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

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PUBLIC STATEMENT ON
SIFROL, DAQUIRAN, MIRAPEXIN (Pramipexole) - SUDDEN ONSET OF SLEEP

The European Commission granted marketing authorisations for the European Union to Boehringer Ingelheim International GmbH on 14 October 1997 for Sifrol®, to Dr. Karl Thomae GmbH on 27 October 1997 for Daquiran® and to Pharmacia & Upjohn S.A. on 23 February 1998 for Mirapexin®. Pramipexole containing medicinal products were first launched in the European Union in June 1998 and are currently marketed as Mirapexin® in Greece, Italy, Spain and United Kingdom and as Sifrol® in Denmark, Finland, Germany, the Netherlands and Sweden. Daquiran® has not yet been launched in the European Union.

Pramipexole is currently authorised in the European Union for the treatment of signs and symptoms of advanced idiopathic Parkinson's disease in combination with levodopa. Pramipexole is available as 0.088 mg, 0.18 mg, 0.7 mg, 0.88 mg and 1.1 mg tablets.

Since July 1997, when pramipexole was launched in the United States, an estimated 100,000 patient years have been treated world-wide, approximately 10% of patients in the European Union. The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP), has been evaluating new safety information as it emerges.

On 25 June 1999, the Marketing Authorisation Holders provided the EMEA with new information relating to sudden onset of sleep associated with pramipexole administration. This information related to a total of 19 cases of sudden onset of sleep reported in the USA. Fourteen of these occurred while patients were driving resulting in 9 car accidents with minor injuries in some cases. These episodes could occur at any time after initiation of the treatment and at any dose within the recommended range. These episodes are potentially life threatening to the patient and others depending on the circumstances and have been reported in some cases without awareness of warning signs and, therefore, may occur unpredictably. Sudden onset of sleep is distinct from drowsiness or sedation as some patients experienced an acute uncontrollable urge to sleep. In most cases, where information was available, sudden onset of sleep did not reoccur after reduction of dosage or termination of pramipexole.

Following an initial review of this information, the EMEA wishes to draw attention to the occurrence of these potentially unpredictable, life threatening, episodes of sudden onset of sleep which have been rarely reported with pramipexole administration.

- **Patients being treated with pramipexole should be strongly advised not to drive or engage in other activities where impaired alertness could put themselves or others at risk of serious injury or death (e.g. operating machines).**
- **Patients that have experienced sudden onset of sleep should immediately contact their physician.**
- **Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with pramipexole.**

As an urgent measure, special warnings and special precautions for use have been introduced to prescribing and patient information through a rapid procedure (see attachment) at the request of the marketing authorisation holders. The companies are in the process of sending out a letter informing health professionals in the European Union. The EMEA thought it necessary to provide this new information to the public at this stage. This will be followed by a more comprehensive evaluation of this issue by the CPMP at their plenary meeting on 27-29 July 1999 and further information will be made available in the July CPMP Press Release.

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PROVISIONAL CHANGES INTRODUCED
TO PRESCRIBING AND PATIENT INFORMATION

INFORMATION TO PATIENTS:

Take special care with Sifrol/Daquiran/Mirapexin if:

- you experience sudden onset of sleep or excessive drowsiness. You should contact your physician

Driving and using machines

SIFROL/DAQUIRAN/MIRAPEXIN can cause hallucinations and drowsiness (somnolence).

Sudden onset of sleep has been rarely reported and can occur at any time during treatment. You are strongly advised not to drive or engage in other activities where impaired alertness could put yourself or others at risk of serious injury or death (for example, operating machines), whilst taking this medication.

Taking other medicines:
Please inform your doctor or pharmacist. You may need a different dose of pramipexole if you are taking or have recently taken any other medicines, in particular those which affect kidney function or are excreted by the kidneys.....e.g. amantadine or drugs that may cause drowsiness (somnolence) or alcohol.

Possible side effects:
Sudden onset of sleep with or without prior feeling of drowsiness (somnolence).

INFORMATION TO PRESCRIBERS:

4.4 Special warnings and special precautions for use

Sudden onset of sleep during daily activities has been reported in rare cases. This can be life-threatening to the patient or others depending on the circumstances. These episodes have been reported in some cases without awareness of warning signs. If this occurs, reduction of dosage or termination of therapy should be considered. Patients being treated with pramipexole should be strongly advised not to drive or engage in other activities where impaired alertness could put themselves or others at risk of serious injury or death (e.g. operating machines). Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with pramipexole (see section 4.7 Effects on Ability to Drive and Operate Machines and section 4.8 Undesirable Effects).

4.5 Interaction with other medicinal products and other forms of interaction

Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with pramipexole.

4.7 Effects on ability to drive and use machines

Rare cases of sudden onset of sleep have also been reported (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). These episodes can be life-threatening depending on the circumstances and have occurred in some cases without awareness of warning signs. Patients being treated with pramipexole should be strongly advised not to drive or engage in other activities where impaired alertness could put themselves or others at risk of serious injury or death (e.g. operating machines).

4.8 Undesirable Effects

Sudden onset of sleep has been rarely reported during post-marketing experience. A number of these episodes have occurred while patients were driving, resulting in motor vehicle accidents. There was no clear relation to the duration of treatment. Some patients were taking other medication with potentially sedating properties. In most cases where information was available there were no further episodes following reduction of dosage or termination of therapy (see section 4.7 Effects on Ability to Drive and Operate Machines and section 4.4 Special Warnings and Special Precautions for Use).

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