ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Comtess 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg entacapone.

Excipients with known effect
Each film-coated tablet contains 0.53 mg soya lecithin, and 7.9 mg sodium as a constituent of the excipients.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Brownish-orange, oval, biconvex film-coated tablet with "COMT" engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Entacapone is indicated as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in adult patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.

4.2 Posology and method of administration

Entacapone should only be used in combination with levodopa/benserazide or levodopa/carbidopa. The prescribing information for these levodopa preparations is applicable to their concomitant use with entacapone.

Posology

One 200 mg tablet is taken with each levodopa/dopa decarboxylase inhibitor dose. The maximum recommended dose is 200 mg ten times daily, i.e. 2,000 mg of entacapone.

Entacapone enhances the effects of levodopa. Hence, to reduce levodopa-related dopaminergic adverse reactions, e.g. dyskinesias, nausea, vomiting and hallucinations, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating entacapone treatment. The daily dose of levodopa should be reduced by about 10-30% by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

If entacapone treatment is discontinued, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms.

Entacapone increases the bioavailability of levodopa from standard levodopa/benserazide preparations slightly (5-10%) more than from standard levodopa/carbidopa preparations. Hence, patients who are taking standard levodopa/benserazide preparations may need a larger reduction of levodopa dose when entacapone is initiated.

Renal impairment
Renal insufficiency does not affect the pharmacokinetics of entacapone and there is no need for dose adjustment. However, for patients who are receiving dialysis therapy, a longer dosing interval may be considered (see section 5.2).

Hepatic impairment
See section 4.3.

Elderly
No dosage adjustment of entacapone is required for elderly.

Paediatric population
The safety and efficacy of Comtess in children below age 18 have not been established. No data are available.

Method of administration
Entacapone is administered orally and simultaneously with each levodopa/carbidopa or levodopa/benserazide dose.

Entacapone can be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to peanut or soya or to any of the excipients listed in section 6.1.
- Hepatic impairment.
- Phaeochromocytoma.
- Concomitant use of entacapone and non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine).
- Concomitant use of a selective MAO-A inhibitor plus a selective MAO-B inhibitor and entacapone (see section 4.5).
- A previous history of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.

4.4 Special warnings and precautions for use

Rhabdomyolysis secondary to severe dyskinesias or neuroleptic malignant syndrome (NMS) has been observed rarely in patients with Parkinson's disease.

NMS, including rhabdomyolysis and hyperthermia, is characterised by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g. agitation, confusion, coma), hyperthermia, autonomic dysfunction (tachycardia, labile blood pressure) and elevated serum creatine phosphokinase. In individual cases, only some of these symptoms and/or findings may be evident.

Neither NMS nor rhabdomyolysis have been reported in association with entacapone treatment from controlled trials in which entacapone was discontinued abruptly. Since the introduction into the market, isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone and other concomitant dopaminergic medicinal products. When considered necessary, withdrawal of entacapone and other dopaminergic treatment should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of entacapone, an increase in levodopa dosage may be necessary.

Entacapone therapy should be administered cautiously to patients with ischaemic heart disease.

Because of its mechanism of action, entacapone may interfere with the metabolism of medicinal

products containing a catechol group and potentiate their action. Thus, entacapone should be administered cautiously to patients being treated with medicinal products metabolised by catechol-O-methyl transferase (COMT), e.g. rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, and apomorphine (see also section 4.5).

Entacapone is always given as an adjunct to levodopa treatment. Hence, the precautions valid for levodopa treatment should also be taken into account for entacapone treatment. Entacapone increases the bioavailability of levodopa from standard levodopa/benserazide preparations 5-10% more than from standard levodopa/carbidopa preparations. Consequently, adverse dopaminergic reactions may be more frequent when entacapone is added to levodopa/benserazide treatment (see also section 4.8). To reduce levodopa-related dopaminergic adverse reactions, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating entacapone treatment, according to the clinical condition of the patient (see sections 4.2 and 4.8).

Entacapone may aggravate levodopa-induced orthostatic hypotension. Entacapone should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

In clinical studies, undesirable dopaminergic effects, e.g. dyskinesia, were more common in patients who received entacapone and dopamine agonists (such as bromocriptine), selegiline or amantadine compared to those who received placebo with this combination. The doses of other antiparkinsonian medicinal products may need to be adjusted when entacapone treatment is initiated.

Entacapone in association with levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease and caution should therefore be exercised when driving or operating machines (see also section 4.7).

For patients experiencing diarrhoea, a follow-up of weight is recommended in order to avoid potential excessive weight decrease. Prolonged or persistent diarrhoea appearing during use of entacapone may be a sign of colitis. In the event of prolonged or persistent diarrhoea, the medicinal product should be discontinued and appropriate medical therapy and investigations considered.

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as Comtess in association with levodopa. Review of treatment is recommended if such symptoms develop.

For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered.

Comtess contains soya lecithin. Patients who are hypersensitive to peanut or soya, should not use this medicinal product.

This medicinal product contains 7.9 mg sodium per tablet. The maximum recommended daily dose (10 tablets) contains 79 mg sodium, equivalent to 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction of entacapone with carbidopa has been observed with the recommended treatment schedule. Pharmacokinetic interaction with benserazide has not been studied.

In single-dose studies in healthy volunteers, no interactions were observed between entacapone and imipramine or between entacapone and moclobemide. Similarly, no interactions between entacapone

and selegiline were observed in repeated-dose studies in parkinsonian patients. However, the experience of the clinical use of entacapone with several medicinal products, including MAO-A inhibitors, tricyclic antidepressants, noradrenaline reuptake inhibitors such as desipramine, maprotiline and venlafaxine, and medicinal products that are metabolised by COMT (e.g. catechol-structured compounds: rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, apomorphine, and paroxetine) is still limited. Caution should be exercised when these medicinal products are used concomitantly with entacapone (see also sections 4.3 and 4.4).

Entacapone may be used with selegiline (a selective MAO-B inhibitor), but the daily dose of selegiline should not exceed 10 mg.

Entacapone may form chelates with iron in the gastrointestinal tract. Entacapone and iron preparations should be taken at least 2-3 hours apart (see section 4.8).

Entacapone binds to human albumin binding site II which also binds several other medicinal products, including diazepam and ibuprofen. Clinical interaction studies with diazepam and non-steroidal anti-inflammatory medicinal products have not been carried out. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the medicinal products.

Due to its affinity to cytochrome P450 2C9 *in vitro* (see section 5.2), entacapone may potentially interfere with medicinal products with metabolism dependent on this isoenzyme, such as S-warfarin. However, in an interaction study with healthy volunteers, entacapone did not change the plasma levels of S-warfarin, while the AUC for R-warfarin increased on average by 18% [CI_{90} 11–26%]. The INR values increased on average by 13% [CI_{90} 6–19%]. Thus, control of INR is recommended when entacapone treatment is initiated for patients receiving warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy
No overt teratogenic or primary foetotoxic effects were observed in animal studies in which the exposure levels of entacapone were markedly higher than the therapeutic exposure levels. As there is no experience in pregnant women, entacapone should not be used during pregnancy.

Breast-feeding
In animal studies entacapone was excreted in milk. The safety of entacapone in infants is unknown. Women should not breast-feed during treatment with entacapone.

4.7 Effects on ability to drive and use machines

Comtess in association with levodopa may have a major influence on the ability to drive and use machines. Entacapone may, together with levodopa, cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

Patients being treated with entacapone in association with levodopa and presenting with somnolence and/or sudden sleep onset episodes must be instructed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes have resolved (see also section 4.4).

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions caused by entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of treatment. Reduction of levodopa dosage decreases the severity and frequency of these reactions. The other major class of adverse reactions are gastrointestinal symptoms, including nausea, vomiting, abdominal pain, constipation and

diarrhoea. Urine may be discoloured reddish-brown by entacapone, but this is a harmless phenomenon.

Usually the adverse reactions caused by entacapone are mild to moderate. In clinical studies the most common adverse reactions leading to discontinuation of entacapone treatment have been gastrointestinal symptoms (e.g. diarrhoea, 2.5%) and increased dopaminergic adverse reactions of levodopa (e.g. dyskinesias, 1.7%).

Dyskinesias (27%), nausea (11%), diarrhoea (8%), abdominal pain (7%) and dry mouth (4.2%) were reported significantly more often with entacapone than with placebo in pooled data from clinical studies involving 406 patients taking the medicinal product and 296 patients taking placebo.

Some of the adverse reactions, such as dyskinesia, nausea, and abdominal pain, may be more common with the higher doses (1,400 to 2,000 mg per day) than with the lower doses of entacapone.

Tabulated list of adverse reactions
The following adverse reactions, listed below in Table 1, have been accumulated both from clinical studies with entacapone and since the introduction of entacapone into the market.

Table 1. Adverse drug reactions*

Psychiatric disorders		
	Common:	Insomnia, hallucinations, confusion, paroniria
	Very rare:	Agitation
Nervous system disorders		
	Very common:	Dyskinesia
	Common:	Parkinsonism aggravated, dizziness, dystonia, hyperkinesia
Cardiac disorders**		
	Common:	Ischaemic heart disease events other than myocardial infarction (e.g. angina pectoris)
	Uncommon:	Myocardial infarction
Gastrointestinal disorders		
	Very common:	Nausea
	Common:	Diarrhoea, abdominal pain, dry mouth, constipation, vomiting
	Very rare:	Anorexia
	Not known:	Colitis
Hepatobiliary disorders		
	Rare:	Hepatic function tests abnormal
	Not known:	Hepatitis with mainly cholestatic features (see section 4.4.)
Skin and subcutaneous tissue disorders		
	Rare:	Erythematous or maculopapular rash
	Very rare:	Urticaria
	Not known:	Skin, hair, beard and nail discolourations
Renal and urinary disorders		
	Very common:	Urine discoloration
General disorders and administration site conditions		
	Common:	Fatigue, sweating increased, fall
	Very rare:	Weight decrease

* Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot

be estimated from the available data, since no valid estimate can be derived from clinical trials or epidemiological studies).

** The incidence rates of myocardial infarction and other ischaemic heart disease events (0.43% and 1.54%, respectively) are derived from an analysis of 13 double-blind studies involving 2,082 patients with end-of-dose motor fluctuations receiving entacapone.

Description of selected adverse reactions
Entacapone in association with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes.

Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as Comtess in association with levodopa (see section 4.4).

Isolated cases of NMS have been reported following abrupt reduction or discontinuation of entacapone and other dopaminergic treatments.

Isolated cases of rhabdomyolysis have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The post-marketing data include isolated cases of overdose in which the reported highest daily dose of entacapone has been 16,000 mg. The acute symptoms and signs in these cases of overdose included confusion, decreased activity, somnolence, hypotonia, skin discolouration and urticaria. Management of acute overdose is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other dopaminergic agents, ATC code: N04BX02.

Entacapone belongs to a new therapeutic class, catechol-O-methyl transferase (COMT) inhibitors. It is a reversible, specific, and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa preparations. Entacapone decreases the metabolic loss of levodopa to 3-O-methyldopa (3-OMD) by inhibiting the COMT enzyme. This leads to a higher levodopa AUC. The amount of levodopa available to the brain is increased. Entacapone thus prolongs the clinical response to levodopa.

Entacapone inhibits the COMT enzyme mainly in peripheral tissues. COMT inhibition in red blood cells closely follows the plasma concentrations of entacapone, thus clearly indicating the reversible nature of COMT inhibition.

Clinical studies
In two phase III double-blind studies in a total of 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 Table 2. In study I, daily ON time (hours) was measured from

home diaries and in study II, the proportion of daily ON time.

Table 2. Daily ON time (Mean ±SD)

Study I: Daily On time (h)			
	Entacapone (n=85)	**Placebo (n=86)**	**Difference**
Baseline	9.3±2.2	9.2±2.5	
Week 8-24	10.7±2.2	9.4±2.6	1 h 20 min (8.3%) CI95% 45 min, 1 h 56 min
Study II: Proportion of daily On time (%)			
	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%

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%.

5.2 Pharmacokinetic properties

General characteristics of the active substance

Absorption

There are large intra- and interindividual variations in the absorption of entacapone.

The peak concentration (C_{max}) in plasma is usually reached about one hour after ingestion of a 200 mg entacapone tablet. The substance is subject to extensive first-pass metabolism. The bioavailability of entacapone is about 35% after an oral dose. Food does not affect the absorption of entacapone to any significant extent.

Distribution

After absorption from the gastrointestinal tract, entacapone is rapidly distributed to the peripheral tissues with a distribution volume of 20 litres at steady state (Vd_{ss}). Approximately 92 % of the dose is eliminated during ß-phase with a short elimination half-life of 30 minutes. The total clearance of entacapone is about 800 ml/min.

Entacapone is extensively bound to plasma proteins, mainly to albumin. In human plasma the unbound fraction is about 2.0% in the therapeutic concentration range. At therapeutic concentrations, entacapone does not displace other extensively bound substances (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam), nor is it displaced to any significant extent by any of these substances at therapeutic or higher concentrations.

Biotransformation

A small amount of entacapone, the *(E)*-isomer, is converted to its *(Z)*-isomer. The *(E)*-isomer accounts for 95% of the AUC of entacapone. The *(Z)*-isomer and traces of other metabolites account for the remaining 5%.

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC_{50} ~4 μM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19) (see section 4.5).

Elimination

The elimination of entacapone occurs mainly by non-renal metabolic routes. It is estimated that 80-90% of the dose is excreted in faeces, although this has not been confirmed in man. Approximately 10-20% is excreted in urine. Only traces of entacapone are found unchanged in urine. The major part (95%) of the product excreted in urine is conjugated with glucuronic acid. Of the metabolites found in urine only about 1% have been formed through oxidation.

Characteristics in patients
The pharmacokinetic properties of entacapone are similar in both young people and elderly. The metabolism of the medicinal product is slowed in patients with mild to moderate liver insufficiency (Child-Pugh Class A and B), which leads to an increased plasma concentration of entacapone in both the absorption and elimination phases (see section 4.3). Renal impairment does not affect the pharmacokinetics of entacapone. However, a longer dosing interval may be considered for patients who are receiving dialysis therapy.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. In repeated dose toxicity studies, anaemia most likely due to iron chelating properties of entacapone was observed. Regarding reproduction toxicity, decreased foetal weight and a slightly delayed bone development were noticed in rabbits at systemic exposure levels in the therapeutic range.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Croscarmellose sodium
Povidone
Magnesium stearate

Film-coating:
Polyvinyl alcohol, partly hydrolysed
Talc
Macrogol
Soya lecithin
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf- life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White high-density polyethylene (HDPE) bottles with white tamper proof polypropylene (PP) closures containing 30, 60, 100 or 175 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/082/001-003
EU/1/98/082/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 September 1998
Date of latest renewal: 3 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Orion Corporation Orion Pharma
Joensuunkatu 7
FI-24100 Salo
Finland

Orion Corporation Orion Pharma
Orionintie 1
FI-02200 Espoo
Finland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Comtess 200 mg film-coated tablets
entacapone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of entacapone.

3. LIST OF EXCIPIENTS

Contains soya lecithin and sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

Carton

30 film-coated tablets
60 film-coated tablets
100 film-coated tablets
175 film-coated tablets

Bottle label

30 tablets
60 tablets
100 tablets
175 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Carton

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

Bottle label

Orion Corporation

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/082/001	30 film-coated tablets
EU/1/98/082/002	60 film-coated tablets
EU/1/98/082/003	100 film-coated tablets
EU/1/98/082/005	175 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

comtess 200 mg [carton only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included [carton only]

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

[carton only]:

PC {number}
SN {number}
<NN {number}>

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comtess 200 mg film-coated tablets
entacapone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comtess is and what it is used for

Comtess tablets contain entacapone and are used together with levodopa to treat Parkinson's disease. Comtess aids levodopa in relieving the symptoms of Parkinson's disease. Comtess has no effect on relieving the symptoms of Parkinson's disease unless taken with levodopa.

2. What you need to know before you take Comtess

Do not take Comtess
- if you are allergic to entacapone or to peanut or soya or any of the other ingredients of this medicine (listed in section 6);
- if you have a tumour of the adrenal gland (known as pheochromocytoma; this may increase the risk of severe high blood pressure);
- if you are taking certain antidepressants (ask your doctor or pharmacist whether your antidepressive medicine can be taken together with Comtess);
- if you have liver disease;
- if you have ever suffered from a rare reaction to antipsychotic medicines called neuroleptic malignant syndrome (NMS). See section 4 Possible side effects for the characteristics of NMS;
- if you have ever suffered from a rare muscle disorder called rhabdomyolysis which was not caused by injury.

Warnings and precautions
Talk to your doctor or pharmacist before taking Comtess:
- if you have ever had a heart attack or any other diseases of the heart;
- if you are taking a medicine which may cause dizziness or light-headedness (low blood pressure) when rising from a chair or bed;
- if you experience prolonged diarrhoea consult your doctor as it may be a sign of inflammation of the colon;

- if you experience diarrhoea, monitoring of your weight is recommended in order to avoid potentially excessive weight loss;
- if you experience increasing loss of appetite, weakness, exhaustion and weight loss within a relatively short period of time, a general medical evaluation including liver function should be considered.

Tell your doctor if you or your family/carer notices you are developing urges or cravings to behave in ways that are unusual for you or you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to review your treatments.

As Comtess tablets will be taken together with other levodopa medicines, please also read the package leaflets of these medicines carefully.

The dose of other medicines to treat Parkinson's disease may need to be adjusted when you start taking Comtess. Follow the instructions that your doctor has given you.

Neuroleptic Malignant Syndrome (NMS) is a serious but rare reaction to certain medicines, and may occur especially when Comtess and other medicines to treat Parkinson's disease are suddenly stopped or the dose is suddenly reduced. For the characteristics of NMS see Section 4 Possible side effects. Your doctor may advise you to slowly discontinue the treatment with Comtess and other medicines to treat Parkinson's disease.

Comtess taken with levodopa may cause drowsiness and may cause you to sometimes suddenly fall asleep. If this happens, you should not drive or use any tools or machines (see Driving and using machines).

Other medicines and Comtess
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular please tell your doctor if you are taking any of the following:
- rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, apomorphine;
- antidepressants including desipramine, maprotiline, venlafaxine, paroxetine;
- warfarin used to thin the blood;
- iron supplements. Comtess may make it harder for you to digest iron. Therefore, do not take Comtess and iron supplements at the same time. After taking one of them, wait at least 2 to 3 hours before taking the other.

Pregnancy, breast-feeding and fertility
Do not use Comtess during pregnancy or if you are breast-feeding.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Comtess taken together with levodopa may lower your blood pressure, which may make you feel light-headed or dizzy. Be particularly careful when you drive or when you use tools or machinery.

In addition, Comtess taken with levodopa may make you feel very drowsy, or cause you to sometimes suddenly fall asleep.
Do not drive or operate machinery if you experience these side effects.

Comtess contains soya lecithin and sodium
Comtess contains soya lecithin. If you are allergic to peanut or soya, do not use this medicinal

product.

This medicine contains 7.9 mg sodium (main component of cooking/table salt) in each tablet. The maximum recommended daily dose (10 tablets) contains 79 mg of sodium. This is equivalent to 4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Comtess

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

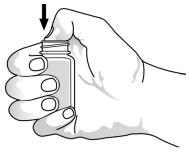
Comtess is taken together with medicines containing levodopa (either levodopa/carbidopa preparations or levodopa/benserazide preparations). You may also use other medicines to treat Parkinson's disease at the same time.

The recommended dose of Comtess is one 200 mg tablet with each levodopa dose. The maximum recommended dose is 10 tablets per day, i.e. 2,000 mg of Comtess.

If you are receiving dialysis for renal insufficiency, your doctor may tell you to increase the time between doses.

To open the bottle for the first time: open the closure, and then press with your thumb on the seal until it breaks. See picture 1.

Picture 1



Use in children and adolescents
Experience with Comtess in patients under 18 years is limited. Therefore, the use of Comtess in children or adolescents cannot be recommended.

If you take more Comtess than you should
In the event of an overdose, consult your doctor, pharmacist or the nearest hospital immediately.

If you forget to take Comtess
If you forget to take the Comtess tablet with your levodopa dose, you should continue the treatment by taking the next Comtess tablet with your next levodopa dose.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Comtess
Do not stop taking Comtess unless your doctor tells you to.

When stopping your doctor may need to re-adjust the dosage of your other medicines to treat Parkinson´s disease. Suddenly stopping Comtess and other medicines to treat Parkinson´s disease may result in unwanted side effects. See Section 2 Warnings and precautions.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Usually side effects caused by Comtess are mild to moderate.

Some of the side effects are often caused by the increased effects of levodopa therapy and are most common at the start of treatment. If you experience such effects at the start of treatment with Comtess you should contact your doctor who may decide to adjust your dosage of levodopa.

Very common (may affect more than 1 in 10 people):
- Uncontrollable movements with difficulty in performing voluntary movements (dyskinesias);
- feeling sick (nausea);
- harmless reddish-brown discolouration of urine.

Common (may affect up to 1 in 10 people):
- Excessive movements (hyperkinesias), worsening of symptoms of Parkinson´s disease, prolonged muscle cramps (dystonia);
- being sick (vomiting), diarrhoea, abdominal pain, constipation, dry mouth;
- dizziness, tiredness, increased sweating, fall ;
- hallucinations (seeing/hearing/feeling/smelling things that are not really there), sleeplessness, vivid dreams, and confusion;
- heart or artery disease events (e.g. chest pain).

Uncommon (may affect up to 1 in 100 people):
- Heart attack.

Rare (may affect up to 1 in 1,000 people):
- Rashes;
- abnormal results in liver function test.

Very rare (may affect up to 1 in 10,000 people):
- Agitation;
- decreased appetite, weight loss;
- hives.

Not known (frequency cannot be estimated from the available data):
- Inflammation of the colon (colitis), inflammation of the liver (hepatitis) with yellowing of the skin and whites of the eyes;
- discolouration of skin, hair, beard and nails.

When Comtess is given at higher doses:
In doses of 1,400 to 2,000 mg per day, the following side effects are more common:
- Uncontrollable movements;
- nausea;
- abdominal pain.

Other important side effects which may occur:
- Comtess taken with levodopa may rarely make you feel very drowsy during the day, and cause you to suddenly fall asleep;

- Neuroleptic Malignant Syndrome (NMS) is a rare severe reaction to medicines used to treat disorders of the nervous system. It is characterised by stiffness, muscle twitching, shaking, agitation and confusion, coma, high body temperature, increased heart rate, and unstable blood pressure;

- a rare severe muscle disorder (rhabdomyolysis) which causes pain, tenderness and weakness of the muscles and may lead to kidney problems.

You may experience the following side effects:

- Inability to resist the impulse to perform an action that could be harmful, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences;
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive;
  - uncontrollable excessive shopping or spending;
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger).

  Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing the symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comtess

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle label. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comtess contains
- The active substance is entacapone. Each tablet contains 200 mg of entacapone.
- The other ingredients in the tablet core are microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate.
- The film-coating contains partly hydrolysed polyvinyl alcohol, talc, macrogol, soya lecithin, yellow iron oxide (E 172), red iron oxide (E 172) and titanium dioxide (E 171).

What Comtess looks like and contents of the pack
Comtess 200 mg film-coated tablets are brownish-orange, oval tablets with "COMT" engraved on one side. They are packed in bottles.

There are four different pack sizes (bottles containing 30, 60, 100 or 175 tablets). Not all pack sizes may be marketed.

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Manufacturer
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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.