



European Medicines Agency  
*Pre-authorisation Evaluation of Medicines for Human Use*

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**WITHDRAWAL ASSESSMENT REPORT**  
**FOR**  
**LACOSAMIDE PAIN UCB PHARMA**

International Nonproprietary Name: lacosamide

**Procedure No. EMEA/H/C/894**

D180 Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.

This should be read in conjunction with the “Question and Answer” document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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## **I. RECOMMENDATION**

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Lacosamide Pain UCB Pharma, in the treatment of neuropathic pain associated with diabetic peripheral neuropathy in adults, is not approvable as major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Based on the review of original data and responses from the Applicant, the major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

1. The clinical relevance of the observed low efficacy has not been sufficiently demonstrated.
2. The safety profile, foremost the cardiac related effects, but also the CNS effects in perspective of the intended target population and the treatment length.
3. Benefit/risk relationship given the safety profile and the questionable relevance of the observed effect.

### **Proposal for Questions to be posed to additional Experts**

There is at present no proposal for questions to be posed to additional experts.

### **Inspection issues**

None.

## **II. EXECUTIVE SUMMARY**

### **II.1 Administrative information**

This Day 180 LoQ is based on the Day 150 JAR and the subsequent comments from the CMSs.

### **II.2 Problem statement**

Diabetes affects approximately 246 million people worldwide and it is estimated that 20–30 million people worldwide are affected by symptomatic diabetic neuropathy. Growing rates of obesity and the associated increase in the prevalence of Type 2 diabetes could cause these figures to double by the year 2030. The prevalence of diabetic neuropathy also increases with time and poor glycaemic control, and severe diabetic polyneuropathy can develop in young adults within a few months after the onset of Type 1 diabetes if the diabetes is poorly controlled.

More than 80% of patients with clinical diabetic neuropathy have a distal symmetrical form of the disorder. In this neuropathic pattern, signs and symptoms start—and remain more pronounced—in the feet, and go on to affect more-proximal parts of the lower limbs and eventually the distal parts of the upper limbs, indicating that the longest nerve fibres are affected first. Shorter sensory axons subsequently become involved, accounting for neuropathic manifestations in more-proximal parts of the limbs and eventually the anterior trunk. The neuropathy usually becomes symptomatic several years after the onset of Type 1 diabetes, but can often also reveal diabetes of mature onset. Symptoms of diabetic neuropathy include numbness, burning feet, pins-and-needles sensations and lightning pains. The symptoms are often most pronounced at night, and the burning pains can be exacerbated by contact.

In patients with diabetes mellitus 20% to 24% will eventually experience the painful form of diabetic neuropathy. Because of the difficulties in maintaining long-term glycaemic control, most patients require some form of symptomatic therapy for their pain symptoms.

Attempts to treat diabetic neuropathies can be divided into those directed at modification of the underlying disease process and those directed toward symptom suppression.

For symptom alleviation, diabetic peripheral neuropathic pain has been widely treated with tricyclic antidepressants. However, the utility of substances of this group is limited by side effects associated with their binding to multiple other receptors. Other agents used to treat diabetic peripheral neuropathic pain include antiarrhythmics, selective serotonin reuptake inhibitors, opioids, anticonvulsants and selective serotonin and norepinephrine reuptake inhibitors. Hitherto, all pharmacological treatments of pain associated with diabetic neuropathy have had limited success.

### **II.3 About the product**

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsant drug candidates. Lacosamide has demonstrated antiepileptic activity in different rodent seizure models for generalized and complex partial-onset seizures and status epilepticus, ie, maximal electroshock seizures (MES), hippocampal kindling, audiogenic seizures (AGS), self sustaining status epilepticus (SSSE), and in 1 chemoconvulsant-induced seizure model. It is also effective in animal models of neuropathic pain. Electrophysiological studies have shown that lacosamide enhances the slow inactivation of sodium channels by attenuating the proportion of available channels in a time- and voltage-dependent manner. This leads to a reduction of sodium channel long-term availability which increases activation thresholds and reduces hyperexcitability of neurons characteristic for both epilepsy and neuropathic pain. Lacosamide interacts with collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axon outgrowth. The interaction of lacosamide with CRMP-2 may possibly represent a second mode of action of lacosamide.

### **II.4 The development programme/Compliance with CHMP Guidance/Scientific Advice**

The phase III development program for LCM consists of three placebo-controlled parallel-design trials (SP742, SP743 and SP768) and one withdrawal design trial (SP746-subtrial), all completed, for treatment of diabetic neuropathic pain in adults.

LCM has also been evaluated for the treatment of subjects with mixed neuropathic pain and post-herpetic neuralgia.

A trial is planned investigating the efficacy of 400 mg/day (only) compared with placebo in diabetic neuropathic pain.

Formal scientific advice has not been given by CHMP. There is no paediatric development programme.

### **II.5 General comments on compliance with GMP, GLP, GCP**

All pivotal toxicity studies, including the majority of the safety pharmacology studies were performed in accordance with GLP principles. Statements have been submitted confirming that clinical studies were conducted in accordance with the principles of GCP and in compliance with the Helsinki declaration. There are no GCP inspection issues identified in the dossier. The pharmacokinetic studies were performed in accordance with GCP and GLP. No GMP issues have been identified during assessment of Module 3.

### **II.6 Type of application and other comments on the submitted dossier**

The application is submitted in accordance with Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application, (i.e. complete dossier with administrative, quality, non-clinical and clinical data). The application is submitted within the centralised procedure with Dr Salmonson acting as Rapporteur and Professor Nisticò acting as Co-Rapporteur. The application concerns Lacosamide (LCM; SPM 927, previously referred to as harkoseride) film-coated tablets 50, 100, 150,

200, 250 and 300 mg which contain the active substance [R]-2-acetamido-N-benzyl-3-methoxypropionamide.

### III. SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 Quality aspects

##### Drug substance

###### *General properties and manufacture*

Lacosamide is a new chemical entity, which constitutes the (R)-enantiomer of a derivative of D-serine. Lacosamide is a white to light yellow powder with melting point 140-146°C. It may exist in a number of polymorphic forms, and the drug substance used in the pharmaceutical formulations of this application may comprise the two polymorph modifications 1 and 2. Lacosamide (both modifications 1 and 2) is sparingly soluble in aqueous solvents at both 25°C and 37°C.

The manufacturing process comprises five synthesis steps, which are followed by recrystallization. Briefly, the process involves the conversion of the chiral amino acid, D-serine, to lacosamide.

The two manufactures uses two slightly different synthesis processes

###### *Characterisation of and potential impurities in the drug substance*

The structure of lacosamide is supported by the route of synthesis and has been verified by elemental analysis and suitable spectroscopic measurements.

As regards polymorphism, a comprehensive summary of the formation and characterisation of possible polymorphs of lacosamide has been provided. It has been shown that modifications 1 and 2 are the routinely formed polymorphs in the synthesis process.

These modifications are very similar in physico-chemical properties and exhibit comparable solubility in aqueous media.

For the identification of drug related impurities in the drug substance, laboratory studies comprising HPLC-MS experiments have been conducted and structure proposals for observed impurities have been made.

The impurities observed in drug substance batches under normal conditions and degradation products found under forced/accelerated conditions have been listed. Possible degradation pathways have also been suggested.

###### *Control of drug substance*

The drug substance is controlled according to acceptable and justified specifications. The identity is verified by two independent methods (IR and HPLC) and inorganic impurities are controlled by tests for sulphated ash and heavy metals. Tests for melting point and water content are included in the specification. Residual solvents are acceptably specified and controlled by GC. Chiral purity is confirmed by HPLC and specific optical rotation is routinely monitored. The assay and drug related impurities are determined by HPLC procedure. The specified impurities are in accordance with the ICH recommendations.

The analytical procedures have been suitably validated according to ICH guidelines.

Batch analysis data have been provided for all drug substance batches used in non-clinical, clinical efficacy and safety, bioavailability and primary stability studies. All data complied with specifications.

###### *Stability of drug substance*

Several lacosamide batches have been subjected to ICH stability studies. All results remain within the specification up to 60 months. Also, under intermediate and accelerated conditions no changes have

occurred up to 24 months of storage. Stress testing on the drug substance has also been carried out both on the solid substance and on lacosamide in aqueous solution. No racemization was observed in the solid state upon heat exposure. The stability data provided support a re-test period of 3 years.

## **Drug Product**

### ***Introductory remarks***

Lacosamide has been developed in parallel for two indications, treatment of partial-onset seizures and treatment of neuropathic pain, respectively. For the seizure indication, an application for marketing authorization (MAA) was submitted to EMEA on 2 May 2007 including three different pharmaceutical formulations, film-coated tablets (50, 100, 150, 200, 250 and 300 mg), syrup (15 mg/ml) and solution for infusion (10 mg/ml). The current MAA for lacosamide is submitted for the indication treatment of neuropathic pain associated with diabetic peripheral neuropathy. The strengths initially developed for the oral treatment of neuropathic pain were immediate release tablets containing 50 mg, 100 mg, 150 mg, 200 mg, 250 mg or 300 mg lacosamide. The maximum daily dose is initially proposed was 600 mg, but this has now been reduced to 400 mg and the two highest tablet strengths have therefore been withdrawn from the application. The scientific discussion below will in some instances also include the 250 and 300 mg strengths. The composition of the tablet cores are the same as those developed for epilepsy.

### ***Composition, development and manufacture of the finished product***

Lacosamide film-coated tablets are immediate release, colour coated, oval, biconvex tablets of different size packaged in PVC/PVDC/Al blisters. The compositions of the different strengths are proportional and they are manufactured from one common granulate. The core excipients have widespread use in this type of dosage form and comply with Ph. Eur. monographs or acceptable in-house specifications. The tablets are manufactured by a standard process comprising wet granulation, fluid bed drying, compression and film-coating and are coated with ready-to-use commercial coating agents. Process validation will be performed according to a bracketing design and this is considered acceptable since all strengths of tablets will be manufactured from the same granulate.

The strengths are compositionally proportional and all strengths are manufactured from different amounts of the same granulate.

### ***Control of the finished product***

The finished product specification comprises tests for appearance, identity of lacosamide (by HPLC retention time and UV spectrum), water content, assay, chromatographic purity, dissolution, uniformity of dosage units and microbiological purity. The proposed specifications are generally considered justified, but the shelf-life specification for the assay is not supported by stability data. The applicant is asked to tighten the assay specification in line with the release specification. It has been demonstrated that the (S)-enantiomer does not increase during manufacture or upon storage. The analytical methods have been validated according to ICH guidelines.

The results support the proposed release specifications for the finished product.

### ***Stability of the finished product***

Primary stability data are reported for twelve batches of white-coated (50 mg, 200 mg, 300 mg) tablets and for six batches coated with different colours (all 50 mg). The data provided from the primary batches comprise up to 24 months long term data for the white tablets and 18 months for the differently coloured batches. Regarding the supportive batches (clinical formulation), up to 60 months long term data is included in the dossier. The ICH stability data provided support a shelf-life of 3 years with no special storage requirements for the lacosamide film-coated tablets. No sign of degradation has been observed at accelerated, intermediate or long term conditions. The dissolution results are within specification and in the vast majority of cases stage 1 testing was sufficient.

The primary stability studies comprise only the 50, 200 and 300 mg strengths but the post-approval stability commitment protocol includes all tablet strengths in a bracketing/matrixing design.

## III.2 Non clinical aspects

### Pharmacology

The mechanism of action of lacosamide is considered unknown. Two mechanisms of actions have been suggested by the applicant: 1) Binding to the collapsin response mediator protein-2 which is involved in neuronal differentiation and control of axonal outgrowth. 2) Enhancement of sodium channel slow inactivation without effects on fast inactivation which might facilitate control of neuronal hyperexcitability. It is in the CHMP opinion that the findings may be of relevance for the observed therapeutic effects, but should at the moment be regarded as hypotheses and not as proven facts. The SPC text section 5.1 is suggested to be changed.

*In vivo*, lacosamide has demonstrated support for the proposed indication in relevant models of neuropathic pain. However, the exposure levels for pharmacological effect, based on the pharmacodynamic animal studies and sparse available exposure data, are suggested to be higher than the human exposure levels currently tested in clinic. In addition, the lack of separation between doses producing CNS related adverse effects in safety pharmacology studies to pharmacological effective doses in animal pain models is also assessed as a cause of concern.

Safety pharmacology studies in the CNS showed a dose-dependent behavioural depressant effect, accompanied by a decrease in muscle tone. Cardiovascular *in vivo* studies demonstrated a cardiodepressant action including decreases in blood pressure, contractility and cardiac output, slowing of atrial and ventricular conductivity, and, at very high doses, atrioventricular block and atrioventricular dissociation. Due to these findings concerns regarding nonclinical cardiovascular data were posed in the Day 80 assessment report. The Applicant has adequately responded to the raised issues, and these concerns are regarded as resolved.

### Pharmacokinetics

Lacosamide was rapidly absorbed and widely distributed in mice, rats and dogs. Lacosamide distributed mainly to the organs of metabolism and excretion, kidneys, liver and gall bladder. In general, pharmacokinetic parameters did not differ between genders or single or repeat dose administration. No repeat-dose distribution studies were included. However, no obvious signs of accumulation were evident in any tissue. The protein binding was low (<15%) in all tested species. Lacosamide is metabolised by CYP2C19, but to a low extent. In humans, receiving a 100 mg intravenous dose, 40% of the dose was excreted unchanged in the urine, ca. 30% was SPM 12809 and smaller amounts consisted of SPM 6912 and its N-carbamoyl glucuronide, O-desmethyl hydroxyl and p-hydroxy metabolites. The animal species tested formed the metabolites in humans, hence mice, rats and dogs appear suitable species for the toxicity studies. Renal excretion is dominant (>70-90%) in all species, including human. (See human pharmacokinetics for detailed information on available human *in vivo* and *in vitro* data.)

*In vitro* data on interaction potential are assessed in the human pharmacokinetics assessment report.

In the Day 80 assessment report, other concerns regarding the lack of control samples in pivotal studies were put forward, and the Applicant was asked to submit all available individual control data from pivotal studies. Further, the Applicant was asked to submit information on the standard procedures operating in the GLP sites where the non clinical experiments were performed. The Applicant has submitted the asked for data, and these other concerns are regarded as resolved.

A second other concern regarded the lack of repeated-dose distribution studies. The Applicant has reasonably justified the lack of repeated dose distribution studies, and this issue is also considered resolved.

### Toxicology

Lacosamide has been tested in a full set of toxicity studies, where the pivotal studies have been performed according to GLP standards. In principal, in most studies and in all species tested, the central nervous system effects of lacosamide have been dose limiting, hence other signs of toxicity were scarce and of a low magnitude. Also, as a consequence of the low dose levels, the margins over human clinical maximum exposure in respect to  $C_{max}$  and AUC are low or non-existent. This should be clearly stated in the section 5.3 of the SPC.

In mice, no specific target organ was identified. In rats, the liver was the target organ, showing adaptive enzyme induction effects. In the dogs, the target organ was the heart, with increase heart rate, decreased arterial systolic blood pressure and one case of a second degree AV heart block in the 2-week intravenous study. Heart toxicity has also been seen in the clinic, and is discussed below in the clinical section.

Lacosamide was tested for genotoxicity using three *in vitro* and two *in vivo* tests. Even though the positive effects in the mouse lymphoma assay were seen at high concentrations, and the other studies included in the standard genotoxicity battery were negative, the Applicant was asked to submit a weight-of-evidence analysis of these positive effects. Such an analysis has been submitted and this issue is considered resolved.

Lacosamide did not hold a carcinogenic potential when tested in 2-year studies in rats and mice.

In rats and rabbits no teratogenic effects were seen under the present study conditions. However, the value of these studies in regard to evaluate the possible teratogenicity in rats and rabbits and the potential risk for humans, is severely hampered by the fact that central nervous system effects in the dams were dose limiting. The doses possible to administer, and the exposures reached left small or non-existent margins over human exposure. At maternal toxic doses, fetotoxicity was seen. Considering the above and since there are no adequate data for use of lacosamide in pregnant woman, the potential risk for humans remains unknown. In addition, on basis of the submitted studies in juvenile rats, a potential for reproductive and neurological developmental toxicity cannot be ruled out, and therefore the wording on lactation in section 4.6 should be stricter than proposed by the Applicant. The amended texts have now been accepted by the Applicant.

No formal assessment has been made of the studies regarding juvenile toxicity, since the Applicant applies for use from 16 years and older. However, on basis of the submitted studies in juvenile rats, a potential for reproductive and neurological developmental toxicity can not be ruled out. Further, in rat, lacosamide was excreted in milk and therefore the wording on lactation in section 4.6 should be stricter than proposed by the Applicant.

Lacosamide was non-irritating to the skin when applied to intact and abraded rabbit skin. When instilled in to rabbit eye, lacosamide caused corneal opacity, irritation of the iris and conjunctival redness and is classified as “irritating to eyes”.

The Applicant should have made a greater effort within the submitted dossier to discuss the dependence potential of lacosamide. However, there were no signs of withdrawal symptoms clinically, and further preclinical studies would not add any relevant information to the overall risk/benefit of the patient. It is the opinion of the CHMP that lacosamide is unlikely to hold a potential for behavioural and/or physical dependence on withdrawal.

It was unclear from the nonclinical summary/toxicology and study reports, what the actual amount of the impurity SPM 14018 was in batch PEH-A-188(2), used for the genotoxicity tests (Ames and mouse lymphoma assay). The Applicant was asked to clarify what the actual amount of SPM 14018 was in the batch used for the genotoxicity tests performed, and justify the claim of a 0.3% qualification limit. The Applicant has now decided to tighten the acceptance limit for SPM 14018 in lacosamide drug substance to NMT 0.15% based on batch analysis data, i.e. below the ICH Q3A (R) qualification threshold. Thus, toxicological qualification is no longer required.

Concerning the ERA, a water sediment study (OECD 308) is awaited by Q4/2008 and should be submitted.

### III.3 Clinical aspects

#### Pharmacokinetics

##### **Absorption and formulations**

Lacosamide is a modified aminoacid with a fast and complete absorption. The bioavailability after oral administration approaches 100%. The formulation applied for is film-coated tablets 50, 100, 150 and 200 mg. The highest strengths, 250 and 300 mg, have been withdrawn by the applicant following limitation of the maximum dose to 400mg (see earlier, *Drug Product – Introductory remarks*). The tablet intended for marketing is slightly different than the clinical trial formulation but has not been studied *in vivo*. A biowaiver from studying bioequivalence between the marketing tablet formulation and the clinical trial formulation can be granted as the formulation can be classified as BCS class I and have similar and fast dissolution at different pH *in vitro*, the drug has high permeability, apparently little intestinal transporter involvement, and the excipients in the formulation are unlikely to affect transport proteins.

##### **Distribution**

Lacosamide has a low protein binding and a volume of distribution of 40-60 L.

##### **Elimination**

The elimination half-life is 11-16 hours and clearance ca 3 l/h. The inter-individual variability is low (ca 20%). Lacosamide shows 1-compartment kinetics and the kinetics is dose and time proportional in the therapeutic range. Lacosamide is eliminated partly (30%) through renal excretion and partly by metabolism. The non-renal elimination has not been fully characterised. However, the formation of the metabolite is said to be catalysed by CYP2C19 but absence of inhibition of CYP2C19 only gave a 7-17% reduction of oral clearance. Thus, either the contribution of the pathway is rather small or another enzyme is contributing to the SPM12809 formation. The applicant has tried to identify the remaining metabolic pathways and enzymes responsible as catalysts, but although quite extensive investigations, no further information has been collected. The identification of dose-related compounds in plasma is borderline acceptable. Only a pooled plasma sample from all time points of a full sampling curve was studied. The rough estimation results in lacosamide contributing to 60-100% of plasma radioactivity. SPM12809 was the only metabolite found in plasma. The pharmacokinetics of SPM12809 has been investigated in several studies. The exposure of SPM12809 is usually 15% of the lacosamide exposure.

##### **Chirality**

Lacosamide has one chiral centre and is administered in the R-form. There is no significant interconversion *in vivo*.

##### **Special populations**

Impaired renal function gives an expected increase in lacosamide exposure (47% in severe renal impairment). The drug is eliminated by haemodialysis and an additional half morning dose should be taken after end of dialysis. A maximum dose of 250 mg (in stead of 400mg) is recommended for patients with severe renal impairment and in patients with end-stage renal disease. Very high concentrations of SPM12809 were noticed in patients with severe impairment and end-stage renal disease. The exposure margin to preclinically obtained exposures is, as for the parent drug, small or non-existent. In patients with end-stage renal disease, the plasma concentrations were increased and continued to rise during the complete sampling period. Thus, AUC could not be determined. However, no pharmacological activity of the metabolite has been observed. A recommendation of caution when treating patients with end-stage renal disease is proposed in the SPC. The AUC of lacosamide was increased by 60% in moderately impaired hepatic function. However, the studied patients also had an impaired renal function and it was estimated that the increase in AUC resulting from a decrease in non-hepatic clearance was 19%. The exposure was also similar in Asians, Blacks and Whites. Elderly women had ca. 50% higher mean AUC than young men both after the first dose and at steady state, and elderly men had ca. 33% higher exposure than young men. After normalising the parameters for bodyweight, the differences were reduced (to 23% for elderly women and 26% in elderly men as compared to young men). Only a minor part of the difference is likely to be due to decreased renal

function. The tolerability of LCM is reduced in the elderly group as regards GI and CNS side-effects, while no mention is done as regards cardiac tolerability, which is an important issue. These data contrast with the lower clinical efficacy of LCM (up to -0.7 units in LCM 600 mg group) in these subjects and with the total lack of a dose-response effect. A reduced starting dose and slower titration is proposed in the elderly. The pharmacokinetics in children has not been studied. However, studies in this age group are planned. Weight appears to modestly influence the pharmacokinetics of lacosamide. The population PK analysis supported that women will have an increased lacosamide exposure and indicated that decreased weight will lead to increased exposure. Combining information from the various sources indicates that elderly females with low body weight may have increased lacosamide exposure. The pharmacokinetics in children has not been studied. However, studies in this age group are planned.

### **Interactions**

*In vitro* studies indicate that CYP3A4 may both be induced and inhibited by lacosamide. The signal is not very strong but nevertheless, it may not be excluded that lacosamide can affect this enzyme activity in a moderate way. The applicant is intending to study this in a multiple dose study with oral midazolam and has discussed the protocol with the rapporteur.

A Caco-2 cell transport study indicates that there is some efflux transport. The concentration dependency of the transport has not been evaluated. The concentrations used in the study are quite high and the possibility of lacosamide to be transported by amino acid transporters or peptide transporters such as PEPT1 may not be excluded. However, as there are no indications of relevant transporter involvement *in vivo* (high permeability, no active renal or biliary excretion), no further investigations are needed. Lacosamide does not affect digoxin transport *in vivo* and the transport was not affected by the Pgp inhibitor verapamil *in vitro*. *In vivo* interaction studies showed that multiple-dose omeprazole (40 mg q.d.) increased lacosamide exposure by 19%, lacosamide slightly (9%) increased ethinylestradiol and levonogestrel exposure, did not affect the pharmacokinetics of digoxin. There was no interaction between lacosamide and metformin, valproic acid and carbamazepine. However, the interaction study with carbamazepine did not include a sufficiently long carbamazepine treatment period at the target dose for full induction to be reached. The population analysis indicated that concomitant treatment with phenytoin, phenobarbital and carbamazepine moderately decrease lacosamide exposure.

### **PK/PD relationship**

Lacosamide increases the PR interval. The effect is dose-dependent and a relationship between concentration and increase in PR interval has been found. There is one PK-PD analysis on efficacy which estimates that the plateau in response will be reached at higher lacosamide doses than indicated by the clinical efficacy data. However, the analysis is a very rough estimation.

### **Clinical efficacy**

The initial application was based on three trials; SP742, SP743 and SP768. Data from a fourth trial SP874, with an almost identical protocol as the three mentioned, were reported as parts of the response to the Day 120 LoQ.

In the primary assessment (Day 80) it was concluded that:

- The primary endpoint (within-subject change in the average daily pain score from the Baseline week to the last 4 weeks of the Maintenance Phase using an 11-point Likert scale (0-10) in the Full analysis set (FAS) with Last observation carried forward (LOCF)) could indicate a pain relieving effect.
- The LOCF method combined with a high differential (placebo – active arms) rate of withdrawals due to adverse events can introduce a substantial bias.
- The rate of early withdrawals because of adverse events for the daily 400 mg dose was 11.3% - 24.0% increasing considerably to 23.3% - 42.3% for the 600 mg dose. For placebo the corresponding numbers were 5.4% - 13.3%. Therefore the conservative and robust method using a responder analysis defining non-completers as non-responders will have a considerable influence on the final efficacy assessment.

A metaanalysis (**FAS using LOCF**) of the primary endpoint from the three « pivotal » trials gave the following results :

|                       | Placebo | LCM<br>200mg/day | LCM<br>400mg/day | LCM<br>600mg/day |
|-----------------------|---------|------------------|------------------|------------------|
| N                     | 228     | 230              | 360              | 355              |
| Pain reduction LSMean | -1.57   | -1.87            | -2.14            | -2.02            |
| Treatment difference  |         | -0.30            | -0.57            | -0.45            |
| p-value vs placebo    |         | 0.1103           | <b>0.0006</b>    | <b>0.0072</b>    |
| 95% CI                |         | -0.67 , 0.07     | -0.90 , -0.24    | -0.78 , -0.12    |

A responder was defined as having  $\geq 30\%$  or  $\geq 2$ -point pain reduction.

A metaanalysis (**FAS using LOCF**) of responders from the three « pivotal » trials gave the following results (Calculations made by the Assessor):

|                                                                       | Placebo | LCM<br>200mg/day | LCM<br>400mg/day | LCM<br>600mg/day |
|-----------------------------------------------------------------------|---------|------------------|------------------|------------------|
| N                                                                     | 228     | 230              | 360              | 355              |
| Number with specified reduction (in subjects who completed the trial) | 96      | 120              | 187              | 189              |
| Rate (%)                                                              | 42.1    | 52.2             | 51.9             | 53.2             |
| Odds Ratio                                                            | -       | 1.5              | 1.5              | 1.6              |
| P-value                                                               | -       | <b>0.0319</b>    | <b>0.0224</b>    | <b>0.0108</b>    |
| 95% CI of the Difference                                              | -       | 1.02, 2.20       | 1.05, 2.10       | 1.10, 2.22       |

However, when non-completers were recorded as non-responders, the following results were found (Calculations made by the Assessor):

|                                                                       | Placebo | LCM<br>200mg/day | LCM<br>400mg/day | LCM<br>600mg/day |
|-----------------------------------------------------------------------|---------|------------------|------------------|------------------|
| N                                                                     | 228     | 230              | 360              | 355              |
| Number with specified reduction (in subjects who completed the trial) | 88      | 97               | 144              | 115              |
| Rate (%)                                                              | 38.6    | 42.1             | 40.0             | 32.4             |
| Odds Ratio                                                            | -       | 1.2              | 1.1              | 0.8              |
| P-value                                                               | -       | 0.4475           | 0.7951           | 0.1307           |
| 95% CI of the Difference                                              | -       | 0.78, 1.72       | 0.74, 1.51       | 0.53, 1.10       |

With this latter analysis, the recommended dose 400 mg/day, showed an Odds ratio of 1.1 while the 600 mg/day showed an Odds ratio of 0.8! The 600 mg/day dose has been removed from the Posology section of the SPC text, but remains in the Pharmacodynamic section.

The differences in the two responder analysis suggests that the first one (FAS with LOCF) over-estimates the size of the effect. A positive result was brought forward in patients that could not benefit from it (since they did not complete treatment). Similar risk of over-estimating the efficacy is also true for the primary analysis as this one is also based on LOCF.

This risk of over-estimating the effect is not too surprising in a situation where both ADRs and efficacy are dose- (concentration-) dependent. Patients showing largest effect may have higher exposure and thus at an increased risk of not complete treatment.

As been mentioned above the response to the Day 120 LoQ include data from the newly finished trial SP874.

The following table shows the responder data (non-completers = non-responders) for the recommended dose 400 mg/day :

|                                                                       | SP742        | SP743        | SP768        | SP874        | Combined     |
|-----------------------------------------------------------------------|--------------|--------------|--------------|--------------|--------------|
| N                                                                     | 91           | 149          | 120          | 177          | 537          |
| Number with specified reduction (in subjects who completed the trial) | 40           | 55           | 49           | 98           | 242          |
| Rate (%)                                                              | 44.0         | 36.9         | 40.8         | 55.4         | 45.1         |
| Odds Ratio                                                            | 1.12         | 1.08         | 1.07         | 1.11         | 1.06         |
| P-value                                                               | 0.6987       | 0.7950       | 0.8155       | 0.5950       | 0.6228       |
| 95% CI of the Difference                                              | 0.623, 2.026 | 0.603, 1.932 | 0.579, 2.002 | 0.737, 1.699 | 0.823, 1.384 |

It is clear that the outcome from the new study confirms the results from the previous three trials.

The low Odds ratio values (1.06 in the combined data) is probably most driven by the high withdrawal rate due to adverse events and low efficacy vs placebo (the outcome in the placebo groups are in line with the widespread observation in other DNP trials that there is a considerable pain reduction as a result of being included in such a clinical trial.

If using a responder definition including only subjects with a pain reduction of  $\geq 30\%$ , the Odds ratios are almost the same as for  $\geq 30\%$  and  $\geq 2$  point reduction.

The high withdrawal rate, especially for the 600 mg/day dose, is further increase with a more intensive titration. If a slower titration (by time to dose increments or lowering each dose) than the one used in the trials (100 mg increase each week up to 400 mg/day) and recommended in the proposed SPC is not known.

The Applicant makes indirect comparisons with other drugs used for the same indication). However, these comparisons have significant limitations because no formal head-to-head comparison has been performed between these drugs. In patients with inadequate pain relief from other DNP drugs there was a slight response (-0.58 to -0.77). If the magnitude of this response was higher, lower or equal with earlier response is not reported (“inadequate” can not be assumed as no effect). Therefore, if LCM was better for these patients than the previous drug treatment can not be assessed. In theory, the partly new mode of action of LCM vs. other DNP drugs may have an added value to the therapeutic arsenal but this remains to be shown in clinical studies.

The argument made by the Applicant on the inclusion in LCM trials of patients failing on other drugs usually given to control pain can be contrasted by saying that this is not a surrogate measure to imply that LCM is more efficacious than these drugs. In addition, the proportion of patients receiving those drugs was fairly low (ranging from 9.5 to 17.1%). Finally, the context supporting a better efficacy of LCM, indicated as a percent difference in response, can be contended in the absence of direct comparisons. In this case, the results may be also explained by the “regression-to-the-mean” phenomenon.

The persistence of drug effects can be accepted as evidence of durable efficacy of LCM. However, this refers to a subgroup of patients in whom the drug was found effective and apparently well-tolerated. Even in these cases, one cannot know if a similar durable response was obtained with other drugs, which may have been found ineffective after periods of time longer than that of LCM.

In the primary assessment (Day 80) it was also concluded that:

- The additional secondary efficacy endpoints e.g. Patient’s Global Impression of Change in pain, pain interference with sleep and activity, percentage of pain-free days, use of rescue medication and Quality of Life should not have had rejected a robust positive primary efficacy endpoint, but as for now, these secondary endpoints have not the strength to shift the suggestion of an effect of LCM as seen in the primary efficacy variable to a confirmation of a

true effect. The results from the secondary efficacy endpoints are also based on the LOCF method and subject to bias.

This conclusion remains.

The Applicant has not identified any subgroup/subgroups in the DNP population that could benefit more from an LCM treatment than the general population now investigated.

## Clinical safety

In the primary assessment (Day 80) it was concluded that:

- [There is] a wide variety of symptoms related to CNS functioning and most are obviously dose-dependent. Dizziness, fatigue and tremor are most common. The gastro-intestinal system is also affected; here nausea is most frequently reported. Even if this symptom is belonging to the GI-system according to MedDRA, there is probably some influence from CNS. These adverse events may be very disturbing but severe adverse events leaving sequels directly related to the drug seem rare. There is, of course, an increased risk for trauma with dizziness and fatigue.
- The AV-conduction problem in the heart may be more troublesome. Even if systematic knowledge on conduction problems in diabetics is sparse, there seems to be an increased vulnerability for such conditions in the diabetic population.

Adverse events frequencies are listed below:

**Treatment-emergent AEs leading to discontinuation in  $\geq 1\%$  of subjects in any LCM group.**  
(Randomized parts of the pivotal trials)

| Preferred term         | Placebo<br>N=291 | LCM<br>200mg/day<br>N=234 | LCM<br>400mg/day<br>N=426 | LCM<br>600mg/day<br>N=363 | LCM<br>Total<br>N=1023 |
|------------------------|------------------|---------------------------|---------------------------|---------------------------|------------------------|
|                        | <b>n (%)</b>     |                           |                           |                           |                        |
| Any system organ class | 22 (7.6)         | 25 (10.7)                 | 70 (16.4)                 | 125 (34.4)                | 220 (21.5)             |
| Dizziness              | 0                | 2 (0.9)                   | 12 (2.8)                  | 34 (9.4)                  | 48 (4.7)               |
| Nausea                 | 0                | 4 (1.7)                   | 5 (1.2)                   | 19 (5.2)                  | 28 (2.7)               |
| Tremor                 | 0                | 0                         | 9 (2.1)                   | 8 (2.2)                   | 17 (1.7)               |
| Fatigue                | 0                | 2 (0.9)                   | 3 (0.7)                   | 7 (1.9)                   | 12 (1.2)               |
| Vomiting               | 0                | 3 (1.3)                   | 2 (0.5)                   | 6 (1.7)                   | 11 (1.1)               |
| Balance disorder       | 0                | 1 (0.4)                   | 2 (0.5)                   | 7 (1.9)                   | 10 (1.0)               |
| Somnolence             | 0                | 1 (0.4)                   | 3 (0.7)                   | 6 (1.7)                   | 10 (1.0)               |
| Vertigo                | 0                | 1 (0.4)                   | 0                         | 8 (2.2)                   | 9 (0.9)                |
| Coordination abnormal  | 1 (0.3)          | 1 (0.4)                   | 1 (0.2)                   | 6 (1.7)                   | 8 (0.8)                |
| Headache               | 0                | 2 (0.9)                   | 1 (0.2)                   | 4 (1.1)                   | 7 (0.7)                |
| Diplopia               | 0                | 0                         | 0                         | 4 (1.1)                   | 4 (0.4)                |

**Composite frequency of treatment-emergent serious cardiac-related or potentially cardiac-related AEs during the Treatment Phase in completed, placebo-controlled DNP trials**  
(Randomized parts of the pivotal trials)

| Adverse event<br>MedDRA preferred term | Placebo<br>N=291 | All LCM<br>N=1023 |
|----------------------------------------|------------------|-------------------|
| n (%)                                  |                  |                   |
| <b>Rhythm-Conduction</b>               |                  |                   |
| Bradycardia                            | 0                | 2 (0.2)           |
| Bradyarrhythmia                        | 0                | 1 (<0.1)          |
| Supraventricular tachycardia           | 0                | 1 (<0.1)          |
| Atrial fibrillation                    | 0                | 2 (0.2)           |
| Atrial flutter                         | 0                | 2 (0.2)           |
| <b>QRS-ST-T wave</b>                   |                  |                   |
| Ventricular fibrillation               | 0                | 1 (<0.1)          |
| Myocardial ischemia                    | 1 (0.3)          | 0                 |
| Cardiac arrest                         | 0                | 1 (<0.1)          |
| Bundle branch block left               | 2 (0.7)          | 0                 |
| ECG QTc interval prolonged             | 0                | 1 (<0.1)          |
| <b>Other</b>                           |                  |                   |
| Chest pain                             | 1 (0.3)          | 2 (0.2)           |
| Coronary artery disease                | 0                | 2 (0.2)           |
| Angina unstable                        | 1 (0.3)          | 3 (0.3)           |
| Cardiac failure congestive             | 1 (0.3)          | 0                 |
| Loss of consciousness                  | 0                | 2 (0.2)           |
| Palpitations                           | 0                | 1 (<0.1)          |
| ECG abnormal                           | 0                | 1 (<0.1)          |

As commented in the Clinical efficacy summary above, a more intensive titration scheme as the one used in the pivotal trials increase the adverse events. The safety profile of a less intense titration is not known.

In the submitted trials subjects with any significant cardiovascular disease were excluded. As LCM has negative effects on the cardiac rhythm regulation special caution is necessary until further safety data indicate otherwise. There are uncertainties that the drug may be unsafe in an unknown number of patients. Accordingly, a simple statement to be placed in the Precautions section is not sufficient to prevent patients at risk of developing symptomatic cardiac conduction abnormalities from developing adverse treatment effects when exposed to LCM.

The percentage of outliers with treatment-emergent increase in PR interval of >200ms is up to 17.5% with LCM 600mg/day (placebo 8.5%) and in PR interval of >220ms is up to 9.0% with LCM 600mg/day (placebo 4.6%). The percentage of outliers with treatment-emergent increase in QRS duration values of >100ms is up to 49.6% (LCM 600mg/day); (placebo 32.3%) and in QRS duration values of >120ms is up to 4.8% (LCM 600mg/day); (placebo 3.9%).

Multivariate analysis confirms LCM dose as an independent predictor of dizziness and prolonged P-R interval.

With present knowledge, a reasonable opinion is that subjects outside any clinical trials should not use LCM if they have AV block II or III and/or severe cardiac conditions. Grade I AV block seems to have a low risk to progress into more severe disturbances. ECG findings before taking LCM seem not to predict the occurrence of ECG abnormalities during treatment, and thus an ECG should not be necessary as a screening instrument.

There seems to be a low risk for inducing liver enzyme disturbances as well as for inducing hypertension.

The combined pharmacokinetic and clinical data seem to indicate that elderly subjects, and possibly more women than men, are more vulnerable to the negative effects of LCM than other subjects.

## **Pharmacovigilance system**

The pharmacovigilance system has been described satisfactorily.

## **Risk Management plan**

The plan in general describes the risks with the product. Comments on specified sections have been given in this document. The suggestions by the Applicant how to follow the risk for suicide/suicidal ideation were not satisfactorily described. The applicant should complete this section in the RMP with new alternatives.

## **IV. ORPHAN MEDICINAL PRODUCTS**

N/A

## **V. BENEFIT RISK ASSESSMENT**

### **V.1 Benefits**

Lacosamide has a favourable pharmacokinetic profile with fast oral absorption, full bioavailability, low protein binding, dose- and time-independent kinetics and elimination through both hepatic metabolism and renal excretion. No circulating pharmacologically active metabolites have been identified. The interaction potential appears low but an *in vivo* study with a CYP3A4 substrate is planned to investigate the possibility of weak to moderate induction and inhibition of this enzyme. So far, there are few identified situations with increased lacosamide exposure.

When using the FAS population and LOCF, the combined data in the submitted application suggest a pain relieving effect of LCM in DNP. The meta analysis of the three pivotal trials SP742, SP743 and SP768 did show a statistical significant difference between LCM 400 mg/day vs. placebo for the primary endpoint. However, taken separately only study SP742 by itself was statistically significant. Moreover, in a responder analysis defining a responder as a subject reporting  $\geq 30\%$  or  $\geq 2$  points reduction in pain intensity for the FAS using LOCF, none of the trials is statistically significant for LCM 400 mg/day vs. placebo.

There is a substantial dose dependent withdrawal rate due to adverse events for LCM treatment that motivates a conservative responder analysis. For this reason non-completers were defined as non-responders. For the combined trial data, the differences between LCM 400 mg/day vs. placebo nearly vanish: 38.6% of the placebo subjects were responders and the corresponding figure for LCM 400 mg/day is 40.0% with no statistically significant difference.

The new drug mechanism of action could be an advantage. However, if an LCM treatment has any superior effect over earlier “failed” drug treatments is not convincingly demonstrated.

No subpopulation with a response pattern indicating benefits superior to that found in the whole trial populations has been identified by the Applicant.

### **V.2 Risks**

LCM affects the CNS in a more or less pronounced way, leading to troublesome adverse events, in a substantial number of trial participants. Induced disturbances of the cardiac nervous conduction system, which is already affected in many diabetes patients, may lead to the most serious consequences.

Even though there is no apparent correlation between cardiac conduction defects (mostly represented by prolonged P-R interval) and clinical adverse events, the duration of randomized clinical trials is still limited; thus, in patients with diabetes an increased risk of cardiac abnormalities cannot be excluded after prolonged exposure to LCM. In this context, as the efficacy of the drug is at best modest, and even an apparently low risk cannot be taken.

### **V.3 Balance**

The benefits demonstrated in the primary LOCF-analysis indicate that Lacosamide is active in painful DNP. However, due to the differential withdrawal pattern, the estimate of the effect magnitude is not reliable. Neither are there any data demonstrating that a clinically relevant effect can be obtained with a slower dose titration scheme.

The responder analysis further strengthens this view. In light of this and as the adverse event spectrum must be considered troublesome the benefit/risk ratio is not in favour for LCM in treating a patient from the general diabetic population with painful DNP.

### **V.4 Conclusions**

The overall B/R of Lacosamide Pain UCB Pharma is negative.