Summary

• Based on current evidence, entacapone provides clinically important improvement in function for patients with Parkinson’s disease (PD) suffering from symptoms of motor fluctuations. Long-term efficacy data beyond 6-month follow-up are not currently available.

• Entacapone was generally well tolerated in clinical trials. Most adverse events are mild and do not lead to discontinuation of treatment.

• The impact of entacapone on disease progression is unclear. There is no evidence to consider adjunctive therapy with entacapone at the onset of levodopa therapy.¹

• The ability of entacapone to delay the onset of motor fluctuations in PD patients not currently experiencing these fluctuations, requires further study.

The Technology

Entacapone is manufactured by Orion Corporation, Orion Pharma (Espoo, Finland) and marketed in North America under the trade name Comtan®, by Novartis Pharmaceuticals Corporation (East Hanover, N.J. 07936, USA).

The clinical symptoms of Parkinson’s disease are caused by the death of cells that produce dopamine in the midbrain. The cause of this cell death is unknown and it results in a reduction and deficiency of dopamine. Dopamine is used by nerves to transmit impulses.

Levodopa, which is metabolized to dopamine, is the mainstay treatment for parkinsonian symptoms. Levodopa is predominantly metabolized by the enzymes dopa decarboxylase (DDC) to dopamine and by catechol-O-methyltransferase (COMT) to 3-O-methyldopa (3-OMD).² Entacapone is in the drug class called nitrocatechols, which are selective and reversible inhibitors of COMT. Entacapone, which is to be taken with levodopa and a DDC inhibitor, inhibits COMT in peripheral tissues resulting in an increase in the bioavailability of circulating levodopa without increasing the peak concentration or absorption of levodopa.³ The resultant increased and more sustained levels of levodopa are theorized to produce more consistent dopaminergic stimulation and therefore decrease motor complications associated with peak levodopa concentrations. Entacapone taken alone has no effect on parkinsonian symptoms.⁴

Regulatory Status

Comtan® was licensed in the European Union in September 1998¹ and approved for use in the United States (FDA) on October 19, 1999. It is to be used with levodopa and a DDC inhibitor in the treatment of patients with idiopathic Parkinson’s disease.
Parkinson’s disease who experience motor fluctuations. As of October 2000, entacapone has not been approved for use in Canada.

**Patient Group**

Parkinson’s disease (PD) is a chronic neurodegenerative disorder characterized clinically by onset of bradykinesia (slowness of movement), rigidity, and resting tremor. The presence of two of these symptoms is usually used to make the diagnosis. Clinical symptoms only become apparent once 70-80% of the dopaminergic neurons have died.

PD accounts for approximately 2.6% of all neurological diagnoses. The annual incidence is estimated to be approximately 20.5/100,000 while the prevalence is approximately 300/100,000. The prevalence increases with age (few patients under 45 years have Parkinson’s, while up to 2% of those older than 85 years have the disease). The mean age at onset in Canada is estimated at 52 years.

In later stages of PD progression many patients suffer from increased disability due to levodopa-related motor fluctuations. These include dyskinesias (involuntary movements), “end-of-dose” or “wearing-off” effect and the “on-off” effect. Wearing-off occurs when the therapeutic effect starts to decline prior to the timing of the next dose. “On-off” effect refers to the sudden and usually unpredictable shift between mobile and immobile states and occurs with no relation to the timing of medication or plasma levodopa concentrations.

**Current Treatments**

At this time, treatment for PD is limited to controlling the symptoms rather than preventing further neuronal degeneration. Various drugs are used, alone or in combination, to treat Parkinson’s. These include dopaminergic agents (dopamine agonists, amantadine), levodopa combined with a DDC inhibitor, the monoamine oxidase type B inhibitor selegiline, and anticholinergic agents.

When treating patients with advanced PD a balance is sought between increasing “on” time (time with symptom improvement) while avoiding dyskinesias. Later stage disease is invariably treated with levodopa therapy combined with a peripherally acting DDC inhibitor such as benserazide or carbidopa. This combination increases the percent of the oral dose of levodopa reaching the brain from about 1% to 5-10%.

The effectiveness of levodopa treatment diminishes over time. About 75% of patients develop motor fluctuation complications after approximately six years of therapy. Wearing-off fluctuations are associated with low plasma levels of levodopa, whereas dyskinesias are usually linked with higher plasma levels. Possibly more troublesome and more difficult to deal with are the “on-off” effects, due to their sudden and unpredictable nature.

To reduce fluctuations in response to levodopa, currently available treatment options include adjustment of levodopa dose regime, use of controlled-release levodopa, use of concurrent dopamine agonists, and, where available, concurrent use of a COMT inhibitor. Combination therapy with other antiparkinsonian agents (selegiline, amantadine, and anticholinergic agents) are substantially less effective than the above mentioned strategies. Surgical options exist for patients with disabling motor fluctuations who do not respond to medical therapy.

Adjustments of levodopa dose regime or use of controlled-release levodopa are not usually sufficient to provide relief from troublesome “on-off” motor fluctuations thus necessitating the addition of another agent. The necessity of dose titration for dopamine agonists may confer some advantage to the use of entacapone when additive treatment is considered. Dopamine agonists improve end-of-dose wearing off but are thought to be less effective in eliminating the “on-off” fluctuations and may cause psychotic disturbances.
Dosage and Potential Cost

The recommended dosage of entacapone is one 200 mg tablet taken orally, without regard to meals, with each levodopa/DDC dose. It can be administered with standard or extended-release preparations of levodopa/DDC inhibitor.

In the U.S. the wholesale price of Comtan® is $1.68/200 mg tablet. The number of tablets taken per day is dependent upon the number of concurrent levodopa tablets (combined with a DDC inhibitor). The maximum daily dose is 8x200 mg. The average dose frequency in one trial was 5.8 times a day. This translates into US$9.75/day, or about C$14.50/day: about 1.5 times more expensive than the most costly dopamine agonist (pergolide).

Generic versions of levodopa (250 mg)/carbidopa (25 mg)(APO-levocarb) cost about $0.38 per tablet. This combination, including Comtan®, would result in a per day drug cost of about $16.70. Using Sinemet®, or Sinemet® CR in place of generic formulations doubles the cost of the levodopa/carbidopa. Some small savings will occur with the reduction of levodopa dose.

Improved and consistent motor function should enhance the quality of life of an individual with PD, and may lead to cost savings in other resource uses.

Projected Rate of Diffusion

Currently about 1/100 Canadians over the age of 60 is diagnosed with PD. There is no cure. Given that many PD patients are living into their eighties the number of patients experiencing disabling motor fluctuations is likely to increase. Entacapone will provide an additional way to manage late stage motor fluctuations associated with levodopa therapy. This will be of greatest benefit for patients whose symptoms are not optimally controlled with existing therapies.

A PD consensus group examined the use of entacapone, from approval in the United Kingdom in September 1998 to March 1999, and found worldwide use by approximately 20,000 patients per year.1

Tolcapone (Tasmar®), the first COMT inhibitor marketed in many countries (approved in Canada, October 1997), has been taken off the market in both Europe and Canada (November 1998), due to reports of several deaths from fatal fulminant hepatitis. Although there have been no such reports with entacapone, concern may limit uptake of therapy with any COMT inhibitor.

Concurrent Developments

New drugs are being designed to work within neurons while others are being designed to slow neuronal death. Work on non-drug interventions includes research into neurotrophic growth factors as a means of neuroprotection, gene transfer and surgical management. Three surgical approaches which have been used in a limited number of patients are ablative surgery (pallidotomy or thalmotomy), deep brain stimulation, and cell transplant.

Spheramine™ (Titan), made from cultured dopamine-producing human retinal-pigmented epithelial cells to be implanted into the brains of PD patients, is undergoing phase I/II trials. Animal studies of Spheramine™ have shown promising results.

Assessing the Evidence

Five phase III randomized controlled trials evaluating entacapone have been fully published while two phase III trials are available in abstract form. All of these trials reported, as an outcome, duration of effect or mean “on” time, often measured through the use of home diaries. Several secondary outcomes were also gathered in these studies, including impact on the Unified Parkinson Disease Rating Scale (UPDRS: a rating tool to follow the longitudinal course of Parkinson’s disease) and global evaluation, as well as adverse events. The two largest published studies and the abstracts were similar in design, evaluating entacapone over six months. The remaining studies were smaller and of
shorter duration. One study compared entacapone plus standard levodopa (Sinemet®) with entacapone plus controlled-release levodopa (Sinemet® CR). Entacapone was given as a 200 mg dose with each dose of levodopa. All studies consistently reported:

- A statistically significant improvement in “on” time. Mean baseline “on” time, as reported in one study, was reported as 9.2 hours. The duration of the improvement ranged from an additional 0.5 hours to 2.1 hours. The study comparing entacapone with standard or controlled-release levodopa found greater improvement with the controlled-release levodopa regime (0.5hrs vs. 0.8hrs). Patients experiencing lower baseline “on” time were seen to derive greater benefit.

- An improvement based on the UPDRS rating scale. The improvement was noted predominantly with subscales II (activities of daily living) and III (motor function), but was also seen in total scores. Again, the controlled-release levodopa regime showed greater improvement than the standard preparation.

- A decrease required in levodopa dosing, ranging from 12% to 50%. The decrease in levodopa dosing was required due to increased dopaminergic effects which lead to increased dyskinesias (a regularly reported adverse event attributed to levodopa).

### Adverse Effects

Worsening of dyskinesias (both duration and magnitude), nausea, diarrhea, and urine discoloration occurred more often in patients treated with entacapone. Although nausea and diarrhea were experienced more frequently in the entacapone treated patients, few patients withdrew from trials for these reasons (2-5%). Patients on entacapone also complained of shortness of breath (8%), ataxia (7%), forgetfulness, vomiting and somnolence (4%) significantly more often than those taking placebo (p = 0.03). The increase in dyskinesias is not surprising as this is a side effect of levodopa therapy. The dyskinesias tended to occur early in treatment and were usually managed by reducing the dose of levodopa.

### Implementation Issues

The studies cited above have demonstrated that entacapone enhances therapeutic response to levodopa by increasing “on” time. However a number of concerns and questions exist.

- How truly blind were the patients to the medications in the trials? The subjectivity (home diaries) of the assessment of the primary outcome (“on” time) and the fact that almost 37% of patients in one study noted urine discoloration may have led to exaggerated effects. To the credit of the investigators they evaluated whether patients knew what drug (entacapone or placebo) they were taking. Although a high proportion of patients guessed their treatment assignment correctly, the majority reported improvement in symptoms, or lack thereof, as the reason for their guess. It is unclear if the investigators became unblinded, which could have biased their global evaluation.

- For what period of time will the patient benefit from the drug? The currently available efficacy data covers only a 6-month follow-up period.

- Although no cases of hepatic failure have been noted with entacapone, none were noted during clinical trials with tolcapone either (see ‘Projected Rate of Diffusion’).


22. New drug overview: entacapone. 
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This brief was prepared by Ms. Laura McAuley; CCOHTA and has been peer reviewed. The contents of this early assessment are current as of publication date, however new information is anticipated.

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