ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

COMTESS 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: entacapone
Each film-coated tablet contains 200 mg entacapone

3. PHARMACEUTICAL FORM

Film-coated tablet
Brownish-orange, oval, biconvex film-coated tablet with Comtess engraved on one side.

4. CLINICAL PARTICULARS

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.

4.1 Therapeutic indications

Entacapone is indicated as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in 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

Method of Administration

Entacapone is administered orally and simultaneously with each levodopa/carbidopa or levodopa/benserazide dose. Entacapone can be used with standard preparations of levodopa. Efficacy of entacapone as an adjunct to controlled-release levodopa/dopa decarboxylase inhibitor preparations has not been proven.

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

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 effects, 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 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 Pharmacokinetic properties).

Elderly: No dosage adjustment of entacapone is required for elderly patients.
Children: As entacapone has not been studied in patients under 18 years of age, the use of the medicinal product in patients under this age cannot be recommended.

4.3 Contraindications

Known hypersensitivity to entacapone or any of the excipients of the medicinal product (see section 6.1 List of excipients).

Pregnancy and breast-feeding (see section 4.6 Pregnancy and Lactation).

Liver impairment.

Entacapone is contraindicated in patients with pheochromocytoma due to the increased risk of hypertensive crisis.

Concomitant use of entacapone and non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine) is contraindicated. Similarly, concomitant use of a selective MAO-A inhibitor plus a selective MAO-B inhibitor and entacapone is contraindicated. Entacapone may be used with selegiline (a selective MAO-B inhibitor), but the daily dose of selegiline should not exceed 10 mg (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and special precautions for use

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-methyl dopa, and apomorphine (see also section 4.5 Interaction with other medicinal products and other forms of interaction).

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, undesirable dopaminergic effects may be more frequent when entacapone is added to levodopa/benserazide treatment (see also section 4.8 Undesirable effects). To reduce levodopa-related dopaminergic adverse effects, 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 section 4.2 Posology and method of administration and 4.8 Undesirable effects).

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 medications may need to be adjusted when entacapone treatment is initiated.

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 drugs, including MAO-A inhibitors, tricyclic antidepressants, noradrenaline reuptake inhibitors such as desipramine, maprotiline and venlafaxine, and catechol-structured medicinal products that are metabolised by COMT is still limited. Concomitant use of entacapone with these medicinal products is not recommended (see also section 4.3 Contraindications and section 4.4 Special warnings and special precautions for use).

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 Undesirable effects).
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 drugs have not been carried out. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the medicinal products.

4.6 Use during 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 (see 4.3 Contraindications).

**Lactation**

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 (see 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

Comtess together with levodopa may cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

4.8 Undesirable effects

The most frequent undesirable effects 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 effects. The other major class of undesirable effects are gastrointestinal symptoms, including e.g. nausea, vomiting, abdominal pains, constipation and diarrhoea. Urine may be discoloured reddish-brown by entacapone, but this is a harmless phenomenon.

Usually undesirable effects caused by entacapone are mild to moderate. Most commonly undesirable effects leading to discontinuation of entacapone treatment have been gastrointestinal symptoms (e.g. diarrhoea, 2.5%) and increased dopaminergic undesirable effects 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.

Some of the adverse events, such as dyskinesia, nausea, and abdominal pain, may be more common with the higher doses (1400 to 2000 mg per day) than with the lower doses of entacapone.

Undesirable effects occurring in at least 2% of patients treated for 6 months with entacapone or placebo with levodopa/DDCI (dopa decarboxylase inhibitors) in double-blind phase III studies are presented in the following table:

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS</th>
<th>Preferred term</th>
<th>Entacapone (n = 406)</th>
<th>Placebo (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTONOMIC NERVOUS SYSTEM DISORDERS</td>
<td>Hypotension postural</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>BODY AS A WHOLE - GENERAL DISORDERS</td>
<td>Fatigue</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Sweating increased</td>
<td>2.7</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>CENTRAL &amp; PERIPHERAL SYSTEM DISORDERS</td>
<td>Dyskinesia</td>
<td>27.3</td>
<td>13.9</td>
</tr>
<tr>
<td>SYSTEM ORGAN CLASS</td>
<td>Entacapone (n = 406)</td>
<td>Placebo (n = 296)</td>
<td>% of patients</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Preferred term</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism aggravated</td>
<td>8.1</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.4</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>2.7</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>2.5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cramps legs</td>
<td>2.0</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>1.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>1.2</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Gait abnormal</td>
<td>0.7</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td><strong>GASTRO-INTESTINAL SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11.1</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8.4</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7.1</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Mouth dry</td>
<td>4.2</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>3.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td><strong>PSYCHIATRIC DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.4</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>3.4</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Paroniria</td>
<td>2.0</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td><strong>SECONDARY TERMS-EVENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>2.0</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td><strong>URINARY SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine abnormal</td>
<td>12.6</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>
Slight decreases in haemoglobin, erythrocyte count and hematocrit have been reported during entacapone treatment. The underlying mechanism may involve decreased absorption of iron from the gastrointestinal tract. During long-term treatment (6 months) with entacapone a clinically significant decrease in haemoglobin have been observed in 1.5% of patients.

Rare reports of clinically significant increases in liver enzymes have been received.

4.9 Overdose

No cases of overdose have been reported with entacapone. The highest dose of entacapone given to man is 2400 mg daily. Management of acute overdosing is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: catechol-O-methyl transferase inhibitor, ATC code: NO4BX02.

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 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.
Study I

<table>
<thead>
<tr>
<th></th>
<th>Entacapone (n=85)</th>
<th>Placebo (n=86)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (±S.D.)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>9.3±2.2</td>
<td>9.2±2.5</td>
<td></td>
</tr>
<tr>
<td><strong>Week 8-24</strong></td>
<td>10.7±2.2</td>
<td>9.4±2.6</td>
<td>1h 20 min</td>
</tr>
<tr>
<td></td>
<td>(8.3%)</td>
<td></td>
<td>CI95% 45 min, 1 h 56</td>
</tr>
</tbody>
</table>

Study II

<table>
<thead>
<tr>
<th></th>
<th>Entacapone (n=103)</th>
<th>Placebo (n=102)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>60.0±15.2</td>
<td>60.8±14.0</td>
<td></td>
</tr>
<tr>
<td><strong>Week 8-24</strong></td>
<td>66.8±14.5</td>
<td>62.8±16.80</td>
<td>4.5% (0 h 35 min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CI95% 0.93%, 7.97%</td>
</tr>
</tbody>
</table>

*daily ON time (h)
**proportion ON time%

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

a) 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 a 200 mg entacapone tablet. The drug 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 181 litres. Approximately 92 % of the dose is eliminated during β-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 drugs (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam), nor is it displaced to any significant extent by any of these drugs at therapeutic or higher concentrations.

Metabolism

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%.
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.

b) Characteristics in patients

The pharmacokinetic properties of entacapone are similar in both young and elderly adults. 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 both in the absorption and elimination phases (see section 4.3 Contra-indications). 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

Preclinical data revealed 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

Microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, hypromellose, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide, red iron oxide, titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and content of container

White high-density polyethylene (HPDE) bottles with white tamper proof HD- polyethylene closures containing 30, 60, 100 or 350 tablets.
6.6 Instructions for use and handling, and disposal (if appropriate)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II
THE MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE
A. MANUFACTURING AUTHORISATION HOLDER

Manufacturer responsible for batch release

Orion Corporation, Orionintie 1, FIN-02200 Espoo, Finland

Manufacturing Authorisation issued on 10 March 1997 by the National Agency for Medicines (Lääkelaitos Läkemedelsverket), Finland.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER AND IMMEDIATE PACKAGING

Comtess 200 mg film-coated tablets
Entacapone

30 film-coated tablets
For oral use

1 tablet contains 200 mg of entacapone.
It also contains excipients such as mannitol.

Medicinal product subject to medical prescription
Keep out of the reach of children

Marketing Authorisation Holder:
Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

Exp. date: month/year
Batch No.

EU/0/00/000/000
Comtess 200 mg film-coated tablets
Entacapone

60 film-coated tablets
For oral use
1 tablet contains 200 mg of entacapone.
It also contains excipients such as mannitol.

Medicinal product subject to medical prescription
Keep out of the reach of children

Marketing Authorisation Holder:
Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

Exp. date: month/year
Batch No.
EU/0/00/000/000
PARTICULARS TO APPEAR ON THE OUTER AND IMMEDIATE PACKAGING

Comtess 200 mg film-coated tablets
Entacapone

100 film-coated tablets
For oral use

1 tablet contains 200 mg of entacapone.
It also contains excipients such as mannitol.

Medicinal product subject to medical prescription
Keep out of the reach of children

Marketing Authorisation Holder:
Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

Exp. date: month/year
Batch No.
EU/0/00/000/000
Comtess 200 mg film-coated tablets
Entacapone

350 film-coated tablets

For oral use

1 tablet contains 200 mg of entacapone.
It also contains excipients such as mannitol.

Medicinal product subject to medical prescription
Keep out of the reach of children

Marketing Authorisation Holder:
Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

Exp. date: month/year
Batch No.

EU/0/00/000/000
B. PACKAGE LEAFLET
COMTESS 200 MG FILM-COATED TABLETS

Entacapone

Please read this leaflet carefully before you start to take your medicine. It provides important information about your medicine. If you have any further questions or are not sure about anything, please contact your doctor or pharmacist.

1. COMPOSITION OF THE COMTESS TABLET

The active substance of Comtess is entacapone. Each tablet contains 200 mg of entacapone. In addition to entacapone, the Comtess tablet consists of microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, hypromellose, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide (E172), red iron oxide (E172), and titanium dioxide (E171).

Comtess is available in bottles containing 30, 60, 100 or 350 tablets.

PHARMACO-THERAPEUTIC GROUP

Catechol-O-methyl transferase inhibitor, antiparkinsonian medicinal product

2. MARKETING AUTHORISATION HOLDER AND MANUFACTURING AUTHORISATION HOLDER

Marketing Authorisation Holder and Manufacturer
Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

3. WHAT COMTESS IS USED FOR AND HOW IT WORKS

Comtess is an enzyme inhibitor used in the treatment of Parkinson’s disease in conjunction with levodopa therapy.

In Parkinson's disease the amount of dopamine is decreased in certain areas of the brain and oral levodopa is given to compensate for this decrease. Levodopa is converted to dopamine in the brain, but part of the dose is broken down by an enzyme to an inactive compound before it reaches the brain. Comtess inhibits the enzymatic degradation of levodopa, and therefore increases the amount of levodopa reaching the brain. When taken together with levodopa, Comtess improves the efficacy of levodopa therapy in alleviating the symptoms of Parkinson's disease. Comtess is used in patients in whom the effect of each levodopa dose becomes shorter (wearing-off) and who subsequently experience fluctuations in the symptoms of Parkinson’s disease. Comtess has no antiparkinsonian activity without levodopa.

4. WHEN COMTESS SHOULD NOT BE USED

Comtess must NOT be used if you:
- have a history of hypersensitivity to entacapone or any other components of the Comtess tablet (see above Composition of the Comtess tablet).
- have pheochromocytoma (a tumour of the adrenal gland), because it may increase the risk of severe hypertensive reactions.
- are taking certain antidepressants (both MAO-A and MAO-B inhibitors simultaneously, or non-selective MAO-inhibitors). If you are taking antidepressants and need further information, please ask your doctor or pharmacist whether your antidepressive medication can be taken together with Comtess.
- have liver disease.
- are pregnant or breast-feeding.

Comtess is NOT recommended if you:
- are under 18 years of age.

5. PRECAUTIONS TO BE OBSERVED BEFORE STARTING COMTESS THERAPY

Comtess enhances the absorption of levodopa. Within the first few days or weeks of therapy you may therefore experience more frequently levodopa-related undesirable effects, e.g. involuntary movements, nausea, vomiting and
hallucinations. To reduce these undesirable effects your doctor may adjust your levodopa dosage in the first few days or weeks after starting treatment with Comtess.

If you stop taking Comtess, the dosage of your other antiparkinsonian therapy may need to be adjusted to prevent the worsening of your parkinsonian symptoms. Hence, you should not stop taking Comtess treatment without first consulting your doctor.

Together with levodopa, Comtess may lower your blood pressure. This may cause dizziness. You should be careful if you are taking other medicinal products which may decrease blood pressure.

Comtess is always given in conjunction with levodopa treatment. Hence, the precautions applicable to levodopa treatment should also be taken into account when taking Comtess.

This product has been prescribed for you personally and you should not pass it on to other persons.

6. COMTESS AND OTHER MEDICINES

Comtess may increase the effects of other medicinal products such as those containing rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methylidopa, and apomorphine. Therefore, always let your doctor know of other medicines that you are taking, even those not prescribed.

Comtess may impair the absorption of iron from the gastrointestinal tract. Therefore, Comtess and iron-containing medicinal products should be taken at least 2-3 hours apart.

See section 5 Precautions to be observed before starting Comtess therapy.

7. DRIVING OR USING MACHINES WHEN TAKING COMTESS

Comtess together with levodopa may cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or operating machines.

8. INSTRUCTIONS ON HOW TO USE COMTESS

Comtess is used in combination with levodopa preparations, either levodopa/carbidopa or levodopa/benserazide. You may also use other antiparkinsonian medicinal products simultaneously.

From the beginning of Comtess treatment you should take one 200 mg tablet with each levodopa dose. If you are receiving dialysis for renal insufficiency, your doctor may tell you to extend the interval between doses. The maximum recommended dose is 200 mg ten times a day, i.e. 2,000 mg of Comtess.
What if you miss a dose?

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. To obtain the maximum benefit from your antiparkinsonian therapy always take all medicines, including Comtess, exactly as prescribed by your doctor.

In case of overdose

In the event of accidental overdose, consult your doctor or the nearest hospital immediately.

9. POSSIBLE UNDESIRABLE EFFECTS DURING THE USE OF COMTESS

The most frequent undesirable effects reported with Comtess are involuntary movements (dyskinesias), nausea, aggravated symptoms of Parkinson’s disease, urine discoloration, dizziness, diarrhoea, abdominal pain, constipation and dryness of the mouth. Usually undesirable effects caused by Comtess are mild to moderate.

The most frequent undesirable effects caused by Comtess relate to the increased effects of levodopa therapy. This occurs most commonly at the beginning of the treatment. Some of the undesirable effects, such as dyskinesia, nausea and abdominal pains, may also be more common with higher doses (1400 to 2000 mg per day) than with lower doses. Hence, if for example you notice a disturbing increase in involuntary movements (dyskinesias) after starting treatment with Comtess, you should contact your doctor for possible adjustment of your levodopa dosage to decrease the severity and frequency of these effects.

The colour of your urine may be turned reddish-brown by Comtess. However, this phenomenon is harmless and no action is required.

Sometimes abnormal results have been found in blood and urine tests and for heart rate and blood pressure in people taking Comtess for prolonged periods.

If any of the undesirable effects you notice are severe or disturbing, please inform your doctor.

10. STORAGE CONDITIONS

- Please note the expiry date on the pack. Do not use Comtess after this date.
- Keep out of the reach of children.
11. WHERE TO GO FOR FURTHER INFORMATION

For further information about Comtess, please contact the local representative of the Marketing Authorisation Holder:

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12. **DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED**