



The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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PRESS RELEASE

ENTACAPONE (COMTESS/COMTAN) – UPDATE OF PRODUCT INFORMATION

In September 1998 the European Commission granted Orion Corporation and Novartis Europharm Ltd marketing authorisations for Comtess and Comtan (entacapone) respectively. Entacapone is a catechol-O-methyl transferase (COMT) inhibitor, indicated for the adjunctive treatment of Parkinson's disease and is available in the form of 200 mg film-coated tablets.

Comtess is currently available in the European Union in Denmark, Finland, Germany, Ireland, Sweden, and the United Kingdom. Comtan has not yet been available in the European Union.

The EMEA's scientific committee, the Committee for Proprietary Medicinal Products (CPMP), recommended the suspension of the marketing authorisation for another COMT inhibitor, tolcapone (Tasmar), on 12 November 1998 due to increasing concerns over reports of severe hepatotoxicity. An EMEA Press Release on tolcapone was released on 17 November 1998.

Given the common mechanism of action of entacapone and tolcapone, the CPMP at their plenary meeting on 17-19 November 1998 reviewed the safety data for entacapone. The most recent safety information indicate that entacapone does not appear to be hepatotoxic. However, rare reports of clinically significant increases in liver enzymes have been reported.

The CPMP has recently been made aware that abrupt withdrawal of COMT inhibition or dopaminergic medications have resulted in Neuroleptic Malignant-like Syndrome (NMS) in a rare number of cases. Rhabdomyolysis (grave disease of skeletal muscle) secondary to severe dyskinesia and NMS have also been rarely observed in patients with Parkinson's disease.

NMS 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 (CPK) which may be a consequence of rhabdomyolysis. In individual cases, only some of these symptoms and/or findings may be evident.

Although, treatment with entacapone or its discontinuation have not been associated with either NMS or rhabdomyolysis, the marketing authorisation holders considered it appropriate to introduce provisional changes to prescribing and patient information through a rapid procedure.

The company will send out an information letter to health professionals in the European Union shortly. The EMEA thought it necessary to provide this new information to the public at this stage.

The following information will be introduced in the patient information:

- Comtess/Comtan must not be used if you have a history of Neuroleptic Malignant Syndrome and/or non-traumatic rhabdomyolysis (rare form of muscle disorder).
- If you need to stop taking Comtess/Comtan, please consult your doctor. Withdrawal of Comtess/Comtan treatment may have to be done gradually and your other antiparkinsonian therapy may need to be adjusted to prevent the worsening of your parkinsonian symptoms or unwanted side effects (e.g., rigidity, shakiness, agitation, confusion, fever).

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The following provisional changes have been made to the prescribing information:

- Entacapone is not recommended for patients with a previous history of NMS and/or non-traumatic rhabdomyolysis.
- Rhabdomyolysis secondary to severe dyskinesias or NMS has also been observed rarely in patients with Parkinson's disease, although it has not been reported during entacapone treatment.
- Neuroleptic Malignant Syndrome (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 (CPK) which may be a consequence of rhabdomyolysis. 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. Nevertheless, because NMS has been reported rarely in Parkinson's disease patients when other dopaminergic medications were withdrawn abruptly, prescribers should exercise caution when discontinuing entacapone treatment. When considered necessary, withdrawal should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of entacapone, an increase in levodopa dosage may be necessary.

Healthcare professionals are encouraged to report any new suspected adverse reactions through national adverse drug reaction reporting systems or directly to Orion Corporation (Comtess) or Novartis Europharm (Comtan) directly.

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