
- Clinical notes
- Treatment diaries
- Pain scores recorded on the database

Participants will be asked to provide saliva samples using specialised kits for DNA extraction (Oragene®). The advantage of these kits over blood collection is their non-invasiveness and ease of use. They typically yield large quantities (>100 ug) of high-quality DNA, sufficient for high-throughput applications such as whole-genome or exome sequencing (requiring 1-5 ug DNA). The kits will be stored in the QMRI with Prof Horne as custodian in laboratory refrigerators at 4°C. Analysis may take place in another approved laboratory. . After the study these will be stored, with consent for use in other related studies.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

We have based our sample size on being able to detect a minimally important difference (MID) in NRS scores with high levels of power. Studies have shown the MID in this population to be around 1 point on a 0-10 scale (www.immpact.org/publications.html). Our pilot study showed worst and average pain scores to have standard deviations between 2.0 and 2.5. If the SD is at the lower end of these estimates, 86 patients in each group (172 in total) would be required to have 90% power (p=0.05) to detect a difference of 1 point. If the SD is at the higher end, we could detect the same difference with 80% power (p=0.05) with 100 patients in each group. We have assumed the latter SD (2.5) to be conservative. To account for any increase in the risk of type I error that may be associated with having co-primary outcome measures we have applied a Bonferonni correction (alpha reduced to 0.025 from 0.05) which increases the sample size to 120 per group. Furthermore, to account for an expected average 20% lost to follow-up we will randomise 150 per group, 300 patients in total. Based on previous studies and statistical techniques used to analyse the data (www.fmrib.ox.ac.uk/fsl), we estimate that we will need to recruit 50 women (25 per group) for the fMRI substudy to identify significant differences using mixed effect analyses.

9.2 PROPOSED ANALYSES

Data analysis will be undertaken by BCTU. The analysis will be by intention to treat. Every attempt will be made to gather data on all women randomised, irrespective of compliance with the treatment protocol. Appropriate baseline characteristics, split by treatment group, will be presented for each outcome. Point estimates, 95% confidence intervals and p-values from two-sided tests will be reported. A full Statistical Analysis Plan will be drafted prior to any analysis and provided to independent Data Monitoring Committee for review.

9.2.1 Primary Outcome Analysis

We will use a linear regression model to estimate differences in worst and average NRS scores between the two treatment groups, including baseline score and the minimisation variables (listed in section 5.4.1) as covariates. The p-value from the associated chi-squared test will be produced and used to determine statistical significance. A Bonferroni correction will be applied here as there are two primary outcomes. Further analysis using a repeated measures (multi-level) model will also be performed incorporating all eight recorded scores.

9.2.2 Secondary Outcome Analysis

Data from the other continuous measures (SF-12 quality of life, BPI, PCQ, SAQ, WPAIQ, BFI, PainDETECT™ and GHQ) will be analysed in a similar manner to the primary measure. Other outcome measures (use of permitted analgesic medication, satisfaction) will be analysed using standard methods (tests for trend, absolute/relative risks). Further analysis on pain scores will include an examination of the proportion of women that have a 30% reduction in average and worst score from baseline as the outcome. A log-binomial regression model will be used here to generate adjusted relative risks.

9.2.3 Sub-group analysis

This will be limited to the same variables which were used as minimisation variables. Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the linear regression model) will be performed prior to any examination of effect estimate within subgroups.

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9.2.4 Handling missing data and other sensitivity analysis

Every attempt will be used to collect full follow up data on all women. In particular, participants will continue to be followed up even after protocol treatment violation. It is thus anticipated that missing data will be minimal. Patients with completely missing primary outcome data or with only one of four scores recorded will not be included in the primary analysis. Secondary sensitivity analyses will be performed to investigate the impact of any missing data for the primary outcome, this will include a worst score assumption. We will also simulate missing responses using a multiple imputation approach.

9.2.5 Timing of analyses

An interim report including the analysis of major endpoints will be provided in strict confidence to a Data Monitoring Committee at intervals of at least 12 months, or as to a timetable agreed by the DMC prior to study commencement (see Section 12.3 for further details on trial data monitoring including the use of pragmatic stopping

criteria). Final analysis will be performed once all women have completed full follow-up unless early stopping is recommended by the DMC.

9.3 PROPOSED ANALYSES – MECHANISTIC STUDY

The fMRI data will be analysed using a voxelwise approach and using a hierarchical linear model. Analysis of variance will be performed to identify the extent of drug effect and to confirm the brain areas on which gabapentin acts in women with CPP. In the gabapentin cohort, univariable and multivariable linear regression will be performed to examine whether baseline scan data can predict response to treatment (NRS). In addition, we will investigate up to nine clinical variables measured at baseline to determine whether they correlate with response to treatment. These will include the minimisation variables (presence of dysmenorrhoea/psychological distress/current use of hormonal treatment) along with measures of intensity and of nature of pain (e.g. PainDETECT^{TM}), number of functional systems involved (as a measure of organ specific versus generalised pelvic pain syndrome) and PUF score.

Pharmacogenetic sub-group analysis: DNA will be extracted from all saliva samples using standard protocols. Genome-wide genetic information related to pharmacogenetics of gabapentin will be analysed in order to obtain a better understanding if there are any genetic reasons differentiating responders from non-responders and possibly enhancing our ability to predict intolerance to that drug. These effects can be readily detectable in sample sizes of a few hundred patients. However, if insufficient for adequate analysis within this study, the data can be pooled with any subsequent work in order to reach a meaningful result and further our understanding of how gabapentin interacts with the human body

10 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Participants will be instructed to contact the clinical research team at any time after consenting to join the trial if they have an event that requires hospitalisation, or an event that results in persistent or significant disability or incapacity. Gabapentin is generally well tolerated in the management of other chronic pain conditions and SAEs are not anticipated. Any SAEs that occur after joining the trial will be reported in detail in the participant's medical notes and followed up until resolution of the event.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC – Appendix 2)

The reference safety information is the section in SmPC that describes the known adverse events and as of the date of the protocol, this is found in the SmPC for 300mg gabapentin whereby Actavis is the manufacturing authorisation holder.

Common or very common expected adverse events (as detailed in the SmPC) will be recorded in the case report form (CRF), but not on the AE log, unless they meet seriousness criteria. Expected AEs which are 'uncommon', 'rare' or where the

frequency is 'unknown', will be recorded on the AE log and reported as an SAE if seriousness criteria is met.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be reported in detail in the CRF (common/very common expected AEs) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs present at the last visit must be followed up until resolution of the event.

Any SAEs that occur after joining the trial will be reported in detail in the participant's medical notes and followed up until the event has resolved or a final outcome has been recorded or reported as necessary.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria. Hospitalisation for an exacerbation of their pelvic pain will not be reported as an SAE as this is a known reason for hospitalisation in this population group.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC) or Investigators Brochure.

10.2 IDENTIFYING AEs AND SAEs

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until end of treatment. During the 4 week pre-treatment screening period, only SAEs will be recorded and reported. Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Questions regarding mood are captured in the GHQ questionnaire. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. fMRI. Reports of abnormal findings will be sent to the PI and permission will be asked of the participant to report these findings, if significant, to their GP.

10.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator. For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected (i.e. SUSARs) will be unblinded.

The Investigator is responsible for assessing each AE.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the /Summary of Product Characteristics.

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

10.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SmPC/IB.

Unexpected: the AR is not consistent with the toxicity in the SmPC/IB.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

ACCORD will onward report all SAEs to BCTU. This will be transmitted by email to the GaPP2 trial inbox (GaPP2@adf.bham.ac.uk) within 7 days..

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs.

10.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. The Investigator should follow each AE or SAE until the event has resolved or a final outcome has been recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF, AE log or SAE report form.

11 PREGNANCY

Pregnancy is not considered an AE or SAE; however, the Investigator will collect pregnancy information for any participants who become pregnant while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant participants will be withdrawn from the treatment and will be followed up until the outcome of the pregnancy.

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and Trial Co-ordinator

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

The GaPP2 Trial Office

The Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for the day to day management of the GaPP2 Trial. The Trial Manager, based at University of Edinburgh, will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the data forms for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

The GaPP2 Trial Office will also be responsible for providing all trial materials, including an Investigator Site File (ISF), with copies of all essential documents, and a trial stationary folders containing all required printed materials e.g. participant information sheets, consent forms. These will be supplied to each collaborating centre, after relevant local research governance approval has been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), The Trial Office will help resolve any local problems that may be encountered in trial participation.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial.
The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the International Committee on Harmonisation Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the

possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

The BCTU Trial office will forward TSC meeting minutes to the Sponsor and funder. Terms of reference of the Trial Steering Committee and the draft template for reporting will be agreed at the inaugural meeting.

12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. If one treatment really is substantially better or worse than any other with respect to the primary outcome, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than any other. To protect against this, during the main period of recruitment to the study, interim analyses of the primary outcome and adverse events will be supplied, in strict confidence, to the independent DMC, along with updates on results of other related studies, and any other analyses that the DMC may request. The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) "proof beyond reasonable doubt"[1] that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

The BCTU Trial office will forward DMC open meeting minutes to the Sponsor and funder. Terms of reference of the Trial Steering Committee and the draft template for reporting will be agreed at the inaugural meeting.

INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.4 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

12.5 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the central monitoring plan which will be determined by the sponsor's risk assessment.

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by either the ACCORD Clinical Trials Monitor and/or Trial Coordinator as and when required who would require direct access to source data and documents as requested.

1 Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p<0.001$ (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

The study will also adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the trial data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables.

Trusts may also be subject to inspection by the Medicines and Healthcare Products Regulatory Agency and/ or by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF. This will be written by the trial manager in collaboration with ACCORD monitors.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14 STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

14.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 24 hours of becoming aware of the violation.

14.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.5 END OF STUDY

The end of study is defined as the last participant's last treatment dose.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

14.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Participants will be unblinded at the end of the study and if taking gabapentin will have the option to continue on treatment or will be tapered off treatment. Participants who have been on placebo will be given the choice to start on gabapentin which will be prescribed by their clinician.

14.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

APPENDIX 1: GaPP2 Study - Flowchart

Possible recruit identified by clinician

- Pelvic pain for >3 months
- No pathology at laparoscopy <36 months >2 weeks
- Not on gabapentin/pregabalin
- Not pregnant – planning pregnancy
- Asked permission to be approached by research staff

Approach by research staff

- GaPP2 Patient Information Sheet (PIS)
- fMRI substudy PIS (Scotland)
- Asked permission to be contacted regarding entry to study

Visit 1 (Pre-trial entry eligibility) (weeks -4)

Participant	Research Team
• Informed consent • Pre -screening	• Eligibility • Contact details

Weekly contact (weeks -4 - -1)

- NRS worst and average scores
- Option to withdraw
- fMRI (Scotland only) (Blood sample)**Visit 1A**

Visit 2 (Baseline week 0)

Participant	Research Team
• Screening • Randomised • Treatment diary • Questionnaires • Saliva sample	• Confirm eligibility • Review SAEs • Option to withdraw

Visit 3 (week 4)

Participant	Research Team
• Collect medication *(if required)*	• Review treatment diary • Review AEs • Option to withdraw

Visit 4 (week 10) *(can be remote consultation)*

Participant	Research Team
• Collect medication *(if required)*	• Review treatment diary • Review AEs • Option to withdraw

Weekly text message (weeks 13-16)

- NRS worst and average scores
- Option to withdraw
- fMRI (Scotland only) (Blood sample) **Visit 4A**

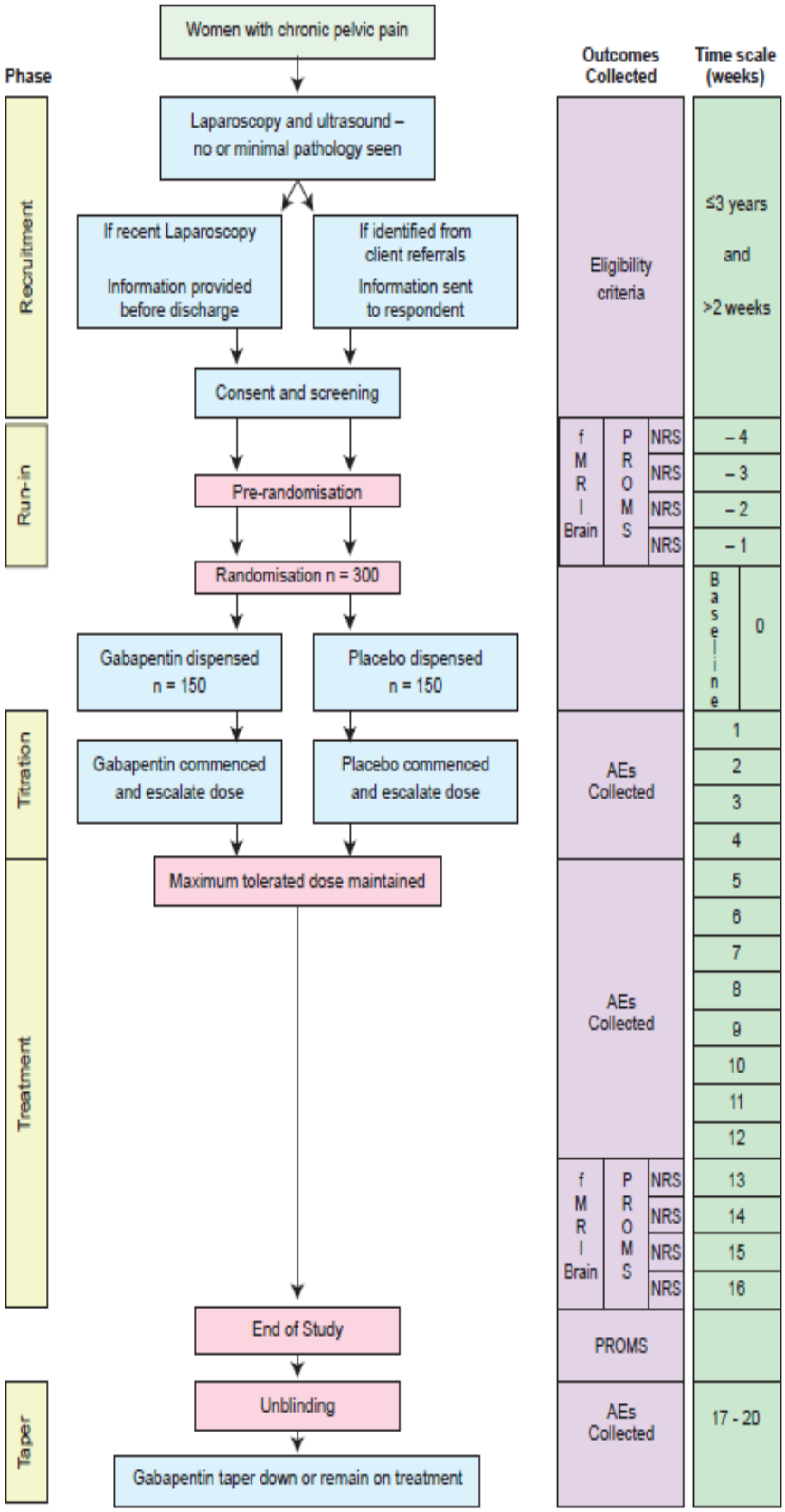
Visit 5 (week 16)

Participant	Research Team
• Questionnaires • Unblinding	• Collect diary • Collect medication • Review AEs • Review treatment

Taper down of treatment (weeks 17-19)

As required and remote consultations

Flowchart: A multi-centre randomised controlled trial of the efficacy and mechanism of action of gabapentin for the management of chronic pelvic pain in women



16 Gabapentin 300mg Capsules

Summary of Product Characteristics Updated 03-Aug-2015 | Actavis UK Ltd

1. Name of the medicinal product

Gabapentin Actavis 300mg capsules

2. Qualitative and quantitative composition

Each capsule contains 300mg of gabapentin

For excipients, see 6.1

3. Pharmaceutical form

Capsules,hard

Size 1, yellow-yellow, hard gelatin capsules printed with C and GK.

4. Clinical particulars

4.1 Therapeutic indications

Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation in adults and children aged 6 years and above (see section 5.1).

Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalisation in adults and adolescents aged 12 years and above.

Treatment of peripheral neuropathic pain

Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

4.2 Posology and method of administration

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid intake (e.g. a glass of water).

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1		
DOSING CHART – INITIAL TITRATION		
Day 1	Day 2	Day 3
300mg once a day	300mg two times a day	300mg three times a day

Epilepsy

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy. When in the judgment of the clinician there is a need for dose reduction, discontinuation, or substitution with an alternative medication, this should be done gradually over a minimum of one week.

Adults and adolescents:

In clinical trials, the effective dosing range was 900 to 3600mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300mg/day increments every 2-3 days up to a maximum dose of 3600mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800mg/day is one week, to reach 2400mg/day is a total of 2 weeks, and to reach 3600mg/day is a total of 3 weeks.

Dosages up to 4800mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

Children aged 6 years and above:

The starting dose should range from 10 to 15mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to

35mg/kg/day. Dosages up to 50mg/kg/day have been well tolerated in a long term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.

Peripheral neuropathic pain

Adults

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300mg/day increments every 2-3 days up to a maximum dose of 3600mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800mg/day is one week, to reach 2400mg/day is a total of 2 weeks, and to reach 3600mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

Instruction for all areas of indication

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

Use in elderly patients (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

Use in patients with renal impairment Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin 100mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

Table 2

DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION

Creatinine Clearance (ml/min)	Total Daily Dose[a] (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150[b] -600
<15[c]	150[b] -300

[a] Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79ml/min).

[b] To be administered as 300mg every other day.

[c] For patients with creatinine clearance <15ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15ml/min receive).

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400mg, then 200 to 300mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300mg dose following each 4-hour haemodialysis treatment is recommended.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has 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 Gabapentin.

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.

Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking antiepileptic drugs including gabapentin (see section 4.8).

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered (see section 4.8).

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractory patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Dizziness, somnolence, loss of consciousness, confusion, and mental impairment

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should

be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Laboratory tests

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

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

In a study involving healthy volunteers (N=12), when a 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Coadministration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.

4.6 Pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely.

It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms.

Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

4.8 Undesirable effects

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (> 1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100) and rare (>1/10,000; <1/1,000). Additional reactions reported from the post-marketing experience are included as frequency 'not known' (cannot be estimated from the available data). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Very Common: Viral infection

Common: Pneumonia, respiratory infection, urinary tract infection, infection, otitis media

Blood and the lymphatic system disorders

Common: leucopenia

Rare: thrombocytopenia

Immune system disorders

Rare: allergic reactions (e.g. urticaria)

Not known: Hypersensitive syndrome, a systemic reaction with a variable presentation that can include fever, rash, hepatitis lymphadenopathy, eosinophilia and sometimes other signs and symptoms.

Metabolism and Nutrition Disorders

Common: anorexia, increased appetite

Uncommon: hyperglycaemia (most often observed in patients with diabetes)

Rare: hypoglycaemia (most often observed in patients with diabetes)

Not known: hyponatraemia

Psychiatric disorders

Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal

Rare: hallucinations

Nervous system disorders

Very Common: somnolence, dizziness, ataxia,

Common: convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes

Uncommon: hypokinesia, mental impairment

Rare: movement disorders (e.g. choreoathetosis, dyskinesia, dystonia), loss of consciousness

Not Known: myoclonus, syncope

Eye disorders

Common: visual disturbances such as amblyopia, diplopia

Ear and Labyrinth disorders

Common: vertigo

Rare: tinnitus

Cardiac disorders

Rare: palpitations

Vascular disorder

Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Gastrointestinal disorders

Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence

Rare: pancreatitis

Hepatobiliary disorders

Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders

Common: facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne

Rare: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia

Not known: Drug rash with eosinophilia and systemic symptoms (see section 4.4)

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia, myalgia, back pain, twitching

Renal and urinary disorders

Common: incontinence

Rare: acute renal failure

Reproductive system and breast disorders

Common: impotence

Not known: breast hypertrophy, gynaecomastia

General disorders and administration site conditions

Very Common: fatigue, fever

Common: peripheral or generalized oedema, abnormal gait, asthenia, pain, malaise, flu syndrome

Uncommon: fall

Rare: withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain.

Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.

Investigations

Common: WBC (white blood cell count) decreased, weight gain

Rare: Blood glucose fluctuations in patients with diabetes, elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin

Injury and poisoning

Common: accidental injury, fracture, abrasion

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear (see section 4.4).

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49g. 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, minimize toxicity from overdoses.

Although gabapentin can be removed by haemodialysis, based on prior experience it is usually not required.

However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000mg/kg.

Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Other antiepileptics

ATC code: N03AX12

The precise mechanism of action of gabapentin is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives. The binding site for gabapentin has been identified as the alpha$_2$-delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine or N-methyl-daspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems *in vitro*, but only at concentrations greater than 100µM, which are not achieved *in vivo*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*.

Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder

rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years). The data from this additional post-hoc analysis are summarised in the table below:

Response (≥ 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2µg/ml and 20µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300mg (N = 7)	400mg (N = 14)	800mg (N=14)

	Mean	%CV	Mean	%CV	Mean	%CV
C_{max} (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
t_{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) µg•hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

C_{max} = Maximum steady state plasma concentration

t_{max} = Time for C_{max}

T1/2 = Elimination half-life

AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose

Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose

NA = Not available

Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Metabolism

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced.

Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

5.3 Preclinical safety data

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000mg/kg/day and to rats at 250, 1000, and 2000mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumors was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000mg/kg/day are 10 times higher than plasma concentrations in humans given 3600mg/day. The pancreatic acinar cell tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade

surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. 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.

Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000mg/kg (approximately five times the maximum daily human dose on a mg/m^2 of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600mg, (four, five or eight times, respectively, the human daily dose on a mg/m^2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hind limbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000mg/kg/day during organogenesis and in rats given 500, 1000, or 2000mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600mg on a mg/m^2 basis.

No effects were observed in pregnant mice given 500mg/kg/day (approximately 1/2 of the daily human dose on a mg/m^2 basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000mg/kg/day in a fertility and general reproduction study, 1500mg/kg/day in a teratology study, and 500, 1000, and 2000mg/kg/day in a

perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600mg on a mg/m^2 basis.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose Monohydrate

Maize Starch

Talc

Capsule shell

Titanium dioxide, E171

Yellow iron oxide, E172

Gelatin

Printing ink

Shellac, E904

Propylene glycol, E1520

Black iron oxide, E172

Potassium hydroxide, E525

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Aluminium/transparent PVC blisters

Each pack will contain either 30, 50, 60, 100 or 120 capsules.

Each blister strip will contain 10 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Actavis UK Limited (Trading style: Actavis)

Whiddon Valley

Barnstaple

North Devon

EX32 8NS

8. Marketing authorisation number(s)

PL 0142/ 0567

9. Date of first authorisation/renewal of the authorisation

28/10/05

Renewal – 20.01.2015

10. Date of revision of the text

01.06.2015

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