#### SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Stalevo. For information on changes after approval please refer to module 8.

### 1. Introduction

Parkinson's disease (PD) is caused by depletion of dopamine in the corpus striatum of the brain. This can be corrected by admistration of levodopa that is converted to dopamine through decarboxylation. Levodopa is very effective in controlling the cardinal signs of PD, such as rigidity, hypokinesia and tremor. Levodopa is always combined with a peripheral dopa decarboxylase (DDC) inhibitor in order to avoid the systemic adverse effects of dopamine and to increase the availability of levodopa to the brain. During the early stages of the disease, the clinical response following a single levodopa dose is stable and lasts for several hours. Unfortunately, the majority of PD patients develop motor complications, such as motor fluctuations (ON-OFF fluctuations, wearing off phenomena) and dyskinesias, during long-term therapy. Thus, the clinical benefit after a single dose of levodopa will become progressively diminished. Entacapone is a selective peripherally acting catechol-O-methyltransferase (COMT) inhibitor. It slows the clearance of levodopa resulting in an increased availability of levodopa to the brain. Consequently, the clinical response to each dose of levodopa is enhanced and prolonged.

Stalevo (Levodopa/Carbidopa/Entacapone, LCE) is a fixed combination of levodopa, carbidopa, and entacapone. Of the three components, levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone modify the peripheral metabolism of levodopa. Carbidopa is a DDC inhibitor that is routinely combined with levodopa. The goal of Stalevo is to simplify the treatment of PD.

Three different tablet strengths have been developed and investigated; containing 50, 100 or 150 mg of levodopa and 12.5, 25 and 37.5 mg of carbidopa respectively. Furthermore, each tablet contains 200 mg of entacapone.

The following therapeutic indication is proposed: "Stalevo is indicated for the treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/DDC inhibitor treatment."

The maximum recommended daily dose provides 1500mg of levodopa, 375mg of carbidopa, and 2000mg of entacapone. Except for carbidopa, these daily doses are within the range recommended for current levodopa/carbidopa and entacapone products. The proposed SmPC provides guidance for switching patients taking levodopa/DDC inhibitor (carbidopa or benserazide) preparations and entacapone tablets to Stalevo. In addition, it is proposed that some patients taking levodopa/ DDC inhibitor (carbidopa or benserazide) preparations could initiate Stalevo without previous introduction of entacapone taken separately. Safety and efficacy has not been demonstrated in children. No special dose adjustments are recommended for the elderly or for patients with mild to moderate renal insufficiency.

Fixed combination products of levodopa and carbidopa have been used extensively within the EU and worldwide for approximately 27 years. The efficacy and safety of entacapone with levodopa/DDC inhibitor (including carbidopa) in the treatment of patients with Parkinson's disease (PD) experiencing end-of-dose wearing-off motor fluctuations has been established previously. CPMP granted a positive opinion of entacapone (as Comtess / Comtan) in 1998 as an adjunct to levodopa/DDC inhibitor in such patients.

The application for Stalevo is, on one hand, based on the Comtess/Comtan applicant's own dossier and, on the other hand, refers to the well-established use (WEU) of the levodopa/carbidopa fixed combination. The applicant has included a WEU-justification document, which covers all the indents of Directive 2001/83/EC set out in Annex I Part 3 (I) and Part 4(I).

The original data in part IV of the dossier aim to show the bioequivalence of the proposed LCEproduct to fixed combinations of levodopa / carbidopa (Sinemet) and entacapone. In addition, new analyses of data from previous clinical trials with Comtess/Comtan have been performed to support the feasibility of the fixed combination. The proposed SPC is based on the SPC of Comtess and Sinemet (in U.K.), relevant literature as well as on data from the new bioequivalence studies.

The CPMP issued a scientific advice in November 1999 on preclinical and clinical issues. The CPMP acknowledged the practical advantage of the fixed LCE combination and accepted the pharmacokinetic approach to demonstrate bioequivalence to the originators (Sinemet, Comtess/Comtan).

# 2. Part II: Chemical, pharmaceutical and biological aspects

## Composition

Stalevo is presented in the form of film-coated tablets and contains three active substances, levodopa, carbidopa and entacapone. Three different tablet strengths have been developed, each in 4:1 ratio of levodopa (50, 100 and 150 mg) to carbidopa (12.5, 25 and 37.5 mg) and combined with 200 mg of entacapone.

The qualitative composition is the same in all three formulations. Excipients include croscarmellose sodium, magnesium stearate, maize starch, mannitol, povidone in the tablet core, and glycerol 85 %, hypromellose, magnesium stearate, polysorbate 80, red iron oxide, sucrose, titanium dioxide, yellow iron oxide in the film coating.

The tablets are packed in a HD-polyethylene container with child-resistant polypropylene closure.

### Active substances

### **Levodopa**

Levodopa complies with the monograph of the Ph Eur, and the certificate of suitability has been provided. Batch analysis data are provided for three batches and are analyzed in accordance with the testing methods of the Ph. Eur. monograph.

Stability data of four years on three batches stored at 25°C/60% RH are provided. The re-test period proposed is compatible with the stability data presented.

# <u>Carbidopa</u>

Information on carbidopa has been supplied in the form of an EDMF.

Carbidopa is presented in the form of monohydrate and is described in the Ph Eur. The evidence of structure is based on the spectroscopic analysis. One asymmetrical carbon atom is present in the carbidopa molecule and therefore, two isomers of carbidopa are theoretically possible. Carbidopa used in this product is the L-form. Physico-chemical characterization was given, and it was stated that no polymorph forms were present in the carbidopa raw material. The synthesis is performed in four steps.

Carbidopa specifications includes test for description, identity, assay, related substances, heavy metals, residual solvents, particle size, specific optical rotation, etc.

Batch analysis data are provided for three batches and comply with the proposed specifications.

The process, specifications and control of methods are adequately described in the restricted section of the EDMF.

Stability data covering five batches demonstrate compliance with the Ph Eur monograph for up to the proposed re-test period at the storage condition  $+25^{\circ}C \pm 2^{\circ}C/60\%$  RH  $\pm 5\%$ . Additional batches were incorporated into the study program, comprising eight batches with storage periods of 9 - 48 months.

Stability data for three batches of carbidopa stored in the same type of containers as those used for shipment of the product at the accelerated condition  $+40^{\circ}C \pm 2^{\circ}C/75\%$  RH  $\pm 5\%$  for 6 months was provided.

The re-test period proposed is acceptable according to the stability data submitted.

### **Entacapone**

Information on entacapone has been supplied in the form of an EDMF.

Entacapone is not described in a EU pharmacopoeia. The synthesis process, specifications and analytical methods for entacapone are the same as accepted earlier in an EU authorised product containing entacapone alone.

Batch analysis data are provided for six batches and comply well with the accepted specifications. The process, specifications and control of methods are adequately described in the restricted section of the EDMF.

The tests and limits in the specifications are considered appropriate for controlling the quality of the active substances.

The re-test period proposed for entacapone drug substance has been approved in an earlier entacapone tablets centralised application, and remains satisfactory.

### Other ingredients

Other ingredients include croscarmellose sodium, magnesium stearate, maize starch, mannitol, povidone in the tablet core, and glycerol 85 %, hypromellose, magnesium stearate, polysorbate 80, red iron oxide, sucrose, titanium dioxide, yellow iron oxide in the film coating. All of them except colour are described in the Ph. Eur. Colours meet the general requirement as described in EC Directive 95/45/EC.

Regarding the TSE compliance of the excipients, there is no TSE risk in polysorbate 80 and glycerol 85% raw materials, because they are produced from vegetable originThe TSE certificate of Ph Eur for magnesium stearate is provided.

The tablets are packed in a HD-polyethylene container with child-resistant polypropylene closure. The specifications and testing standards for the primary packaging components used are presented and are acceptable.

### Product development and finished product

The aim of the development work has been to develop an stable finished product, which is bioequivalent with reference products containing entacapone and levodopa/carbidopa combination. In addition tablets are developed to have an appropriate size in order to be easily swallowed and the manufacturing process is developed to be robust.

Solubility, particle size, and polymorphism of the active substances have been taken into consideration during development. A number of studies have also been carried out to define the compatibilities of the active substances with each other and with the pharmaceutical excipients.

Different granulation processes were examined during development. The excipients were selected for further development studies on the basis of properties of granules and tablets. The final formulation was selected on the basis of the stability and bioavailability results.

Granulation and solubility properties of the active substances were considered during the product development.

The manufacturing process is comprised of several steps: the granules are mixed together with filler, disintegrant and lubricant, ant the obtained mass is compressed into tablets. The tablets are coated with a coating suspension.

The process has been validated by a number of studies for the major steps in three production-scale batches of each strength. The manufacturing process has adequately been validated and is satisfactory.

In process controls are adequate.

The batch analysis data show that the film coated tablets can be manufactured reproducibly according to the agree finished product specification, which is suitable for control of this oral preparation

The specifications of the intermediate product (release and shelf-life) include tests by validated methods for appearance, identification, assay, degradation products and microbial purity tested at the end of the shelf-life. Batch analysis data are available for three batches.

The shelf life of intermediate product proposed can be accepted based on stability data submitted.

#### **Product Specification**

The product specifications include tests by validated methods for appearance, identification, assay, degradation products of the active substances, microbial purity, dissolution of the active substances, etc.

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the release and shelf life specification for the finished product are appropriate to control the quality of the finished products for their intended purpose.

Batch analysis data on three production-scale batches (validation batches) for each of three tablet strengths confirm satisfactory uniformity in the product at release.

## Stability of the product

The shelf-life specifications for the finished product are the same as at release. The following parameters are included in the shelf-life specifications: physical appearance and colour of tablet, average mass, disintegration time (not in release-specifications) and dissolution of the active substances, assay and degradation products of the active substances and microbiological purity.

The stability data provided include information gained from 18/24 month long term (25°C/60% RH and 30°C/60% RH during 18/24 months), and 6 month accelerate (40°C/75% RH) and supportive stability studies (36 months, 25°C/60% RH, and 30°C/60% RH, and 6 months, 45°C/75% RH) on the finished product. In addition, the photostability of the coated tablets and the sensitivity to repeated freezing thawing have been tested. Results of consumption study were also available.

Based on available stability data, the proposed shelf-life stated in the SPC is acceptable.

#### Discussion on chemical, pharmaceutical and biological aspects

In general, the quality of Stalevo film coated tablets is adequately established, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. Relevant ICH/CPMP guidelines and Pharmacopoeia requirements have been taken into account in the quality documentation and there are no major deviations from EU and ICH requirements.

Acceptable specifications have been presented for the three active substances (levodopa, carbidopa and entacapone). The synthetic pathway is presented for the three active substances and the structure and impurity profile are characterized and are in line with current ICH guidelines. The stability data on the active substance supports the proposed re-testing period.

The excipients are of pharmaceutical grade and commonly used in tablet formulation.

The development and the manufacturing process of the finished products are properly described, the results from validation batches show that the manufacturing process is successfully validated, and are suitable to ensure consistent quality of the active substance and the finished product.

Based on available stability data, the proposed shelf life stated in the Summary of Product Characteristics can be accepted.

At the time of the CPMP opinion, there was an unresolved quality issues without impact on the clinical efficacy or safety of the product, therefore the applicant made a commitment to resolve these as post-opinion follow-up measures

## 3. Part III: Toxico-pharmacological aspects

The current application is a bibliographic application with mixed data from the applicant.

This non-clinical documentation includes data on levodopa/carbidopa essentially from published literature as part of its well-established use. Other toxico-pharmacological data on entacapone and the levodopa/carbidopa/entacapone (LCE) combination originate from the applicant.

### Pharmacodynamics

PD is characterised by a progressive degeneration of dopaminergic nigrostriatal neurones leading to a dopamine deficiency in the striatum. Levodopa is an immediate precursor of dopamine. In contrast to dopamine it penetrates the blood-brain barrier and is converted to dopamine in the brain. Consequently levodopa restores striatal dopamine to more normal levels ("dopamine replacement therapy"). Virtually all patients respond favourably to levodopa initially. Unfortunately, the majority of PD patients develop motor complications, such as motor fluctuations (ON-OFF fluctuations, wearing off phenomena) and dyskinesias, during long-term therapy.

Carbidopa reversibly inhibits the DDC enzyme in the periphery. It is a pharmacologically inert substance in the absence of levodopa. Thus, the effect of carbidopa is purely pharmacokinetic. In combination with carbidopa the daily levodopa dose can be decreased by an average 75%. As the peripheral conversion of levodopa to dopamine is reduced by carbidopa the peripheral side effects of levodopa, such as nausea, vomiting, hypotension and cardiac arrhythmias are reduced. Currently levodopa is almost invariably administered as a combination preparation of levodopa(L/C)

Entacapone has been shown to inhibit selectively the COMT enzyme in crude enzyme preparations from various rat tissues (brain, liver, duodenum and red blood cells) and from human red blood cells with IC50-values in the nanomolar range (10-160 nM), as compared to tyrosine hydroxylase and Dopamine  $\beta$ -hydroxylase (bovine adrenal medulla), Dopa-decarboxylase and Monoaminooxidase from rat brain. The (*Z*)-isomer of Entacapone (approximately 5% of total drug in human plasma), has also shown COMT inhibitory properties with IC50 values of 20-280 nM.

The efficacy of the LCE combination has been studied in animal models of Parkinson's disease and compared to the prevailing treatment with L+C.

The models used include the MPTP-model, reserpinised mice and turning behavior (rats bearing a unilateral lesion created by 6-OHDA).

In these models, entacapone potentiates the antiparkinsonian effects of L/C treatment and in some models, significantly delays the reappearance of motor dysfunction. Taken together, the data indicate that entacapone is a potent, selective and reversible inhibitor of COMT. This may lead to an enhancement of the bioavailability of L-dopa in the brain, as evidenced by changes in the concentrations of its metabolites.

• General and safety pharmacology programme

The general and safety pharmacology of entacapone alone have been investigated adequately.

Entacapone seems to be devoid of any marked central effect, at least in single dose experiments, which is in agreement with its low penetration into the CNS. Entacapone did not change body temperature in rats, after single (400 and 800 mg/kg) or repeated administration (200 mg/kg bid for 7 days) in contrast to tolcapone and dinitrophenol indicating that *in vivo* conditions entacapone does not uncouple oxidative phosphorylation.

No adverse effects of clinical relevance were observed with respect to the cardiovascular, respiratory, renal or gastrointestinal systems.

Following intravenous administration (0.003-3 mg/kg) to anesthetised normotensive rats, no effect on blood pressure, heart rate or ECG was observed. Also, high doses of entacapone (300 mg/kg/day) have no effects on ECG in dogs when measured 1 and 24 hours after the last dose in a 51-week oral chronic toxicity study.

Entacapone administered in rats pre-treated with L/C combination, slightly decreased the body temperature in contrast to entacapone alone.

No safety pharmacology information is available with the LCE combination. Toxicology studies with the combination indicate that a detailed safety pharmacology experimentation would have been difficult to perform since at high doses of the combination, the pharmacodynamic effects due to prominent increase in brain DA would cause serious behavioural signs and thus limit the information gained from safety pharmacology experiments.

There is, however, a large amount of information collected on the clinical safety studies of the L/C combination during the quarter of century use of this combination justifying the lack of additional animal data.

• Summary of salient findings

The pharmacodynamic action and the pharmacology of entacapone and its combination with L/C have been well characterised in the literature and by *in vitro/in vivo* studies performed by the applicant.

### Pharmacokinetics

# Levodopa/Carbidopa (L/C)

Pharmacokinetic data of levodopa and carbidopa are available from the literature.

Levodopa exhibits a considerable inter- and intra-patient variability in absorption, a rapid elimination  $(t_{1/2el} approximately 1 h)$  and an extensive metabolism (more than 30 metabolites have been identified in urine). However, the main metabolic pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT). Due to short half-life levodopa plasma concentrations fluctuate considerably throughout the day and contribute to the clinical fluctuations and no true accumulation of levodopa occurs when it is administered repeatedly.

Carbidopa is absorbed more slowly than levodopa from the standard levodopa/carbidopa preparations ( $t_{max}$  for levodopa is approximately 1 h and for carbidopa 2.2 h). The elimination half-life of carbidopa is approximately 2 h. Carbidopa is partially metabolised to two main metabolites but unchanged carbidopa accounts for 30% of the total urinary excretion. A quite variable absorption is characteristic also for carbidopa.

Carbidopa increases levodopa AUC and  $C_{max}$  by 2-4 fold. However, carbidopa does not change or only moderately prolongs the elimination half-life of levodopa. As carbidopa inhibits peripheral DDC the excretion of decarboxylated metabolites of levodopa, such as dopamine and homovanillic acid, are decreased while the relative amounts of dopa and 3-O-methyldopa, a COMT metabolite, are increased.

### Entacapone

The pharmacokinetics of entacapone has been investigated in rats and dogs. A few qualitative and quantitative differences across species were found. The pharmacokinetic profile of entacapone is sufficiently similar in animals and humans to allow the extrapolation of animal data for human safety.

Absorption of unchanged entacapone after single oral administration is quite rapid both in rats and in dogs. In rats and in humans, the absolute bioavailability was dose-dependent and ranged from 20% to 55%, following single dose of 10, 65 and 400 mg/kg, in rats and from 29% to 49%, following single dose of 5, 25, 50, 100, 200, 400 and 800 mg, in humans.

*In vitro*, the protein binding of entacapone  $(5\mu g/ml)$  was high with species differences: about 98% in man, rabbit and monkey; 5% in mouse and pig and 10% in dog.

The overall elimination half-life of entacapone ranged from 30 minutes to 1 hour in dogs and from 1.5 to 3 hours in man. Following repeated administration in rats and in dogs, no accumulation or retention of drug-related material was observed.

Entacapone is extensively metabolised in the liver in all species including humans, the main metabolic pathway being glucuronidation, sulfation and isomerisation from (E)- to (Z)-isomer (active metabolite). In rat and dog, entacapone metabolites are predominantly excreted with the faeces (two/third as glucuronide or sulphate conjugates) and one/third in the urine with less than 1.5% of the entacapone dose as unchanged. After the first hour 30-45% of the dose was recovered in the bile, with an enterohepatic circulation accounting for about 10% of the given radioactivity.

# **LCE** Combination

Kinetic data with the LCE combination are derived from toxicokinetic studies in rats and monkeys treated for up to 13 weeks.

In the rat after 4 weeks or 13 weeks treatment with the LCE combination, entacapone exposure levels followed a linear dose-response but were decreased at high dose in the presence of L/C. As expected from the pharmacology, levodopa plasma levels were increased in parallel with a decrease of the 3-OMD metabolite levels, in the presence of entacapone. Carbidopa plasma levels however, were decreased in the presence of entacapone in rats and monkeys probably due to a decreased absorption

In monkeys, the AUCs of L, C, entacapone and its Z-isomer but not that of other metabolites, were proportional to the LCE combination administered.

# Toxicology

### Levodopa/Carbidopa (L/C)

### Single and Repeat-Dose Toxicity

The acute toxicity of levodopa/carbidopa, conducted by the applicant in rats and mice is low (LD50 >1.5g/kg).

A comprehensive review of toxicological studies of carbidopa and a combination of levodopa and carbidopa has been published by Zwickey et al. (1974, Toxicology and Applied Pharmacology, 29:181-195). They studied single dose toxicity and repeated dose toxicity of levodopa/carbidopa up to one year in monkeys and 96 weeks in rats.

In addition, levodopa/carbidopa has been included to the combination toxicity studies conducted for the LCE product in the repeated dose studies.

## Reproductive function, embryo/foetal and perinatal toxicity

Levodopa alone, and in combination with carbidopa, have caused visceral and skeletal malformations in rabbits. Carbidopa is excreted in milk. Levodopa crosses the placenta of humans and the foetus will be exposed to both levodopa and its metabolites. No information regarding the effects of levodopa/carbidopa on the reproductive function has been published.

#### Mutagenic and carcinogenic potential

Limited amount of *in vitro* mutagenicity information for levodopa and carbidopa, studied separately, has been published. In addition, levodopa/carbidopa has been included into the *in vitro* and *in vivo* mutagenicity studies conducted for LCE-product. According to the results reported by Zwickey et al, 1974 (see above), the combination of levodopa + carbidopa was not carcinogenic in rats. In addition, there is no epidemiological evidence to suggest that levodopa/carbidopa has a carcinogenic effect although epidemiological studies have not been conducted to support this.

In conclusion, according to these preclinical data, levodopa/carbidopa should not be used during pregnancy and breast-feeding. (see SmPC 4.6)

#### Entacapone alone

#### Single and repeat-dose toxicity

Single dose studies were performed in rats and mice with entacapone or the (Z)-isomer alone. The acute toxicity is low: LD50 being about 2 g/kg p.o. in mice and over 2 g/kg p.o. in rats with no difference between (Z)- and (E)-isomer.

Repeated dose toxicity of entacapone was studied orally for up to 12 months in rats, and up to 52week toxicity in dogs. No clear signs of organ toxicity were found in the chronic toxicity studies. The only consistent finding was that entacapone induced a slight anaemia. This may be due to iron deficiency, since high doses of entacapone chelate iron.

#### *Reproductive toxicity*

A full range of reproduction toxicology studies have been performed in rats and a teratology study in rabbits. The highest dosing of entacapone in these studies was 700 - 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits. The exposure factors referring to circulating entacapone levels in humans was in the range of 20 to 40 in rats and 1 to 2 in rabbits.

No effects on fertility and general reproductive performance were observed in the rat. Entacapone administered to the pregnant rats during the period of organogenesis produced no

significant effects upon survival and development in utero. Entacapone administered to the pregnant rabbits resulted in an abnormal body weight gain in mother and in an increased incidence of small foetuses. Skeletal examination of foetuses revealed an apparent slight developmental delay in some bones.

In the peri/post-natal study, gestation length and parturition were unaffected by entacapone. Litter size, survival, sex ratio, weight gain and post-natal development was also normal. The fertility and litter responses of the F1-generation were also unaffected by treatment of F0-generation.

### Genotoxicity

The genotoxicity potential of entacapone was studied in a battery of *in vitro* and *ex vivo* genotoxicity tests, performed according to current requirements. Entacapone was found to be mutagenic in two mammalian cell tests *in vitro*, suggestive of chromosome type damage. However, entacapone has not shown any genotoxicity *in vivo*. Toxicokinetic studies in mice have confirmed high exposure of entacapone after oral administration.

## Carcinogenicity

Carcinogenicity studies were performed in rodents with up to 600 mg/kg/day (mice) or 400 mg/kg/day (rats) entacapone administered orally by gavage. The mouse study did not reveal any treatment-related increase of neoplastic findings. In the rat study (104 weeks), the major finding was an increased number of adenomas and carcinomas in the kidneys of male rats receiving 400 mg/kg/day of entacapone. No such tumours were observed in females. Additional mechanistic studies provided evidence that entacapone-induced tumours are related to male rat specific alpha2µ-globulin nephropathy.

### Environmental risk assessment

The applicant provided adequate information on ecotoxicity and environmental risk associated with the use of entacapone.

### **LCE Combination**

The toxicity of the LCE combination was studied in repeated dose studies for up to 3 months in rats and cynomolgus monkeys, in *in vitro* and *in vivo* genotoxicity studies and embryofetal studies in rats and rabbits. The qualification of impurities and degradation products of carbidopa was also performed. Toxicokinetic data are available from the main combination toxicology studies.

#### Single-dose toxicity

The data, derived from range-finding studies in mice and cynomolgus monkeys show that the acute toxicity of the LCE combination appears to be low.

### *Repeat-Dose Toxicity*

A 1 month rat study and 3 month rat and cynomolgus monkey studies with the LCE combination were performed with a 4/1 ratio of levodopa/carbidopa, which is similar to the intended clinical use. In each study, additional high dose groups with entacapone alone and levodopa/carbidopa only were included.

In the 1 month rat study, reduced weight gain in males and haematological changes (reduced Hb and PCV) were observed at the highest dose of entacapone alone, and of the LCE combination. Behavioural signs were all similar to those known to be related to increased DA concentrations in the brain. Similar observations were made in 28-day rat combination toxicity study, where a fixed combination of L-DOPA/carbidopa/entacapone/ selegiline was used. Thus MAO-B inhibition did not increase the toxicity of the LCE treatment.

In the 13-week rat and monkey studies, dose-related behavioural changes attributed to elevated DA levels in the brain were observed. Entacapone amplified the known behavioural effects of levodopa/carbidopa, due to increased L-DOPA levels and subsequent increased formation of DA. From these data, no unexpected toxicity associated with any of the individual components is apparent.

In summary, the toxicity of entacapone has been adequately studied. Chronic toxicity of LCE combination has not been studied. Keeping in mind that the dopamine-related symptoms would be very severe when higher doses of the combination are used, the information gained from a one year toxicity study would be limited due to relatively low exposures. Furthermore, in current clinical practice, the triple treatment with L-DOPA/carbidopa + entacapone has been well tolerated in a large number of parkinsonian patients.

### Genotoxicity

Entacapone tested in combination with L-DOPA and carbidopa was not mutagenic in bacterial mutagenicity test.

In the *in vivo* micronucleus test, high doses of entacapone in combination with L-DOPA and carbidopa did not induce chromosomal or other damage which might lead to micronucleus formation in polychromatic erythrocytes of treated mice 24, 48 or 72 hours after oral administration.

## *Reproductive toxicity*

The reproductive toxicity of the LCE combination was addressed in two embryo-foetal and perinatal toxicity studies in the rat and in the rabbit where the animals were treated with 3 dose levels of the LCE combination with additional treated groups receiving either L/C only or entacapone alone

There was no indication of maternal or fetal toxicity or abnormalities of F1in the rat study.

No maternal toxicity occurred at the doses used in the rabbit study, however low incidence of internal malformations (hydrocephaly) was seen in the group treated with L/C only. There is literature evidence that L-DOPA may be teratogenic by inducing abnormal development of internal organs and bones in rabbits (Staples and Mattis (1973), *Acta Universitatis Carolinae. Medica. Monographia*; 8:251-253). In addition, levodopa crosses the placenta in humans and the foetus will be exposed to both L-DOPA and its metabolites (Merchant et al. (1995) *Journal of Neural Transmission*; 9:239-242). Taken together, the triple therapy is not recommended during pregnancy in humans.

### Carcinogenicity

No additional carcinogenicity studies have been performed with the LCE combination.

### *Impurities/metabolites:*

There are three impurities and one degradation product of carbidopa in the LCE product that are not covered by the Eur. Ph. or the U.S.P.

In order to qualify the impurities, the applicant performed a 28-day rat study by oral administration of carbidopa with or without impurities, and a supportive 5-day toxicokinetics study as well as a standard battery of genotoxicity testing (Ames test, mouse lymphoma test and *in vivo* mouse micronucleus). In the rat study, no impurity related toxicity was observed. The findings were comparable to those observed in an earlier 13-week repeated dose study.

However, the exposure of carbidopa was lower than expected from other combination studies. According to the applicant who performed a literature review and additional toxicokinetics studies, the kidney is the main organ of clearance of carbidopa in the rat, unlike dogs or humans, and levodopa may decrease the renal excretion of carbidopa explaining the increased exposures with levodopa/carbidopa. In the genotoxicity battery, carbidopa with and without impurities gave similar qualitative results in *in vitro* or *in vivo* tests.

In conclusion, the presence of the degradation product does not affect the benefit/risk of the LCE product, since it is also a human metabolite and has been detected in the reference product. The impurities do not seem to change the toxicity profile of the LCE product as judged by the 28 days rat subacute toxicity study. In addition, the applicant has demonstrated that the other impurities are not unique to their product as they are also present in another marketed levodopa/carbidopa product.

### **Discussion on toxico-pharmacological aspects**

The applicant has provided an adequate bibliographic survey of the preclinical safety aspects of the fixed combination of levodopa/carbidopa. The clinical use of carbidopa at doses exceeding 200mg/day is supported by the relatively low toxicity of carbidopa in animals as well as a wide safety margin in comparison with the human AUC. Further safety data are derived from the results of clinical trials (see clinical part).

The summary of the applicant of the previously submitted preclinical documentation concerning the concomitant use of levodopa/carbidopa and entacapone demonstrates that no new preclinical studies of the safety of the combined use are necessary.

The presence of new impurities in the product does not seem to change the toxicity profile of the LCE product and therefore do not affect significantly the benefit/risk of the LCE product.

## 4. Part IV: Clinical aspects

Stalevo (Levodopa/Carbidopa/Entacapone, LCE) is a fixed combination of levodopa, carbidopa, and entacapone. Three different tablet strengths have been developed and investigated; containing 50, 100 or 150 mg of levodopa and 12.5, 25 and 37.5 mg of carbidopa respectively. Each tablet contains 200 mg of entacapone.

Fixed combination products of levodopa and carbidopa have been used extensively within the EU and worldwide for approximately 27 years. The efficacy and safety of entacapone with levodopa/DDC inhibitor (including carbidopa) in the treatment of patients with Parkinson's disease (PD) experiencing end-of-dose wearing-off motor fluctuations has been established previously. CPMP granted a positive opinion to entacapone (Comtess/Comtan) in September 1998 as an adjunct to levodopa in such patients.

The company presented an application with data from the literature to justify the well-established use (WEU) of the levodopa/carbidopa fixed combination and data from the original entacapone (Comtess/Comtan) application. New clinical data aim to show the bioequivalence of the proposed LCE-combinations to fixed combination of levodopa and carbidopa (Sinemet) as well as to entacapone (Comtess/Comtan). In addition, the Clinical Expert Report contains certain new analyses of data from previous clinical trials with Comtess/Comtan to support the feasibility of the fixed combination. Data from two phase IIIb studies and post-marketing data were also provided.

## **Clinical pharmacology**

## Pharmacodynamics

Stalevo is a fixed combination of levodopa, carbidopa, and entacapone. Of the three components, levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone modify the peripheral metabolism of levodopa. Levodopa is a precursor of dopamine. The conversion of levodopa to dopamine in the brain is required for the therapeutic effect. Carbidopa is a selective, reversible and peripherally acting dopa decarboxylase (DDC) inhibitor that is routinely combined with levodopa. Entacapone is a reversible and peripherally acting catechol-O-methyltransferase (COMT) inhibitor. Both carbidopa and entacapone inhibit the metabolism of levodopa to the CNS from a single dose.

Entacapone has been demonstrated to dose-dependently and reversibly inhibit COMT activity in red blood cells of healthy volunteers. Maximum inhibition (approximately 60%) was reached within 60 min with a single dose of 200 mg. The activity returned to baseline within 8 hours. Reversible inhibition was also observed following repeated dosing for 10 days. Entacapone has no antiparkinsonian effect *per se*. In the treatment of PD, entacapone is always administered with a levodopa/DDC inhibitor.

See also below the section on pharmacokinetics (in particular interaction studies).

### **Pharmacokinetics**

• General

The main pharmacokinetic characteristics of levodopa, carbidopa, and entacapone are displayed in the following table.

Variable	Levodopa	Carbidopa	Entacapone
Bioavailability (%)	15 – 33	40 - 70	29 – 46 (35 for 200 mg)
$t_{max}(h)$	0.5 - 2.2	1.5 – 5	0.4 - 0.9
C <sub>max</sub> and AUC	Dose- proportional, non-linear	?	Dose-proportional, linear
$t_{1/2\beta}\left(h\right)$	0.6 – 1.3	2-3	0.4 – 0.7 (β-phase) 2.4 (γ-phase)
Vd (L/kg)	0.36 - 1.6	not available	0.27
Clearance (L/kg/h)	0.55 - 1.38	not available	0.70

**Levodopa**: the absorption of levodopa (an L-isomer of dihydroxyphenylalanine) is relatively poor (15-33%). Certain types of meals may delay or reduce the absorption of levodopa. However, there is no recommendation on the dosing and meals. Binding to plasma proteins is negligible. No accumulation is expected in the repeated administration. In the elderly, absorption is better and the elimination is slower. The difference in absorption between the elderly and the younger individuals was not seen in the co-administration with carbidopa. Levodopa is undergoing an extensive metabolism in which decarboxylation (by dopa decarboxylase, DDC) and O-methylation (by catechol-O-methyltransferase, COMT) are the most important pathways.

**Carbidopa**: the absorption of Carbidopa is somewhat slower than that of levodopa, the Tmax being one hour. Like levodopa, it exhibits a significant interindividual variation in absorption, the oral bioavailability being 40-70%. There are two main metabolites and approximately 30% of carbidopa are excreted unchanged in urine.

**Entacapone** pharmacokinetics are comparable with levodopa. It is absorbed rapidly after oral administration ( $t_{max}$  0.5-1 h), its bioavailability is about 35% and its elimination half-life is short (β-phase about 0.5 h,  $\gamma$ -phase 2.4 h). There seems to be no accumulation of entacapone during repeated administration. There are substantial inter- and intraindividual variations in the absorption of entacapone, particularly concerning its C<sub>max</sub>. Food does not significantly affect the absorption of entacapone is extensively bound to protein (approximately 98%), mainly to albumin. Entacapone is almost completely metabolised prior to excretion; only about 0.2% of the dose is found unchanged in urine. The main metabolic pathways are glucuronidation of entacapone and its active metabolite, the cis-isomer, which accounts for about 5% of the total amount in plasma. 10% of the entacapone dose is excreted in urine, the rest is eliminated via the faeces by biliary excretion. Age does not significantly affect the pharmacokinetics of entacapone. The AUC was shown to be approximately two-fold in patients with mild to moderate hepatic impairment compared with healthy subjects. Renal impairment does not essentially affect the pharmacokinetics of entacapone.

**Levodopa + carbidopa/benserazide**: Carbidopa increases levodopa AUC and  $C_{max}$  by 2-4 fold, on average. Due to increased AUC, the daily levodopa dose can be decreased by an average 75%. Carbidopa does not significantly change the  $t_{max}$  of levodopa. Carbidopa reduces the clearance of levodopa by about 50%, while the distribution volume either remains unchanged or is slightly decreased. In the elderly, the AUC increase is mainly due to the reduced levodopa clearance rather than to the increased bioavailability. In the presence of carbidopa, levodopa follows linear pharmacokinetics. Carbidopa treatment decreases the levels of the decarboxylated metabolites of levodopa, such as dopamine, DOPAC and HVA, in urine by about 70-80%, whereas excretion of unchanged dopa is considerably increased. However, carbidopa neither reduces plasma levodopa fluctuations markedly nor eliminates the significant intra- and intersubject variability in levodopa absorption.

Levodopa + carbidopa + entacapone: When peripheral DDC is inhibited, O-methylation becomes the major metabolic route for levodopa. This results in an accumulation of 3-OMD, which is an inactive and potentially adverse metabolite. The aim of adding a COMT inhibitor to the levodopa/DDC inhibitor combination is to reduce the formation of 3-OMD and to increase and prolong the plasma level of levodopa. Pharmacokinetic studies have demonstrated that entacapone increases the AUC and prolongs the elimination half-life of levodopa, although it does not increase Cmax when used with a standard levodopa/DDC inhibitor preparation. The plasma levels of 3-OMD are significantly decreased. Thus, with entacapone, more levodopa is available for transport to the brain. The optimum dose of entacapone is 200 mg with each dose of levodopa/DDC inhibitor. A population pharmacodynamic model showed that the concentration-effect curve of levodopa was not affected by entacapone.

In summary, the following table describes the effects of a DDC inhibitor and a DDC inhibitor plus entacapone on the pharmacokinetics of levodopa

Variable	Levodopa + DDC inhibitor <sup>a</sup>	Levodopa + DDC inhibitor + entacapone <sup>b</sup>
C <sub>max</sub>	+	0
AUC	+	+
t <sub>max</sub>	0	0
T <sub>1/2</sub>	0/+	+

<sup>*a*</sup> compared to levodopa alone

<sup>*b*</sup> compared to levodopa + DDC inhibitor

0, no essential change; +, increase

**Benserazide**: Entacapone increases the bioavailability of levodopa from standard levodopa/benserazide preparations slightly (5-10%) more than from standard levodopa/carbidopa preparations.

The placebo-controlled pharmacokinetic study 2939083 addressed the concomitant use of entacapone with levodopa/carbidopa products with different levodopa/carbidopa ratios. The effect of concomitant entacapone 200 mg and placebo on AUC of 6 different levodopa/carbidopa doses with different levodopa/carbidopa ratios was evaluated in a 4-way cross-over protocol and 3 parallel groups. The results show that, after addition of entacapone, the exposure to levodopa from tablets with 10:1 and 4:1 levodopa/carbidopa ratios will increase in the same proportion whereas, in absolute terms, more from tablets with a ratio of 4:1. This result has implications to the posology of Stalevo when initiating the fixed combination.

• Bioequivalence studies on the LCE products:

The bridge from the reference products Sinemet (a fixed combination of levodopa and carbidopa) and Comtess/Comtan (entacapone) is based on four new pharmacokinetic studies (Studies 2939085, 2939093, 2939095, and 2939096) that support the bioequivalence of the LCE product and the reference products.

The studies had a randomised single dose replicated cross-over design. The applicant used the 4 period - 2 sequence design and not the conventional 2 period – 2 sequence design. Following CPMP's request, the applicant analysed the data on "2-period-2-sequence basis" using the first two periods only. The results of these analyses were closely similar to the results originally submitted and summarised in the present report.

The studies involved healthy cucasian adults. In one study (2939085), they were young (< 41 years) males, and in three studies middle aged or elderly people (45 - 80 years).

The analytical methods were sufficiently validated and the statistical methods were in compliance with the CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence. Concentrations of levodopa and carbidopa in plasma were analysed using reversed-phase ion-pair high-performance liquid chromatography (HPLC) with calorimetric detection. The limit of quantification was set at 20 ng/ml for levodopa and 5 ng/ml for carbidopa. Analysis of entacapone concentration in plasma was carried out by reversed-phase HPLC with amperometric detection. The limit of quantification was set at 10 ng/ml of entacapone.

In accordance to the previous CPMP scientific advice, the applicant was allowed to establish broader limits for the  $C_{max}$  values of entacapone in agreement with the concept of highly variable drugs, provided that the broader limits were pre-specified in the protocols for evaluation of the bioequivalence. This was done but only occasionally these broader limits were needed to consider the bioequivalence. For the large majority of the parameters in all studies, bioequivalence was established within the usual Confidence Intervals [0.80-1.20].

In general, the bioequivalence has been demonstrated (see the Table 1 for AUC and Table 2 for Cmax).

Study	Substance	Dose (mg)	Test product	Test (mean±SD)	Reference (mean±SD)	Geom. mean ratio	Log 90% CI
2939085	Levodopa	100	LCE 100	$1757\pm359$	$1756\pm344$	1.00	0.97 - 1.04
2939093	Levodopa	100	LCE 100	$2840\pm697$	$2745\pm708$	1.04	1.01 - 1.07
2939095	Levodopa	50	LCE 50	$998\pm310$	$970\pm287$	1.03	0.98 - 1.08
2939096	Levodopa	150	LCE 150	$\begin{array}{rrr} 3717 & \pm \\ 1101 & \end{array}$	3824 ± 1116	0.97	0.94 – 1.01
2939085	Carbidopa	25	LCE 100	431 ±169	420 ± 166	1.02	0.94 - 1.11
2939093	Carbidopa	25	LCE 100	$633 \pm 211$	$645 \pm 220$	0.98	0.92 - 1.04
2939095	Carbidopa	12.5	LCE 50	$150 \pm 64$	$150 \pm 56$	0.98	0.92 - 1.05
2939096	Carbidopa	37.5	LCE 150	$488 \pm 180$	$551 \pm 192$	0.88	0.82 - 0.93
2939085	Entacapon e	200	LCE 100	$1234 \pm 373$	$1228\pm350$	1.00	0.95 - 1.05
2939093	Entacapon e	200	LCE 100	$1439\pm377$	$1383\pm357$	1.05	1.01 – 1.09
2939095	Entacapon e	200	LCE 50	$1249 \pm 522$	$1255 \pm 424$	0.96	0.92 - 1.00
2939096	Entacapon e	200	LCE 150	$1233 \pm 373$	$1216 \pm 440$	1.03	0.98 - 1.08

Table 1:	AUC data (h.ng/ml) for levodopa, carbidopa and entacapone in four bioequivalence
	studies in healthy subjects

AUC<sub>0-10h</sub> in the studies 2939085, 2939093, 2939095; AUC<sub>0-12h</sub> in the study 2939096

Study	Substance	Dose (mg)	Test product	Test (mean±SD )	Reference (mean±SD )	Geom. mean ratio	Log 90% CI
2939085	Levodopa	100	LCE 100	$653\pm165$	$704 \pm 189$	0.93	0.88 - 0.98
2939093	Levodopa	100	LCE 100	$975 \pm 247$	$\begin{array}{rrr} 1036 & \pm \\ 308 & \end{array}$	0.96	0.91 - 1.00
2939095	Levodopa	50	LCE 50	$473 \pm 154$	$489 \pm 153$	0.96	0.90 - 1.03
2939096	Levodopa	150	LCE 150	$\begin{array}{rrr} 1272 & \pm \\ 329 \end{array}$	$\begin{array}{rrr} 1384 & \pm \\ 445 \end{array}$	0.94	0.89 – 0.99
2939085	Carbidopa	25	LCE 100	$99 \pm 39$	$98 \pm 37$	1.00	0.93 – 1.08
2939093	Carbidopa	25	LCE 100	$125 \pm 42$	$126 \pm 42$	0.98	0.92 – 1.04
2939095	Carbidopa	12.5	LCE 50	$39 \pm 16$	$39\pm14$	0.98	0.91 - 1.06
2939096	Carbidopa	37.5	LCE 150	$107\pm42$	$121 \pm 45$	0.88	0.82 - 0.94
2939085	Entacapon e	200	LCE 100	$\begin{array}{rrr} 1016 & \pm \\ 503 & \end{array}$	1020 ± 511	0.99	0.88 – 1.11
2939093	Entacapon e	200	LCE 100	1259 ± 712	$\begin{array}{rrr} 1070 & \pm \\ 460 & \end{array}$	1.12	1.00 – 1.26
2939095	Entacapon e	200	LCE 50	1199 ± 884	$\begin{array}{rrr} 1152 & \pm \\ 558 & \end{array}$	0.94	0.84 - 1.06
2939096	Entacapon e	200	LCE 150	$\begin{array}{rrr} 1211 & \pm \\ 738 \end{array}$	$\begin{array}{rrr} 1052 & \pm \\ 792 & \end{array}$	1.18	1.03 – 1.35

 Table 2:
 C<sub>max</sub> data (ng/ml) for levodopa, carbidopa and entacapone in four bioequivalence studies in healthy subjects

# Pharmacokinetics in the elderly

After combination of carbidopa with levodopa, the absorption of levodopa is similar between the elderly and the young, but the AUC is 1.5 fold greater in the elderly due to decreased DDC inhibitor activity and lower clearance by aging. Entacapone pharmacokinetics are independent of age.

Three studies (2939093, 2939095 and 2939096) were carried out in healthy volunteers including elderly people. In these studies, totally 57 out of 132 volunteers were at least 60 years of age, and further 27 at least 65 years of age. Age had a significant effect on the oral bioavailability of levodopa, as expected according to literature. In study 2939096 with the levodopa dose of 150 mg, this effect was not statistically significant. According to subgroup analysis of data in the elderly, higher AUC<sub>0-t</sub> values of levodopa were noticed with the LCE 50/12.5/200 mg tablet strength but not with the two other tablet strengths in subjects over the age of 65 years. Since dosing of levodopa in parkinsonian patients is individually adjusted according to clinical response, this finding is not considered to be clinically relevant. Elderly volunteers tended to have also higher AUC of entacapone after 200 mg dose. There was no difference in effect of age between LCE combination and LC + E.

### Effect of gender

Effect of gender on pharmacokinetics was studied in subgroup analyses. There existed a tendency for higher bioavailability of levodopa in women (primarily due to the difference in body weight), but the difference between the genders was statistically significant only in study 2939093. The weight-adjusted AUC of levodopa in women was on average 40 % greater than that in men after 100 mg dose of levodopa. No statistically significant gender-effect was observed in AUCs of two other active ingredients.

## Effect of food on bioavailability

When levodopa is taken without any food there is a very fast, but brief increase in plasma levels. All PK-studies with LCE combnation tablet were carried out in standardised conditions after an over-night fast. The effect of food on the rate and extent of absorption of fixed dose combination tablets of levodopa/carbidopa/entacapone has not been evaluated.

### Renal and hepatic impairments

The metabolism of entacapone is slowed in patients with mild to moderate liver insufficiency (Child-Pugh Class A and B) leading to an increased plasma concentration of entacapone both in the absorption and elimination phases. No particular studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment are reported. Therefore, Stalevo should be administered cautiously to patients with mild to moderate hepatic disease. Severe hepatic impairment is a contraindication.

Renal impairment does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment. Therefore, Stalevo should be administered cautiously to patients with severe renal impairment.

### Clinical efficacy

## Levodopa/carbidopa

Standard levodopa was never tested against placebo. However, the symptomatic benefits of levodopa are indisputable. Levodopa is generally very effective in controlling the cardinal signs of PD, such as rigidity, hypokinesia and tremor. Virtually all patients respond favourably to levodopa initially. During the early stages, the clinical response following a single levodopa dose is stable and long-lasting (several hours or even days). Unfortunately, the majority of PD patients develop motor complications, such as motor fluctuations (ON-OFF fluctuations, wearing off phenomena) and dyskinesias, during long-term therapy. The clinical benefit after a single dose of levodopa progressively shortens. It has been demonstrated that the more constant plasma levodopa levels are, the less fluctuation the patient has. Several approaches have been used to achieve a more constant levodopa plasma profile, e.g. by producing controlled-release levodopa preparations or by combining entacapone with levodopa/carbidopa treatment. Levodopa may not affect the natural progression of the disease. The question whether levodopa significantly prolongs life is controversial. Levodopa continues to be effective throughout the course of PD indicating that a complete tolerance will not develop to levodopa in chronic use.

The efficacy of levodopa/carbidopa is well established. With regard to the efficacy of levodopa/carbidopa, the applicant refers to the published literature, text books of medicine, pharmacology, neurology and to summary of product characteristics for levodopa/carbidopa products, e.g. Sinemet.

### Entacapone

Efficacy of the triple association derives directly from the data of the clinical development of entacapone. The clinical documentation of the efficacy of entacapone as an adjunct to levodopa/DDCI consists of two pivotal phase III 6-month double-blind studies, one pivotal phase II short-term crossover double-blind study and five "supportive" small, short-term phase II studies. In two phase III double-blind studies in altogether 376 patients with Parkinson's disease and end-of-dose motor fluctuations, entacapone or placebo was given with each levodopa/dopa decarboxylase inhibitor dose. The results are given in the following table. In study I, daily ON time (hours) was measured from home diaries. In study II, the proportion of daily ON time was measured. There were corresponding decreases in OFF time. The % change from baseline in OFF time was -24% in the entacapone group and 0% in the placebo group in study I. The corresponding figures in study II were -18% and -5%.

Study I						
	Entacapone(n=85)	Placebo(n=86)	Difference			
	Mean (±S.D.)	Mean (±S.D.)				
Baseline*	9.3±2.2	9.2±2.5				
Week 8-24*	10.7±2.2	9.4±2.6	1h 20 min			
			(8.3%)			
			CI <sub>95%</sub> 45 min, 1 h 56 min			
		Study II				
	Entacapone(n=103)	Placebo(n=102)	Difference			
Baseline**	60.0±15.2	60.8±14.0				
Week 8-24**	66.8±14.5	62.8±16.80	4.5% (0 h 35 min)			
			CI95% 0.93%, 7.97%			

\* daily ON time (h)

\*\* proportion ON time%

These placebo controlled pivotal studies support the efficacy of entacapone as an adjunct to levodopa/DDCI in the treatment of idiopathic Parkinson's disease in patients with end-of-dose fluctuations. The documentation does not support efficacy in non-fluctuating patients. Long-term efficacy of entacapone has only been demonstrated up to 6 months in double-blind studies.

The feasibility of the fixed levodopa/carbidopa/entacapone combination

As compared to the approved dosing of the reference products (Sinemet and Comtess/Comtan), the proposed dosing for Stalevo would provide the same dose of entacapone, a lower maximal dose of levodopa (1500mg/day vs. 2000mg/day) and a higher maximal dose of carbidopa (375mg/day vs 200mg/day).

The LCE tablet fulfils the pharmacokinetic and pharmacodynamic criteria of a fixed combination asset by the CPMP note for guidance. Based on an analysis of the levodopa doses in previous phase III clinical trials, Stalevo strengths would cover more than 80% of the need among patients with fluctuating PD. The fixed combination seems to cover the levodopa dose range of most patients since daily levodopa dose rarely exceeded 1500mg. About ten percent of patients have a carbidopa dose exceeding 250mg. Thus, the fixed combination is a feasible option for most patients with a fluctuating disease that cannot be stabilised on the conventional levodopa/DDC-inhibitor combination products, especially when the separate entacapone tablet has already been introduced. Nevertheless, flexibility of the LCE fixed combination for dose titration and recommendations for the switch to the LCE fixed combination were questioned.

The CPMP questioned whether the LCE tablets provide the same flexibility for levodopa dose titration as the current levodopa/carbidopa tablets, in particular for patients who would need less than 50mg reduction of levodopa per dose. Individual daily doses not covered by the 3 dose strengths are very rare. Typically, these patients would have a high daily levodopa dose and levodopa-associated AE such as dyskinesia.

An uncomplicated switch to the fixed combination Stalevo tablets is expected in patients who are already treated with separate conventional levodopa/carbidopa and entacapone tablets that provide the same dose of levodopa. According to the analyses of the applicant, such patients comprise a majority of the potential target population.

The possible risk of switching other patients from fixed dose levodopa/carbidopa or levodopa/benserazide tablets to the fixed combination LCE tablets is an increase of dopaminergic adverse effects. Thus, a careful titration of the levodopa dose may be necessary in cases where an increased exposure to levodopa is expected.

To support recommendations in the proposed summary of product characteristics for switching patients to the treatment with fixed LCE combination, the applicant presented data of two clinical Phase IIIb multicentre studies.

Switch from levodopa/DDCI and entacapone to LCE

The primary objective of STUDY 2939098-SIMCOM was to evaluate the potential patient/physician preference of LCE compared to previous treatment with separately administered levodopa/DDC inhibitor and entacapone. The other objectives were to investigate the proportion of patients who could be successfully switched to LCE. The study was an open, single group, cross-over study and involved treatment comprised either levodopa/carbidopa 52 patients. Their levodopa or/and levodopa/benserazide in a standard release formulation. In addition, only one dose of sustained-release levodopa for night was allowed in their previous levodopa treatment regimen. The study consisted of three consecutive periods. During the first 4-week period, each subject used his/her own levodopa/DDC inhibitor therapy concomitantly with entacapone (200 mg). During the following 4week treatment period, all subjects were treated with LCE tablets. After study treatment with LCE, each subject returned to his/her own previous levodopa/DDC inhibitor and entacapone treatment for the 2-week follow-up period. The mean age of the patients was 61 years, the mean duration of the disease 8.2 years, and the mean daily levodopa dose 509mg/day. The other key characteristics of the original medication were as follows:

DDC inhibitor at baseline

Carbidopa, (%)32 (62)Benserazide, (%)16 (31)Both carbidopa and benserazide, (%)4 (8)Sustained –release l-dopa at baseline16 (31)

Other antiparkinsonian medication, (%)44 (85)Dopamine agonists, (%)36 (69)Selegiline, (%)29 (56)Amantadine, (%)3 (6)Biperiden, (%)3 (6)

The mean daily levodopa dose was  $24.6 \pm 50.9$  mg lower with LCE tablets than the levodopa dose at baseline (p< 0.01). In 60% of subjects, all the levodopa doses used at baseline were directly replaceable with a LCE tablet containing the same amount of levodopa. The most common reasons for the need for dose adjustment were the use of sustained-release levodopa dose at baseline and a mismatch in levodopa dose (mg) to LCE tablets. When only subjects using standard-release levodopa formulations were observed, in 86% of subjects all levodopa doses were directly replaceable by a LCE tablet. In the majority of cases, the switch was successful (see table below).

Treatment success rate 4 weeks after the switch

	Investigator rating		Patient rating	
Clinical condition	Ν	%	Ν	%
Better or no difference	44	85%	39	75%
Better	12	23%	16	31%
No difference	32	62%	23	44%
Worse	8	15%	13	25%

Most patients (54%) preferred the LCE treatment whereas only 31 % preferred the treatment with separate levodopa/carbidopa and entacapone tablets. No major problems were encountered after the switch. This clinical trial has a relative small sample size but the enrolled patients are considered fairly representative of the target population. The switch was successful in the majority of cases and more patients preferred the fixed combination (LCE) than the original treatment.

### Direct switch from levodopa/DDCI to LCE

Direct from a standard levodopa/carbidopa combination to Stalevo was discussed since this may often require levodopa dose reduction and since Stalevo provides less flexibility for dose modification than the separate levodopa/carbidopa combination.

A direct switch to Stalevo is not recommended for patients who have dyskinesias or whose daily levodopa dose is 800mg or more as they will frequently need dose modification (see Table below).

Th	The percentage of PD patients decreasing levodopa dose by 4-6				
we	weeks after entacapone initiation as grouped by baseline				
lev	levodopa dose and presence of dyskinesia (data from previous				
stu	studies [2939033, 2939044, 2939063, 2939065])				
	Levodopa	Levodopa	Levodopa		
	< 600 mg/day	600-800 mg/day	> 800 mg/day		
	(N=180)	(N=153)	(N=105)		
No dyskinesia (N=159)	4 %	21 %	28 %		
Dyskinesia presence (N=279)	31 %	43 %	66 %		

An interim analysis of the other phase IIIb study (Study 2939103 - TCINIT) was presented. This study focuses on the direct switch from levodopa/DDC-inhibitor to the fixed combination (LCE). PD patients without painful dyskinesia experiencing motor fluctuations not stabilized on levodopa/DDCI are enrolled in this study. Entacapone (Comtess/Comtan) administered as an add-on to the original levodopa/DDCI treament is used as a control. All data from patients treated for at least two weeks after the switch were extracted from the database and included in the analysis. The study medications were started on the day following the baseline visit, i.e. day 1. The study visits during the study treatment period took place at weeks 1, 2, 4 and 6 (visits 2-5). Additionally, a mandatory telephone contact was scheduled at day three ( $\pm 1$  day) to assess any adverse events and need for adjustment of levodopa daily dosage. A two-week follow-up period took place after the study treatment period and the end-of-study visit two weeks later (visit 6, week 8). At the time of the interim analysis, 111 patient had been treated for at least 2 weeks, 72 for at least 6 weeks, and 66 had completed the additional 2 weeks follow up as well.

The addition of entacapone was successful in both groups as shown by the results at two weeks. At six weeks, most patients were doing better than before adding entacapone. Due to the low number of patients treated for longer than two weeks, a comparison of the treatment arms was not possible at this stage.

As expected, the percentage of patients with positive symptoms (i.e. symptoms of fluctuations often present) decreased after adding entacapone, either as a separate tablet (control) or as part of the fixed combination tablet. The number of patients with "negative" symptoms (e.g. dyskinesias) was numerically slightly higher when the fixed combination (LCE) was used.

The results of this interim analysis as well as the separate analysis of previous clinical trials in which entacapone was added as a separate tablet provide support for the safety of a direct switch of patients with fluctuating Parkinson's disease from levodopa/DDCI therapy to the fixed LCE combination in a subset of patients. The applicant has justified the direct switch from levodopa/carbidopa to the fixed combination in patients who have no dyskinesias and whose daily levodopa dose is less than 800mg/day. These patients are unlikely to need dose adjustments. Other patients should first be stabilised with separate levodopa/carbidopa and entacapone tablets since the fixed combination does not offer the same degree of flexibility in levodopa dose modification.

### Transferring a patient from levodopa/carbidopa ratio of 10:1 to a ratio of 4:1

It was pointed out that there is a risk of CNS adverse effects when transferring a patient from levodopa/carbidopa with a 10:1 ratio to one with 4:1 ratio plus entacapone.

The analysis of adverse events in the clinical trials showed that, after adding entacapone to levodopacarbidopa there was a higher risk of certain adverse events in the 10:1 ratio group, such as dyskinesia (40% vs. 25.9%), parkinsonism aggravated (30% vs. 13.4%), and nausea (22% vs. 15.1%). The applicant has made a separate analysis of patients with a levodopa dose < 800mg/day because in the higher dose category, the mean levodopa doses were higher in the 10:1 ratio group. This analysis showed a smaller difference with regard to the dyskinesia (29% vs. 21.2%) but a more pronounced difference for nausea (29% vs. 15.2%). The analysis suggests that there is no major problem when the levodopa daily dose is less than 800mg. Nevertheless, patients with a 10:1 ratio of levodopa/carbidopa are usually not suitable for a direct switch without first adding entacapone separately.

### Discussion on clinical efficacy

According to the applicant, most patients on levodopa/carbidopa and levodopa/benserazide with endof-dose motor fluctuations can be switched to the fixed levodopa/carbidopa/entacapone combination. Results of study 2939098-SIMCOM seem to confirm the favourable benefit/risk of a switch from separate levodopa/DDC-inhibitor and entacapone to the fixed LCE combination. The doses of levodopa and entacapone matched in most patients. However, for some patients a dose titration may become necessary. The same is true for patients on levodopa/benserazide and entacapone and for patients using levodopa/carbidopa with 10:1 ratio instead of 4:1 ratio.

The potential risk of a direct switch is the aggravation/triggering of levodopa-associated adverse effects. The CPMP expressed a concern that the possible levodopa-related adverse effects would be more difficult to manage by dose modification with the fixed LCE combination. Fortunately, the need for a dose modification can be predicted on the basis of the presence of dyskinesias and the dose. Patients without dyskinesias and with a levodopa dose less than 600mg will rarely need dose modification after addition of entacapone, and patients with a dose between 600mg and 800mg have a 21% risk of dose modification. However, the applicant has demonstrated that the flexibility of the fixed LCE combination is sufficient for dose modification in most patients.

The fact that a direct switch is suitable only for a certain subgroup of PD patients is highlighted in the SmPC. Thus, it is stated that usually, patients are switched to the fixed LCE combination only after they have been stabilised by using separate levodopa/DDCI and entacapone. The recommendation that a direct switch is feasible only in patients with a daily levodopa dose less than 800mg and without dyskinesias is supported by previous experience. For other patients it is advisable to introduce entacapone treatment as a separate medication (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Stalevo.

Patients who are on modified-release levodopa products and patients who are having a daily levodopa dose exceeding 1500 mg should not be switched directly to the fixed LCE combination.

### **Clinical safety**

### Levodopa/carbidopa

Levodopa/carbidopa has been in extensive clinical use for long time (>25 years) within the EU. Thus, the safety profile of this combination is well known. Carbidopa reduces the peripheral side effects of levodopa, such as nausea, vomiting, hypotension and cardiac arrhythmias, but not the central side effects. Motor fluctuations and dyskinesias are the most problematic long-term adverse effect of levodopa. The most common form is end-of-dose deterioration or wearing-off phenomenon. Entacapone treatment has reduced these fluctuations, as documented in Comtess/Comtan dossier. The most common levodopa-related dyskinesia is the so-called "peak-dose" dyskinesia, occurring when the plasma levodopa levels are high. Another form of levodopa-related dyskinesia is the so-called diphasic dyskinesia. It is characterised by a sequence of parkinsonism-dyskinesia-improvement-dyskinesia-parkinsonism following levodopa administration. Other central side effects of levodopa therapy include psychiatric problems, particularly hallucinations, delusions, and nightmares. The risk factors for neuropsychiatric adverse effects are increasing age, underlying dementia, intercurrent disease, polytherapy and a prior history of psychiatric disease.

## Entacapone

The safety profile of entacapone when used as adjunct to levodopa/carbidopa is acceptable. The most important undesirable effects due to entacapone itself are abdominal pain and diarrhoea. In the majority of the patients these undesirable effects were graded mild or moderate. By adding entacapone to L-dopa the dopaminergic side-effects, especially dyskinesia, are increased during on time.

### Safety of the LCE product

As compared to the approved dosing of the reference products (Sinemet and Comtess/Comtan), the proposed dosing for Stalevo would provide the same dose of entacapone, a lower maximal dose of levodopa (1500mg/day vs. 2000mg/day) and a higher maximal dose of carbidopa (375mg/day vs. 200mg/day).

On the basis of preclinical studies, carbidopa is well tolerated a high dose levels. According to the data provided, a large proportion of patients who participated in the previous clinical studies of entacapone in combination with levodopa/carbidopa had carbidopa doses exceeding 200mg/day. The company performed an analysis of previous entacapone studies with respect to the safety of conventional (i.e.<200mg) and high (i.e.>200mg/day) carbidopa doses in their clinical trial database. With the exception of dyskinesia (29.1 vs 18%) and hyperkinesias (14.5 vs. 6.9%), there were no striking increases in the incidence of adverse events in the high carbidopa dose group as compared to the low dose group. The same difference was seen in the high and low benserazide groups, suggesting that the difference was not due to the DCC-inhibitor but rather due to the higher mean levodopa dose. The incidence of serious adverse events was also higher in the high carbidopa dose group as compared to the low dose group. The difference was seen in the categories of gastrointestinal system disorders, body as a whole - general disorders, and musculoskeletal and connective tissue disorders. By screening the list of SAEs in the high carbidopa dose group, no specific patterns could be observed. The central nervous system effects were compatible with a levodopa effect. Again, the incidence of serious adverse events was also higher for the high dose benserazide groups as compared to the low dose group. In conclusion, the differences between the low and high carbidopa dose groups in terms of tolerability were apparently due to the effects of concomitant levodopa.

### Discussion on clinical safety

Bioequivalence studies demonstrated that the new LCE products produce essentially similar plasma levels of levodopa, carbidopa and entacapone as the separate products. Particularly, no exceptionally high levels of entacapone were observed after the test products compared to the reference products. In these circumstances, the safety profile and vital signs were comparable between products.

Apart from the safety profile as established with entacapone (Contess/Contan) dossier, the safety of a higher maximal carbidopa dose was questioned. The analysis provided by the applicant provided assurance for the safety of carbidopa doses between 200 and 375mg.

# 5. Overall conclusions and benefit/risk assessment

# Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no outstanding quality issues, which have a negative impact on the benefit/risk balance. As a follow-up measure, the applicant will provide data concerning additional analytical methodology, plus further stability results when available

# Preclinical pharmacology and toxicology

The applicant has included a WEU-justification covering all the indents of Directive 2001/83/EC set out in Annex I Part 3 (I) and Part 4(I) for the use of levodopa/carbidopa. Therefore, the legal basis under which the application has been submitted (Article 10 (1) ii) of Directive 2001/83/EC) is valid.

The demonstration of the well-established use of levodopa/carbidopa is also in line with the draft Note for Guidance on the Non-clinical documentation of medicinal products with well-established use by the SWP/CPMP.

The summary of the applicant of the previously submitted preclinical documentation concerning the concomitant use of levodopa/carbidopa and entacapone demonstrates that no new preclinical studies of the safety of the combined use are necessary.

The presence of new impurities in the product does not seem to change the toxicity profile of the LCE product and therefore do not affect significantly the benefit/risk of the LCE product.

### **Efficacy**

The fixed combination of levodopa/carbidopa/entacapone (LCE) fulfills the requirements of the CPMP Note for guidance on fixed combination medicinal products in that all components contribute to the efficacy and that there are no (unknown) adverse PK or PD interactions. The pharmacokinetics of the individual components are also compatible. Bioequivalence has been demonstrated according to the CPMP Note for guidance on the investigation of bioavailability and bioequivalence.

The applicant has shown that the selected strengths will sufficiently cover the doses used in the current clinical praxis.

The clinical benefit of fixed combination products would be, primarily, the simplification of therapy. The reduction of the number of tablets to be swallowed is clinically relevant in advanced PD patients, who may have difficulties in swallowing and who often have to take multiple medicinal products for their PD and for concomitant diseases. Interim results of two ongoing small clinical studies support the feasibility of the fixed LCE combination.

The switch from the fixed combination levodopa/carbidopa tablets and entacapone tablets taken separately to a fixed combination LCE product should be non-problematic when the dose of levodopa in the fixed LCE combination match with the levodopa dose before the switch. For other patients already on both levodopa/carbidopa and entacapone, a dose titration may become necessary. The same is true for patients on levodopa/benserazide and entacapone.

The proposed fixed combination does not provide the same flexibility for the titration of levodopa dose as the reference product. However, based on data provided, situations where the levodopa dose provided by the fixed LCE combination does not match with the desired levodopa dose are rare.

The issue of levodopa dose titration is highlighted in the situation when patients with a fluctuating PD will be transferred directly from a fixed combination levodopa/carbidopa to the fixed LCE combination. On the basis of previous experience, it is expected that the switch will be feasible in patients who are not likely to require dose modifications, i.e. patients with relatively low levodopa daily doses and without dyskinesias. Data from previous clinical trials with entacapone (Comtess/Comtan) as well as preliminary data from ongoing studies with the fixed LCE combination suggest that patients with a levodopa dose less than 800mg and without dyskinesias will rarely need dose titration. For other patients, a dose titration with levodopa/levodopa tablets and with separate entacapone tablets is recommended.

Patients who are on modified-release levodopa products and patients who are having a daily levodopa dose exceeding 1500mg should not be switched to the fixed LCE combination. The SPC has been revised accordingly. (see section 4.2)

### <u>Safety</u>

Based on available data, the safety of the LCE fixed combination products should be comparable with the data obtained from the previous clinical studies of entacapone with separate levodopa/DDC inhibitor and from the post-marketing period of entacapone.

Safety information related to the individual components have been included in the summary of product characteristics.

The safety of the fixed combination will be monitored in the PSURs. Special emphasis will be placed on switch-related AEs.

## Benefit/risk assessment

Based on the well-established use of levodopa/carbidopa, the efficacy and safety data of entacapone in association with levodopa/carbidopa, the bioequivalence between the LCE fixed combination and levodopa/carbidopa plus entacapone, and the practical advantage of the fixed combination, the CPMP considered that the benefit-risk of the fixed combination was positive in the following indication: "Stalevo is indicated for the treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment."

"Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Stalevo was favourable in the treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.