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

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CPMP POSITION STATEMENT
DOPAMINERGIC SUBSTANCES AND SUDDEN SLEEP ONSET

Summary

In February 2000, the CPMP initiated a review of the dopamine agonists (dopaminergic substances) in relation to episodes of sudden onset of sleep[1]. The review was considered necessary following observations of sleep attacks in several patients suffering from Parkinson's disease and treated with the newer dopamine agonists. For pramipexole and ropinirole changes to the Summaries of Product Characteristics had been implemented through Urgent Safety Restrictions across the EU. This class review was carried out by the CPMP and its Pharmacovigilance Working Party (PhVWP).

The objectives of the class review was to evaluate available scientific evidence regarding sudden sleep onset episodes, to review current product information of dopamine agonists and to formulate proposals for regulatory action if required.

The following medicinal products[2] were included in the review:

levodopa (in combinations with carbidopa/benserazide), apomorphine, bromocriptine, cabergoline, α-dihydroergocryptine, lisuride, pergolide, piribedil, pramipexole, quinagolide and ropinirole.

Based on the review of available data from clinical studies, spontaneous reports and published literature, together with data on patient exposure, the following conclusions were drawn by the PhVWP and adopted by the CPMP:

- Sleep disturbances can be a feature of Parkinson's disease and a drug-disease interaction with dopamine agonists may contribute to such disturbances.
- All dopamine agonists, to varying degrees, have been associated with somnolence, which in some patients can be marked. Drug combinations may worsen this adverse reaction.
- Within spontaneous reporting, episodes suggestive of sudden sleep onset have been reported to varying degrees for most of the dopamine agonists. Even taking certain limitations (e.g. under-reporting, stimulated reporting, a wide range in patient exposure) into account, it appeared that these adverse drug reactions are more frequently reported with ropinirole, pramipexole and possibly cabergoline.
- Somnolence and episodes of sudden sleep onset can impair driving and adversely affect activities of daily living.

Based on these conclusions and taking into account the differing reporting frequencies with regard to sudden sleep onset episodes for the various dopaminergic compounds, as well as a difference among the compounds with regard to the approved indications, the following recommendations for changes to the Summaries of Product Characteristics and Package Leaflets are put forward by the CPMP:

[1] Sudden onset of sleep, operative definition: Abrupt episodes of unplanned sleep during activities of daily living where they are not expected to occur (e.g. speaking, eating, drinking, standing, cooking and driving). These episodes may or may not be preceded by somnolence or sedation. Depending on the circumstances the episodes may last a few minutes or hours.

[2] Some of the drugs are approved for other indications than Parkinson's disease: Quinagolide for hyperprolactinemia only; lisuride, bromocriptine and cabergoline for Parkinson's disesase and hyperprolactinemia; α-dihydroergocryptine for Parkinson's disease and cognitive impairment, vascular dementia, prophylaxis for headache and migraine, hyperprolactinemia and lactation inhibition.

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Recommendations for the Summaries of Product Characteristics

For Section 4.4 on Special Warnings and Special Precautions for Use:

for levodopa:
Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

for bromocriptine, piribedil:
<INN> has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with <INN>. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

for pergolide:
Pergolide has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with pergolide. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

for cabergoline, pramipexole, ropinirole:
<INN> has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with <INN>. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

for apomorphine, α-dihydroergocryptine, lisuride, quinagolide:
<INN> has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with <INN>. Patients who have experienced somnolence must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

For Section 4.7 on Effects on Ability to Drive and Use Machines:

for bromocriptine, cabergoline, levodopa, pergolide, piribedil, pramipexole, ropinirole:
Patients being treated with <INN> and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4).

for apomorphine, α-dihydroergocryptine, lisuride, quinagolide:
Patients being treated with <INN> and presenting with somnolence must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) unless patients have overcome such experiences of somnolence (see also Section 4.4).

For Section 4.8 Undesirable Effects:

for bromocriptine, levodopa, piribedil:
<INN> is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

for pergolide:
Pergolide is associated with somnolence and has been associated rarely with excessive daytime somnolence and sudden sleep onset episodes.

for cabergoline, pramipexole, ropinirole:
<INN> is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

for apomorphine, α-dihydroergocryptine, lisuride, quinagolide:
<INN> is associated with somnolence.

Recommendations for the Package Leaflets

For Section on Warnings and Precautions:

for bromocriptine, cabergoline, levodopa, pergolide, piribedil, pramipexole, ropinirole:
During treatment with <(invented) name of product> take special care when you drive or operate a machine. If you experience excessive drowsiness or even a sudden sleep onset episode, refrain from driving and operating machines, and contact your physician.

for apomorphine, α-dihydroergocryptine, lisuride, quinagolide:
During treatment with <(invented) name of product> take special care when you drive or operate a machine. If you experience excessive drowsiness, refrain from driving and operating machines, and contact your physician.

For Section on Driving and Using Machines:

for bromocriptine, cabergoline, levodopa, pergolide, piribedil, pramipexole, ropinirole:
<(Invented) name of product> can cause somnolence (excessive drowsiness) and sudden sleep onset episodes. Therefore you must refrain from driving or engaging in activities where impaired alertness may put yourself or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved.

for apomorphine, α-dihydroergocryptine, lisuride, quinagolide:
<(Invented) name of product> can cause somnolence (excessive drowsiness). Therefore you must refrain from driving or engaging in activities where impaired alertness may put yourself or others at risk of serious injury or death (e.g. operating machines) unless you have overcome such experiences of somnolence.

For Section on Possible Side Effects:

for bromocriptine, cabergoline, levodopa, pergolide, piribedil, pramipexole, ropinirole:
Somnolence (excessive drowsiness)
Sudden sleep onset episodes

for apomorphine, α-dihydroergocryptine, lisuride, quinagolide:
Somnolence (excessive drowsiness)