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

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PUBLIC STATEMENT ON
SIFROL, DAQUIRAN, MIRAPEXIN (Pramipexole)

RECOMMENDATION TO REINFORCE THE WARNING ON 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 is one of the currently available dopaminergic agonists 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 and 1.1 mg tablets.

Following reports of potentially unpredictable, life threatening, episodes of sudden onset of sleep with pramipexole administration, changes to the Summary of Product Characteristics and Package Leaflet of pramipexole were introduced through an Urgent Safety Restriction procedure on 15 July 1999. Information was released in a Public Statement (EMEA/20642/99) by the EMEA on 19 July 1999.

A total of 20 cases of sudden onset of sleep have now been reported in the USA. Fourteen of these occurred while patients were driving resulting in 9 car accidents with minor injuries in some cases.

In a follow-up to the Urgent Safety Restriction procedures, the CPMP carried out a more comprehensive evaluation of this issue at their plenary meeting on 27-29 July 1999 including an oral presentation from the Marketing Authorisation Holders. A further strengthening of the wording in the Summary of Product Characteristics and Package Leaflet was agreed with the Marketing Authorisation Holders:

- **Patients being treated with pramipexole must be informed 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).**

In addition, information about the dose dependency of the somnolence was included in the Summary of Product Characteristics:

- **The incidence of somnolence is increased at doses higher than 1.5 mg/day (salt)**

The CPMP adopted revised Summary of Product Characteristics and Package Leaflets (see attachment) through Type II variations on 29 July 1999.

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.

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CHANGES TO PRESCRIBING AND PATIENT INFORMATION ADOPTED BY THE CPMP ON 29 JULY 1999

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 and without awareness of warning signs. Whilst taking this medicine you should not 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).

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:

4.2 Posology and method of administration

If a further dose increase is necessary the daily dose should be increased by 0.54 mg base (0.75 mg salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.

However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg/day (see section 4.8 Undesirable Effects)

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 must be informed 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 been reported in some cases without awareness of warning signs. Patients being treated with pramipexole must be informed 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). (see section 4.5 Interaction with other medicinal products and other forms of interaction)

4.8 Undesirable Effects

The following adverse events have been reported more frequently during the use of pramipexole than under placebo: nausea, constipation, somnolence and hallucinations. The incidence of somnolence is increased at doses higher than 1.5 mg/day (see section 4.2 Posology and method of administration).

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).