Review of the available evidence on Oral Dopamine Agonists For Parkinson’s Disease

FOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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WHO Model List Application, November, 2014

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1. Summary statement of the proposal

This proposal was produced upon request of the 19th Expert Committee on the Selection and Use of Essential Medicines, that identified dopamine agonists (DAs) in the treatment of idiopathic Parkinson’s Disease (PD) as an important area for a comprehensive review of the biomedical literature. There is a substantial body of evidence on the efficacy and safety of DAs, since they have been evaluated in various trials and systematic reviews (SRs), and national agencies such as the National Institute for Health and Clinical Excellence (NICE) issued recommendations on their use in PD. Moreover, one very large, pragmatic trial published just before the completion of this application provided substantial evidence on the role of DAs, as well as other classes of drugs that can be used instead of - or as an adjunct to - levodopa in the treatment of PD.

In this document the role of drugs other than DAs that could be used in the early stage of PD or as adjunct treatment to levodopa have not been considered.

The available evidence suggests that the use of DAs instead of levodopa in the early stages of PD, although giving a lower risk of motor side effects, does not provide clinically relevant long-term benefits over levodopa in terms of quality of life.

In the advanced stage of PD, as an adjunct treatment to levodopa, DAs may reduce the time spent in the “off” motor state (an unpleasant sensation of difficulty with movement), allow lower doses of levodopa, improve UPDRS scores in patients with levodopa-associated motor complications, while increasing the risk of non motor side effects that, particularly in the elderly, may be at least as important as motor complications for patients and caregivers.

There is no strong evidence suggesting that DAs as add-on therapy to levodopa can provide a clinically positive benefit/risk ratio for all persons with advanced PD; nevertheless, they may confer some benefit in managing levodopa-related motor complications in younger patients.

3. Name of the organization consulted and/or supporting the application
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4. International Nonproprietary Name (INN, generic name) of the medicine:
The International Nonproprietary Name (INN) of the medicines are:
Bromocriptine, Cabergoline, Dihydroergocrytpine mesylate, Pramipexole, Ropinirole.

5. Formulation proposed for inclusion; including adult and pediatric (if appropriate)
Bromocriptine, Cabergoline, Dihydroergocrytpine mesylate, Pramipexole, Ropinirole.

6. International availability - sources, if possible manufacturers (Annex A)
A list of manufacturers that have active status in the Drug Master File of the Food and Drug Administration (FDA) is available in Annex A.
Dopamine agonists are registered in many developed and non developed countries. The choice of the manufacturer for any of the DAs will depend on the price and availability at the local or national level.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group
Listing is requested on the Model List of Essential Medicines as individual medicines, to be included in the section 9 Anti parkinsonism medicines of the WHO EML.
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment on current use, target population)

Definition of Parkinson’s disease

Parkinson’s disease (PD) is one of the most frequent progressive neurodegenerative diseases in the elderly, diagnosed in about 1% of people aged over 65 years, and affecting both males and females. Onset is usually in the fifth or sixth decade of life.

The onset of PD is gradual and it evolves slowly over many years (mean survival is over 10 years). Its commonest clinical manifestations are tremor at rest, rigidity, slowness of movement (bradykinesia) and poverty of movement (hypokinesia). Gait disturbances, postural instability and falls, orthostatic hypotension, and dementia may develop during the course of the disease. Idiopathic PD should be distinguished from other degenerative and non-degenerative conditions presenting with similar clinical features, grouped under the umbrella term of “Parkinsonism”. About 80% of people with Parkinsonism are affected by idiopathic PD. Differentiating PD from other mimicking conditions is important because many do not respond to the treatment used for PD and have a different prognosis from PD. Growing evidence suggests that idiopathic PD itself is a heterogeneous disorder, including different subtypes with variable clinical features and natural history. The diagnosis of PD is primarily a clinical one and depends on the presence of a specific set of symptoms and signs, as well as on the history and on the response to drug therapy. There is no consistently reliable test that can distinguish PD from other conditions that have similar clinical presentations. (WHO Neurological Disorders, 2006; Thenganatt 2014)

Epidemiology of PD

Prevalence
Prevalence estimates of PD vary substantially. Differences in prevalence may be related to environmental risk factors or differences in the genetic background of populations. The increase of new patients being diagnosed each year may in part reflect increased awareness and earlier recognition of the disease (WHO Neurological Disorders 2006).

Both the prevalence and the incidence of idiopathic PD are age-related. The prevalence of PD varies from 100 to 180 per 100,000 of the population, and is increasing with age. European studies suggest similar prevalence across European countries, provided that similar methodologies and diagnostic criteria are used. The overall prevalence estimates range from 0.6% for those aged 65 to 69 years to 3.5% for those aged 85 to 89 years, with an overall prevalence of 1.6% for subjects aged 65 years or older (De Rijk 2001).

Epidemiological data from developing countries are scarce. In sub-Saharan Africa the few available data suggest a crude prevalence rate of 30/100,000 (men), 11/100,000 (women) and 20/100,000 (combined), while in India the overall prevalence is 0.33% population. Age-specific prevalence ratios increase with age (Dotchin 2008; Bharucha 1988).

In China the prevalence of PD seems similar to that in developed countries (1.7% (95% CI 1.5-1.9) for those aged 65 years or older), with an estimated 1.7 million affected people, aged 55 years or older, in the country (Zhang 2005).

Incidence
Studies on incidence of PD are scarce. The estimated overall annual incidence of idiopathic PD ranges from 15 to 20 per 100,000 (NICE 2011). Age-adjusted rates range from 9.7 to 13.8 per 100 000 population per year (WHO Neurological Disorders 2006).

In Europe the Rotterdam study (performed with individual screening) showed an incidence of about 250 per 100,000 person years for the age group 75 to 84 years (De Rijk 2001).
Morbidity
Patients with PD suffer from many problems that, being not directly related to motor function, are referred to as “non-motor symptoms”; these features have a major impact on quality of life and are a very important aspect to be considered in delivering care to people with PD.
A large percentage of patients with idiopathic PD will develop a depression during the course of their disease. Clinically significant depressive symptoms have been reported in 35% to 50% of patients. Dementia (the progressive loss of global cognitive function) also appears in a high frequency in patients during the course of the disease, with prevalence figures varying from 24 to 31%. Other non-motor symptoms that may affect a substantial proportion of patients with idiopathic PD are: excessive daytime sleepiness (prevalence 15% to 54%), orthostatic hypotension (the most frequently reported autonomic disturbance in idiopathic PD, occurring in about half of the community dwelling patients), sialorrhea (excessive saliva or drooling, occurring in 70-80% of patients), impairment of swallowing (dysphagia), psychotic symptoms (particularly visual hallucinations, occurring in 30% to 50% of patients), frequent falls. (SIGN 2010, NICE 2011)
Other non-motor symptoms contributing to the disease burden of PD may be gastrointestinal (weight loss, constipation), urinary (urgency, nicturia, incontinence), sexual (impaired erection/ejaculation, vaginal dryness, anorgasmia) and sleep disturbances (insomnia, restless legs syndrome, REM Sleep Behavior Disorder).

Mortality
The burden of concurrent diseases, particularly dementia and depression, reduces the life expectancy of patients with PD; epidemiological studies report a standardized mortality ratio consistently > 1, ranging from 1.6 to 3.4. Since the early 1970s, survival of patients has increased, possibly due to levodopa treatment and to improvement of the management of patients. (DeRjik 2001)

The global burden of PD
PD has a considerable impact on patients and their families as well as healthcare and social care systems. Impairment is not only functional, but also psychological and social, since motor limitations, causing dependency, have important implications on the patient’s relational, social and professional abilities.
The economic burden of PD includes direct costs (such as drugs, doctor’s fees, diagnostic investigations, transportation expenses) as well as indirect costs (productivity loss due to sickness or early retirement, home nursing care in the advanced stages of the disease). (WHO EML 2013)

According to the Global Burden of Disease Study, in 2012 PD accounted for 2,461,000 disability-adjusted life years (DALYs), where one DALY can be thought of as one lost year of healthy life and the burden of disease as a measure of the gap between current health status and an ideal situation where everyone lives into old age free from disease and disability. This represents 0.1% of the global health burden. (WHO Global Health Estimates 2014)

Treatment of PD
Parkinson’s disease results from the loss of the dopaminergic neurons of the substantia nigra, with resulting decrease of the striatal dopamine availability. Current pharmacological treatment is centered upon dopamine replacement to alleviate symptoms. So far no medicine has proven to be disease-modifying by stopping or reversing the neurodegenerative process that leads to PD, therefore motor symptoms continue to progress, requiring increasing doses of medication, which result in short-term adverse effects and in intermediate- to long-term motor complications.
Since all available drugs have a symptomatic effect, the initial decision in the treatment of PD is whether or not to start pharmacotherapy in the early phase of the disease and which drug to start treatment with; both issues have been widely debated.
A therapeutic strategy adopted by most clinicians is to delay the initiation of drugs until symptoms interfere with everyday life, as recommended by evidence-based guidelines. It has been suggested that the age of the patient with early PD may be considered in the choice of the first-line agent. Initiating treatment with a DA monotherapy allows delaying the introduction of levodopa, therefore giving the advantage of “shifting onwards” the occurrence of levodopa-related motor fluctuations, and of obtaining a better control of motor symptoms in the long term. This aspect might be particularly relevant in younger patients, that may also show a better tolerability of DAs.

Conversely, initiating the treatment with levodopa would lead to a better control of motor symptoms but also to an earlier onset of motor fluctuations (Clarke 2007, Montastruc 1999, Weiner 1999, NICE 2011).

The available pharmacological therapy for the early stages of the disease includes levodopa, dopamine receptor agonists (DAs) and MAOBI. Anticholinergic agents, beta-blockers and amantadine maybe used in selected patients, but are not recommended as first choice drugs. (NICE 2011)

Persons with PD in more advanced stages require levodopa and motor fluctuations are inevitable. The recommended approach in such cases includes associating to levodopa a DA, a MAOBI, or a catechol-O-methyltransferase inhibitor (COMTI).

**Levodopa**

The mainstay of PD treatment is levodopa, the aminoacid precursor of dopamine, combined with a peripheral dopa-decarboxylase inhibitor. It has been the standard symptomatic therapy for PD for over 30 years, and it is already included in the WHO Essential Medicine List. So far no medical or surgical therapy has been shown in controlled trials to provide greater anti-parkinsonian benefit.

The main limitations of the treatment with levodopa are the decrease of efficacy over time and the occurrence (on average after 4-5 years of treatment, the so-called “honeymoon”) of fluctuating responses to the drug. Several factors explain such limitations: the severity of dopamine denervation, the drug’s short half-life (60-90 min), its varying plasmatic concentration during the day, and the variable intestinal absorption of levodopa, resulting in a pulsatile stimulation of dopamine receptors. (Fabbrini 2007, Hardoff 2001)

Fluctuating responses to levodopa can be divided into “on” and “off” motor states. “On” describes a good motor response to levodopa (eg. moving and going through the activities of daily living with relative ease); during these periods though, some persons can experience dyskinesias (involuntary movements with a rotatory, writhing appearance, that can affect the limbs, trunk and face) as the medication effect reaches its peak. The “off” state is referred to as an unpleasant sensation of difficulty with movement, commonly occurring when the medication is losing its effect prior to the next dose (“wearing off”) (SIGN 2010).

“On” and “off” states may be difficult to manage, since attempting to shorten the “off” states by increasing the dose of levodopa may lead to more dyskinesias during the “on” state, whereas a reduction in levodopa dose can reduce dyskinesia but tends to worsen “off”-time.

**Monoamine-oxidase-B inhibitors (MAOBI)**

Selegiline and rasagiline are propargylamines inhibiting the monoamine oxidase type B (MAOB), thereby reducing the turnover of dopamine, and therefore can be used as a first-line monotherapy to delay the initiation of levodopa (not currently recommended by all guidelines) or in association with levodopa in the advanced stages of PD, when motor fluctuations are present, to reduce “off” states. (NICE 2011)
Catechol-O-methyltransferase inhibitor (COMTI)

As previously mentioned, levodopa has a short half-life, and therefore it is combined with an inhibitor of the dopa decarboxylase (carbidopa or benserazide) to block its metabolism and improve its bioavailability. To increase levodopa’s half-life and the rate of the drug crossing the blood-brain barrier, COMTI are used in combination with levodopa to further reduce its metabolism by another enzyme: 3-O-methylidopa by catechol-Omethyl transferase (COMT). Entacapone and tolcapone are the two COMTIs currently available for adjuvant therapy in persons affected by advanced PD with motor fluctuations.

Assessing the response to therapy

Response to therapy is measured by means of rating scales scoring individual symptoms or groups of symptoms. The Unified Parkinson’s Disease Rating Scale (UPDRS) is the most widely used tool to assess the degree of impairment in specific domains and the response to therapy (UPDRS). It covers non-motor and motor symptoms evaluated through an assessment by the investigator as well as a self-assessment by the patient. The UPDRS total score has often been used as a primary efficacy outcome in drug trials, the main limitation of this approach being that the score ranges from 0 (no disability) to 199 (total disability), covering many diverse domains with different clinical meaning. Therefore, translating a variation of the UPDRS into a clinically meaningful improvement often remains difficult, even when the observed differences are statistically significant. Determining which variation in the UPDRS score represents a minimal clinically important change is debatable (Hauser 2011). Moreover, in clinical practice the UPDRS would rarely be routinely used, and may not be the most appropriate tool to make treatment decisions (SIGN 2010).

The Hoehn & Yahr scale (Goetz 2004) is commonly used to define the stage of the disease, while the Schwab and England scale (Schwab 1969) explores the level of dependency in the activities of daily living (ADL).

<table>
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<tr>
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<tr>
<td>I</td>
<td>Mentation, behaviour and mood (Items 1 to 4)</td>
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<tr>
<td>II</td>
<td>Activities of daily living (Items 5 to 17)</td>
<td>0 – 52 points</td>
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<tr>
<td>III</td>
<td>Motor examination (Items 18 to 31)</td>
<td>0 – 108 points</td>
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<tr>
<td>IV</td>
<td>Complications of therapy</td>
<td>0 -23 points</td>
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<tr>
<td>V</td>
<td>Modified Hoehn &amp; Yahr stage</td>
<td>Stages I - V</td>
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<tr>
<td>VI</td>
<td>Modified Shwab &amp; England Activities of Daily Living</td>
<td>Score 0% (no independence) to 100% (total independence)</td>
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9. Treatment details

The dopaminergic effect of DAs depends on their binding with the post-synaptic dopamine receptors. Originally they were introduced as adjuvant therapy to levodopa in the advanced stages of PD, in order to limit motor fluctuations associated with the long-term levodopa therapy but, more recently, trials have examined their effects as initial monotherapy in the hope that they may delay the onset of motor complications. The older DAs, bromocroptine, pergolide, lisuride and dihydroergocryptine mesylate, are ergot derivatives, while ropinirole and pramipexole are non-ergot derivatives. Lisuride and pergolide are not considered in this document, since the former is no more available, and the latter has been withdrawn because of safety reasons (see section 11.2 Description of adverse effects/reactions).
Rotigotine is a non-ergot DA available only as a transdermal patch that it is not considered in this document, focused on orally administered agents only.

The main advantage of DAs over levodopa is a markedly lower occurrence of dyskinesia and motor fluctuations during the first 4-5 years of treatment. Confusion, impulse control disorders (pathological gambling, hypersexual behavior, compulsive shopping), daytime sleepiness and hallucinations may be associated with their use, while ergot derivatives can rarely induce retroperitoneal, pleural and pericardial fibrosis. Growing evidence suggests that chronic use of pergolide and cabergoline may cause thickening and dysfunction of cardiac valves with valvular regurgitation (Rasmussen 2011). The choice on which agent to use as a first line treatment in persons affected by PD should be based on an accurate evaluation of the benefit/risk ratio and on the sustainability of the initial benefits in the long-term. Non-ergot DAs ropinirole and pramipexole are also available as prolonged release formulations. Persons with PD can be switched to such preparations once the therapeutic effect of the immediate release drug is clinically established.

Pharmacodynamics

Dopamine agonists have a complex pharmacology acting directly on post- and pore-synaptic dopamine receptors to mimic the endogenous dopamine. They all exhibit potent D2 properties, although their binding profile at dopamine D1 to D5 (especially D1 and D3) receptors slightly differs.

Bromocriptine

Bromocriptine mesylate is a DA that activates the postsynaptic dopamine receptors. It has an activity as a D-2 agonist with partial D-1 antagonism and it has a relatively high affinity for 5-HT2A receptors; it is metabolized by isozymes CYP3A4 and CYP3A4. The areas of application of bromocriptine are divided into endocrinological and neurological indications. Since it inhibits the secretion of prolactin from the anterior pituitary it is mainly used in the treatment of prolactinoma and endocrinological disorders associated with hyperprolactinaemia, including amenorrhea, galactorrhea, hypogonadism, and infertility in both men and women. Growth hormone secretion may be suppressed by bromocriptine in some patients with acromegaly. Doses of bromocriptine in the treatment of PD, are usually higher than those for endocrinological indications. (FDA drugs@fda, Micromedex, Kvemmo 2006)

Cabergoline

Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D2 receptors. Receptor-binding studies indicate that it has low affinity for dopamine D1, • 1-and • 2-adrenergic, and 5-HT1-and 5-HT2-serotonin receptors. Since cabergoline inhibits the synthesis and release of prolactin from the anterior pituitary gland, it is used not only for the treatment of PD, but also to treat hyperprolactinemia. (FDA drugs@fda; Micromedex)

Dihydroergocryptine Mesilate

(3)H-dihydroergocryptine mesilate has a strong D2-like receptor agonist activity, while its activity on D1-like receptors is still controversial (it is possibly a partial agonist). Dihydroergocryptine mesilate lacks any significant interaction with serotonergic or adrenergic receptors. (Albanese 2003)
**Pergolide**

Pergolide is a synthetic ergot DA, similar in activity to bromocriptine but longer acting and 10 to 1000 times more potent on a milligram per milligram basis in various in vitro and in vivo test systems than bromocriptine. Pergolide possesses both D-1 and D-2 dopamine receptor agonist activity, and is therefore used in the management of PD as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response. The therapeutic and clinical implications of this difference are not well defined, since it is felt that stimulation of the D-2 receptor alleviates the majority of Parkinsonian symptoms. Pergolide has also a high affinity for 5-HT2A and 5-HT2B receptors, on which it acts as an agonist. (Martindale 2009, FDA drugs@fda, Kvemmo 2006)

**Pramipexole**

Pramipexole dihydrochloride is a nonergot DA whose exact mechanism of action as a treatment for PD and restless leg syndrome is unknown. Pramipexole has full intrinsic activity at the D(2) subfamily of dopamine receptors, an even higher affinity for D 3 receptors and a very low affinity for 5-HT2A, 5-HT2B receptors, and D1 receptors. (Kvemmo2006)

**Ropinirole**

Ropinirole hydrochloride is a non-ergoline dopamine agonist that has a higher specificity to D (3) than to D(2) and D(4) subtypes of dopamine receptors. The drug has a moderate affinity for opioid receptors and has insignificant effects on D(1), 5-hydroxytryptamine(1) (5-HT(1)), 5-HT(2), benzodiazepine, gamma-aminobutyric acid (GABA), muscarinic, alpha(1)-, alpha(2)-, and beta-adrenoreceptors. It is suggested that it stimulates the postsynaptic D(2)-type receptor found in the brain's caudate putamen in Parkinson's disease. (Micromedex)

**Pharmacokinetics**

**Bromocriptine**

Bromocriptine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within 1 to 3 hours after oral doses. However, only about 30% of an oral dose is absorbed and, owing to extensive first-pass metabolism, the bioavailability is only about 6%. It has been reported to be 90 to 96% bound to serum albumin in vitro. It is extensively metabolised in the liver, mainly by hydrolysis to lysergic acid and peptides by the isoenzyme CYP3A4; 93% undergoes first-pass metabolism. Oral bromocriptine has a Tmax, of 53 min if fasting, and of 90 to 120 min if administered with food; bioavailability ranges from 65% to 95%.The elimination of bromocriptine is biphasic; it is excreted mainly in faeces via the bile (94% to 98%), with small amounts in urine (2% to 6%). Its elimination half-life is 6 to 20 hours. Few published data on the linearity of bromocriptine's pharmacokinetics are available. In patients with PD, single oral doses of bromocriptine result in very variable peak plasma concentrations ranging from 1.3 to 24.6 nanograms/mL, 30 to 210 minutes (mean 102 minutes) after dosage. Clinical improvement is evident within 30 to 90 minutes of a dose with peak effect at about 130 minutes and in most patients improvement persists throughout 4 hours. A significant relationship between plasma concentrations and concurrent changes in clinical response has been observed. (Martindale 2009; Micromedex)

**Cabergoline**

Cabergoline is absorbed from the gastrointestinal tract and mean peak plasma concentrations are achieved within 2 to 3 hours. It is subject to first-pass metabolism and is extensively metabolised to several metabolites that do not appear to contribute to its pharmacological activity. It has an elimination t1/2 of 63 to 110 hours; therefore, achievement of steady state is expected to take over 3 weeks after the
completion of dose titration. Plasma protein binding has been estimated to be about 40%. Like bromocriptine and pergolide, cabergoline is metabolized primarily by CYP3A4. Cabergoline is mainly eliminated via the faeces (60%); a smaller proportion is excreted in the urine (22%), while about 4% is excreted unchanged. Its pharmacokinetics have been shown to be linear, but only up to 1.5 mg/d, which is below the therapeutic dosing range for PD. (Micromedex; Martindale 2009; Kvemmo2006)

_Dihydroergocryptine Mesilate_

Following a single oral dose, (3)H-dihydroergocryptine mesilate is rapidly absorbed, and peak plasma concentration occurs between 30 and 120 min after administration. Due to an extensive first-pass hepatic metabolism, which generates active metabolites, its bioavailability is poor: less than 5% of the administered dose reaches systemic circulation. The elimination half-life of 25 hours, while its mean distribution half-life is 15 hours (SD +/- 1.5). Binding with serum albumin is around 50%. Total clearance and volume of distribution seem strongly affected by the low oral availability of hydrogenated ergots. Thin layer chromatography indicates the presence of metabolites in urine (Ronca 1996, Albanese 2003).

_Pergolide_

Pergolide mesilate is absorbed from the gastrointestinal tract, and its time to peak concentration ranges from 1 to 3 hours when administered orally. It is reported to be about 90% bound to plasma proteins. It is excreted mainly in the urine in the form of metabolites. Its elimination half-life ranges from 63 to 69 hours. Pergolide is a potent inhibitor of CYP2D6 and appears to be metabolized by CYP3A4A41; thus, coadministration with a CYP3A4 inhibitor may result in increased concentrations of pergolide, as has been noted in vivo for both bromocriptine and cabergoline. Pergolide's pharmacokinetics are linear up to 3 mg/d, which is slightly more than half the therapeutic dosing range for PD treatment. (Micromedex; Martindale 2009; Kvemmo 2006)

_Pramipexole_

Pramipexole is quickly absorbed from the gastrointestinal tract and peak plasma concentrations have been reached within about 2 hours in fasting patients and in about 3 hours when given with food. Oral bioavailability is about 90%. Pramipexole is widely distributed throughout the body and plasma-protein binding is less than 20%. Metabolism is minimal and more than 90% of a dose is excreted via renal tubular secretion unchanged into the urine. The presence of reduced creatinine clearance may require dose adjustment. Elimination half-lives of 8 to 12 hours have been reported. Pramipexole has linear pharmacokinetics over its entire therapeutic range. On the basis of studies in rats, it is thought to be distributed into breast milk. (Kvemmo 2006, Martindale 2009; Micromedex)

_Ropinirole_

Ropinirole is rapidly absorbed from the gastrointestinal tract and mean peak plasma concentrations have been achieved 1.5 hours after oral doses; the rate of absorption, but not the extent, may be reduced if taken with food (a high fat meal increases Tmax by 2.5 hr and decreases Cmax by 25%). Bioavailability is reported to be about 50% (45% to 55%). It is widely distributed throughout the body and plasma protein binding is low (10 to 40%). Ropinirole is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4, and excreted in the urine as inactive metabolites; less than 10% of an oral dose is excreted as unchanged drug. A mean elimination half-life of about 6 hours has been reported. It is thought to be distributed into breast milk on the basis of studies in rats. (Martindale 2009; Kvemmo 2006)
9.1 Indications for use

Due to their action on dopamine receptors, DAs are licensed for the treatment of conditions other than PD. Lisuride has been withdrawn from the market worldwide, and it is no longer used for the treatment of PD. Pergolide is not available in most developed countries. Dihydroergocryptine mesilate is mainly used in the prevention of migraine, and its use in PD is very limited, since there is no robust evidence supporting its use in PD; nevertheless, it has a registered indication for PD in some countries. In the US neither pergolide nor dihydroergocryptine mesilate are marketed.

Therapeutic indications as provided by FDA (FDA drugs@fda) are:

**Bromocriptine mesylate (2.5-5 mg tablets/capsules)**

- **Hyperprolactinemia-Associated Dysfunctions**
  is indicated for the treatment of dysfunctions associated with hyperprolactinemia including amenorrhea with or without galactorrhea, infertility or hypogonadism. Bromocriptine treatment is indicated in patients with prolactin-secreting adenomas, which may be the basic underlying endocrinopathy contributing to the above clinical presentations.

- **Acromegaly**
  - Bromocriptine mesylate is indicated in the treatment of acromegaly. Bromocriptine therapy, alone or as adjunctive therapy with pituitary irradiation or surgery, reduces serum growth hormone by 50% or more in approximately ½ of patients treated, although not usually to normal levels.

- **Parkinson’s Disease**
  Bromocriptine capsules are indicated in the treatment of the signs and symptoms of idiopathic or postencephalitic Parkinson’s disease. As adjunctive treatment to levodopa (alone or with a peripheral decarboxylase inhibitor), Bromocriptine therapy may provide additional therapeutic benefits in those patients who are currently maintained on optimal dosages of levodopa, those who are beginning to deteriorate (develop tolerance) to levodopa therapy, and those who are experiencing “end of dose failure” on levodopa therapy. Bromocriptine therapy may permit a reduction of the maintenance dose of levodopa and, thus may ameliorate the occurrence and/or severity of adverse reactions associated with long-term levodopa therapy such as abnormal involuntary movements (e.g., dyskinesias) and the marked swings in motor function (“on-off” phenomenon). Continued efficacy of Bromocriptine therapy during treatment of more than 2 years has not been established.
  Data are insufficient to evaluate potential benefit from treating newly diagnosed Parkinson’s disease with Bromocriptine. Studies have shown, however, significantly more adverse reactions (notably nausea, hallucinations, confusion and hypotension) in Bromocriptine -treated patients than in levodopa/carbidopa-treated patients. Patients unresponsive to levodopa are poor candidates for Bromocriptine therapy.

**Bromocriptine (0.8 mg tablets)**

Bromocriptine is a dopamine receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

**Cabergoline (0.5 mg tablets)**

Cabergoline tablets are indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

**Pramipexole (0.125; 0.25; 0.5; 0.75; 1; 1.5 mg IR tablets; 0.375; 0.75; 1.5 ; 2.25 ; 3 ; 3.75 ; 4.5 mg ER tablets)**
**IR tablets** and **ER tablets**: Pramipexole is a non-ergot dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic **Parkinson’s disease** (PD);

**IR tablets**: Pramipexole is a non-ergot dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic **Parkinson’s disease** (PD) and for the treatment of moderate-to-severe primary **Restless Legs Syndrome** (RLS).

**Ropinirole** (0.25; 0.5; 1; 2; 3; 4; 5 mg **IR tablets** - 2; 4; 6; 8; 12 mg **ER tablets**)

**IR tablets** and **ER tablets**: Ropinirole is a non-ergoline dopamine agonist indicated for the treatment of Parkinson’s disease (PD)

**IR tablets**: Ropinirole is a non-ergoline dopamine agonist indicated for the treatment of Parkinson’s disease (PD) moderate-to-severe primary and Restless Legs Syndrome (RLS)

A summary of the registered therapeutic indications of DAs from the national drug databases available online can be found in **Annex C**. Countries where drug databases are not available for on-line access have not been assessed in this document.

**9.2 Dosage regimen**

In order to avoid dopaminergic AEs, in persons with PD all DAs - both as monotherapy and as adjunct therapy to levodopa - should be administered gradually and titration should start from the lowest dosage, regardless of the stage of the disease.

**In Parkinson's disease, cabergoline DA should be introduced gradually and during this period the dose of levodopa may be reduced gradually until an optimal response is achieved.** A suggested initial dose of cabergoline given as a single daily dose is 0.5 mg in monotherapy or 1 mg in adjunctive therapy. The dose may be increased in increments of 0.5 or 1 mg at intervals of 7 or 14 days. The EMEA has recommended a maximum dose of 3 mg daily.

**In PD bromocriptine** has been used alone, although it is usually given as an adjunct to levodopa treatment. It should be introduced even more gradually than the regimen above, and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved. In the UK, a suggested initial dose is the equivalent of 1 to 1.25 mg of bromocriptine at night during week 1, increased to 2 to 2.5 mg at night for week 2, 2.5 mg twice daily for week 3, and for week 4, 2.5 mg three times daily; the dose may be increased thereafter by 2.5 mg every 3 to 14 days according to response. The EMEA has recommended a maximum dose of 30 mg daily. In the US, a usual starting dose is 1.25 to 2.5 mg twice daily increased by 2.5 mg every 14 to 28 days to a maximum dose of 100 mg daily if necessary.

**Dihydroergocryptine Mesilate** has been given orally in doses of up to 60 to 120 mg daily for parkinsonism.

**In the treatment of Parkinson's disease, the dose of pramipexole should be increased gradually and the dose of levodopa gradually reduced during the dose-titration and maintenance phases until an optimum response is achieved.** The initial dose of pramipexole hydrochloride is 125 micrograms three times daily increased to 250 micrograms three times daily in the second week and then to 500 micrograms three times daily in the third week according to response. Thereafter the daily dose may be increased if necessary by 750 micrograms at weekly intervals to a maximum of 4.5 mg daily.

**In the treatment of Parkinson's disease, ropinirole should be introduced gradually and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until**
an optimal response is achieved; the concurrent dose of levodopa may be reduced by about 20 to 30%. The daily dosage of ropinirole should be given in three divided doses, preferably with food. The initial daily dose of ropinirole is 750 micrograms increased at weekly intervals in steps of 750 micrograms for the first 4 weeks. After week 4, the weekly increments may be made in steps of 1.5 mg up to a dose of 9 mg daily according to response; subsequent weekly increments may be made in steps of up to 3 mg. The daily dosage should not exceed 24 mg. Optimal response is usually achieved within the range of 3 to 9 mg daily; higher doses may be required if used with levodopa. If it is necessary to stop ropinirole therapy, it should be withdrawn gradually by reducing the number of daily doses over the period of 1 week. Once adequate symptomatic control has been established, ropinirole may be given as once-daily modified-release tablets. (Martindale 2009)

9.3 Duration of therapy

None of the available drugs for the treatment of PD have a disease-modifying effect, therefore being symptomatic the duration of therapy is theoretically indefinite. As previously mentioned, treatment with levodopa is invariably followed by motor fluctuations after 4 to 5 years. These AEs can be in part controlled by adjuvant treatments, but eventually they will not prevent the advanced stage complications of the disease (swallowing difficulties and aspiration, severe motor fluctuations and hyperkinesia/dyskinesia, severe rigidity and functional impairment). In the more advanced stages of the disease, the use of levodopa and adjuvant drugs may be limited not only by the occurrence of AEs but also by the decreased responsiveness to drugs due to the reduction of dopaminergic neurons in the striatum. During the course of the disease dysphagia may prevent the administration of oral drugs, and in some cases levodopa and dopaminergic drugs may be administered by different routes (co-careldopa intestinal gel, transdermal rotigotine, subcutaneous apomorphine).

9.4 Reference to existing WHO and other clinical guidelines

One existing WHO relevant document was identified:

19th Expert Committee on the Selection and Use of Essential Medicines. Application for review. Section 9. Anti parkinsonism medicines; Submission on behalf of Movement Disorder Society. 10th January 2013. (http://www.who.int/selection_medicines/committees/expert/19/applications/Antiparkinsons_9_A_R.pdf) [accessed on December 1, 2014]

Relevant guidelines

A summary of the literature search with the retrieved documents and the reasons for exclusion can be found in Annex D. The following documents were identified:
• from the American Academy of Neurology (https://www.aan.com/Guidelines/home/ByTopic?topicId=17 [accessed on December 1, 2014]):
• from the European Federation of Neurological Societies (EFNS) (http://www.eaneurology.org/berlin2015/Guideline-Archive-by-topic.389.0.html [accessed on December 1, 2014]):
  o Parkinson’s Disease: Joint EFNS/MDS-ES Guidelines on early ( uncomplicated)

- from the Haute Autorité de Santé (HAS) (http://www.has-sante.fr/portail/jcms/c_1242645/fr/guide-parcours-de-soins-maladie-de-parkinson [accessed on December 1, 2014]):

- from the Movement Disorders Society (MDS) (http://www.movementdisorders.org [accessed on December 1, 2014]):

- from the National Institute for Health and Clinical Excellence (NICE) (https://www.nice.org.uk/guidance/cg35 [accessed on December 1, 2014]):
  - Parkinson’s disease. Diagnosis and management in primary and secondary care. Issued June 2006. 6 year review: 2010

- from the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/guidelines/fulltext/113/ [accessed on December 1, 2014]):
  - Diagnosis and pharmacological management of Parkinson’s disease. A national clinical guideline January 2010.

Recommends by the guidelines listed above

Several international guidelines deal with the use of DAs in the pharmacological treatment of PD. Most of them (NICE 2011; SIGN 2010; EFNS 2011) produced distinct recommendations for use of DAs in early stage PD and in advanced stage PD, as adjunct treatment to levodopa. One GL defines the potential role of each drug in early (as a symptomatic therapy) and advanced PD (as a symptomatic adjunct to levodopa), without formulating specific recommendations (MDS 2011).

A summary of the guidelines recommendations can be found in Annex E.

Briefly, all guidelines agreed on levodopa being the mainstay of treatment of PD, and on the following specific recommendations about DAs:

1) In the early stage PD, DAs are recommended among the drugs that may be offered as monotherapy and as a symptomatic treatment. Ergot derivatives are not recommended as first-choice drugs, due to the monitoring required in relation to the risk of fibrosis. One GL (SIGN) recommends against ergot DAs as a first line treatment in early stage PD.

Some GLs (AMDA 2010; HAS 2014) recommend DAs as a preferable choice in younger patients, when delaying the initiation of levodopa may be desirable.

2) In the advanced stage PD, DAs are considered as a therapeutic option for the management of motor complications in patients on treatment with levodopa. The choice regarding the timing and the type of drug has to be made on an individual basis. Non ergot DAs are the preferable choice. One LG (AAN) recommends ropinirole over bromocriptine for reducing off time. One GL (EFNS) recommends to consider switching among different DAs in case one drug is ineffective.

No DA is recommended as universal first-choice drug therapy for people with early or advanced PD.

9.5 Need for special diagnostic or treatment facilities and skills
Dopamine agonists do not require special diagnostic facilities or therapeutic drug monitoring by means of serum concentrations measurements. The treatment of PD with DAs should be prescribed and monitored, if possible, by a physician or a neurologist skilled in the treatment of movement disorders. With respect to other antiparkinsonian drugs, DAs do not require specific competences.

10. Summary of comparative effectiveness in a variety of clinical settings

Idiopathic PD is a chronic condition that is mainly managed in an outpatient clinical setting. Hospitalization may be occasionally needed for acute problems related to complications or for palliative care provision in the late stages of the disease. In evaluating the effectiveness of DAs in treating PD, two clinical stages of the disease should be distinguished: early PD and advanced PD. Since the shift from one stage to the next is marked by the appearance of levodopa-related motor fluctuations, this distinction reflects a different therapeutic purpose in the utilization of DAs. In the early stages of the disease DAs are used as a symptomatic therapy for limiting motor symptoms, while in the advanced stages of PD their use is aimed at controlling motor fluctuations associated with long-term levodopa treatment (NICE 2011).

Most DAs are administered orally. Systematic reviews and trials involving DAs administered intravenously or transdermally were excluded from the assessment in persons with advanced PD, as these may have different properties compared to orally administered agents. Herd et al (see Annex A) provide a SR and metanalysis of the literature including also the transdermal DA rotigotine.

The statements that follow are based on a number of clinical studies, most of which have been cumulated in SRs. Nevertheless, one clinical study published shortly before this review was completed provided substantial evidence in regard to the role of DAs (as well as levodopa, MAOBIIs and COMTIs) in the management of early PD. (PD MED 2014)

In early PD, when compared to placebo, DAs are effective on motor symptoms when assessed by means of motor scores, such as the UPDRS III subscale, and on activities of daily living (ADL) (assessed by means of the UPDRS II). When compared to levodopa, DAs do not show significant differences in terms of improvement on motor function. Indirect comparisons show that treatment with levodopa achieves higher improvements vs. placebo than DAs. Starting treatment with DAs as a monotherapy in the early stage of PD does not seem to offer substantial advantages in terms of quality of life in the long term, as compared to a levodopa-based approach. Notably, results from a large pragmatic trial show that persons with early PD treated with levodopa rated their quality of life more highly than those on DA therapy. Moreover, the proportion of persons with early PD that in the long term discontinue treatment because of adverse events is lower among those that start treatment with levodopa than with DAs.

No significant differences have been shown in terms of efficacy among the available DAs.

In advanced PD with motor fluctuations, when used as an adjunct therapy to levodopa, in comparison with placebo DAs provide a significant reduction of “off” time and an improvement of the UPDRS total score, allowing lower doses of levodopa in patients that developed levodopa-induced motor complications. There are no differences in terms of efficacy among the various available DAs. Data about symptomatic control of PD are often poorly and inconsistently reported by means of diverse outcome measures, and the clinical meaning of the observed differences is often difficult to establish.
### Table – Systematic reviews on DAs in PD

<table>
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<tr>
<th>Reference</th>
<th>Design of included studies</th>
<th>Bibliographic update</th>
<th>Stage of PD</th>
<th>DA</th>
<th>Outcomes</th>
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<td>Jan 2013</td>
<td>Early</td>
<td>Ergot, non ergot</td>
<td>Safety (dyskinesia)</td>
</tr>
<tr>
<td>Thorlund 2014</td>
<td>RCT</td>
<td>Not stated</td>
<td>Early/advanced</td>
<td>Non ergot (pramipexole, ropinirole, rotigotine)</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Kulisevsky 2010</td>
<td>RCT</td>
<td>Nov 2008</td>
<td>Early/advanced</td>
<td>Ropinirole</td>
<td>Safety</td>
</tr>
<tr>
<td>Stowe 2010</td>
<td>RCT</td>
<td>Dec 2008</td>
<td>Advanced</td>
<td>Ergot, non ergot</td>
<td>Efficacy/safety</td>
</tr>
<tr>
<td>Stowe 2008</td>
<td>RCT</td>
<td>Jan 2008</td>
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<td>Jun 2012</td>
<td>Early/advanced</td>
<td>Cabergoline</td>
<td>Safety</td>
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<td>Jun 2010</td>
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<td>Ergot ( pergolide, cabergoline)</td>
<td>Safety</td>
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<tr>
<td>Steiger 2009</td>
<td>Observational</td>
<td>Dec 2007</td>
<td>Early/advanced</td>
<td>Ergot, non ergot</td>
<td>Safety</td>
</tr>
</tbody>
</table>

A summary of the literature search with the retrieved documents and the reasons for exclusion can be found in Annex D.
10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

A summary of the literature search with the retrieved documents and the reasons for exclusion can be found in Annex D.

Guidelines were searched by consulting the following sources (September 2014):

- National Guideline Clearinghouse (NGC)
- National Institute for Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- American Academy of Neurology (AAN)
- Haute Autorité de Santé (HAS)

The strategy adopted was specific to each source. In synthesis, if a “search” function was available the database was checked with the term “Parkinson”; if a “search” engine was not available the documents were searched through the “browse” function. Only guidelines originally developed by the authors were considered; guidelines adapted from other existing guidelines were not included in this document.

Systematic Reviews were searched by consulting the following sources (October 2014):

- National Library of Medicine’s MEDLINE database (from 2008 to October 1, 2014)
- The Cochrane Library

The search strategy adopted was the following:

1  exp Parkinson Disease/ or Parkinson*
2  exp Dopamine Agonists/
3  dopamine agonist*
4  exp Bromocriptine/ or bromocriptine*
5  Parlodel*
6  ropinirole*
7  Adartrel*
8  Requip*
9  Spiroco*
10  Ralnea*
11  cabergoline*
12  cabaser*
13  exp Lisuride/ or lisuride*
14  dopergin*
15  Proclacam*
16  Revanil*
17  exp Pergolide/ or pergolide*
18  exp Piribedil/ or piribedil*
19  trivastal*
20  pronoran*
21  Trivastan*
22  trastal*
23  alpha-dihydroergotamine*
24  alpha DHEC*
25  "CQA 206-291*"
26  Pramipexole
27  Mirapexin*
28  rotigotine
29  neurop*
30  Pardoprunox
31  "SLV-308*"
32  "SME-308*"
33  aplindore
34  "DAB-452*"
35  OR/2-34
36  1 and 35

Limit: 2008-; systematic reviews
The search was not started from January 2008, referring to the latest search update of two systematic reviews (SRs) performed by the Cochrane Movement Disorders Group, focused on the efficacy and safety of DAs in early PD (search updated up to January 2008) (Stowe 2008), and on the efficacy and safety of adjuvant treatment to levodopa therapy in advanced PD (search updated up to December 2008) (Stowe 2010).

The search included also technology assessment reports, and was limited to publications in English language. Efficacy and safety were assessed only for orally administered DAs; RSs and involving only DAs administered intravenously, subcutaneously or transdermally were excluded, as these may have different properties compared to orally administered agents.

Systematic reviews were assessed only if they included RCTs (for the evaluation of efficacy and safety) or observational studies (for the evaluation of safety); SRs including studies of different or mixed design were not considered for assessment.

**RCTs** published after the SRs by Stowe on early PD (Stowe 2008) were updated with a search performed on October 29, 2014; methods and results are described in a separate paper produced specifically for this application by Herd C. et al. in the *ANNEX A*. 


10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome measures, summary of results)

We performed a search of SRs on the use of DAs in persons with PD taking as a starting reference two comprehensive Cochrane SRs focused on the early (Stowe 2008) and the advanced (Stowe 2010) stages of PD, with literature updates at January 2008 and at December 2008, respectively. These two SRs have been graded by means of the GRADE method (see tables on Annex F) 1. Since then 8 other SRs have been published. Five of them included RCTs, while three included observational studies. Among SRs including RCTs, one included only persons with early PD, and was focused on safety issues (Chondrogiorgi 2014). The remaining four SRs (Thorlund 2013, Zhou 2014A, Zhou 2014, Kulisevsky 2010) included both persons with early and with advanced PD, and three of them (Thorlund 2013, Zhou 2014A, Zhou 2014) provided separated analyses of efficacy and/or safety for early and advanced PD patients. One network metaanalysis (Thorlund 2013) explored the comparative efficacy of the non ergot DAs rotigotine, ropinirole, and pramipexole on key efficacy outcomes. Two other SRs examined the efficacy and safety of non ergot long acting DAs, vs placebo (Zhou 2014) and vs standard DAs (Zhou 2014 A). The SR by Kulisevsky et al. investigates the tolerability and safety of ropinirole vs other DAs. (Kulisevsky 2010).

Three SRs including observational studies focused on the risk of cardiac valvular fibrosis associated with ergot DAs (Steiger 2009; Rasmussen 2011; De Vecchis 2013). One included both ergot and non ergot DAs (Steiger 2009), one included cabergoline and pergolide (Rasmussen 2011), and one was focused on cabergoline only (De Vecchis 2013).

Early PD (see also Annex A, Update of the Cochrane systematic review of dopamine agonist therapy in early Parkinson’s disease)

In the SR by Stowe et al (Stowe 2008) it was difficult to provide a cumulated quantitative estimate of the effectiveness of DAs in early PD, mainly because of the methodological limitations of clinical trials. The poor quality of trials including persons with early PD poses a substantial risk of bias, mainly because:
- allocation concealment is often not reported,
- it is often not clear whether all randomized patients were included in the analysis, although most studies state that an intention-to-treat analysis has been performed,
- data of patients lost at follow up were often handled by means of the last observation carried forward method, that may systematically bias the results, particularly if the proportion of patients with missing data is substantial. Most data are reported in a graphical form, with no clear information on the number of patients included in the analysis,
- diverse rating scales have been used to describe the effects of DAs on the symptoms of disease, thus making it difficult to combine results (Stowe 2008).

Among motor symptoms of PD, freezing was reported as more frequent among trial participants treated with DAs (OR 1.58, 95% CI 1.14 to 2.18, P = 0.005). When compared to placebo DAs always show a significant improvement in symptom control, but when they are combined with levodopa and compared with levodopa alone, there is usually no difference between treatment arms. A network metaanalysis on non ergot DAs found that pramipexole, and ropinirole provide a significant improvement at the UPDRS II (activities of daily living) and III (motor examination) and the improvement

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1 The GRADE method - The SRs by Stowe et al. (Stowe 2008, 2010) and the PD MED trial (PD MED 2014) have been synthesized in tables of evidence (Annex F) using the GRADE profile software (http://tech.cochrane.org/revman/gradepro). The tables are divided into two sections, appraising the quality of the available evidence and summarizing the findings of studies. Both the quality of the evidence and the summary of findings are described by outcome. The GRADE method (http://www.gradeworkinggroup.org/publications/index.htm), recommends a ranking of the outcomes by relevance (as “critical”, “important” or “not important”), performed by a multidisciplinary panel. The purposes of this document do not imply involving a multidisciplinary work group, therefore we have considered as relevant all the outcomes for which a statistically significant difference was observed. Quality assessment of the studies considered for each outcome takes into account study design, limitations, inconsistency, indirectness and imprecision, as defined by the GRADE workgroup. A qualitative scoring of the study quality for each outcome is given: high, moderate, low, or very low. Specific motivations for quality ratings and comments about the clinical implications of the differences observed are reported in footnotes.
observed at 11 to 16 weeks was maintained also at 24 to 28 weeks. Mean differences vs. placebo for the UPDRS II at 11 to 16 weeks were statistically significant for both DAs tested pramipexole (-1.15, 95%CI -1.77 to -0.38) and ropinirole (-1.28, 95%CI -3.44 to -0.87) and for levodopa, that however showed a better improvement (-1.77, 95%CI -3.15 to -0.38). Similarly, at 24 to 48 weeks improvements with both DAs were slightly lower than with levodopa. A markedly better improvement with levodopa was observed for the UPDRS III (motor examination) at 11 to 16 weeks (- 6.09, 95%CI -8.29 to -3.89), as compared to the improvements achieved with DAs (pramipexole -3.40, 95%CI -4.56 to -2.44; ropinirole -2.85 95%CI -5.09 to 0.89).

The metanalysis suggests that in early PD improvements vs. placebo achieved with levodopa are consistently better than those achieved with pramipexole and ropinirole, particularly when assessed with motor examination scores. When compared with levodopa, ropinirole and pramipexole did not show any significant difference at any time point and with any score system. Conversely, when compared vs levodopa or vs each other the differences observed were not significant at any time point (Thorlund 2013).

The 2014 update by Herd et al (see Annex A) support the conclusions of the SR by Stowe et al., providing data on quality of life which were not available for analysis in the 2008 review. The DA therapy gave clinically significant improvements in UPDRS sub-scores ADL (-1.24), motor (-3.35) and combined ADL and motor (-6.6) compared with placebo. An improvement in PDQ-39 score was also found for this comparison of -2.38 points.

The PD MED trial

The PD MED trial is a large, independent, pragmatic trial, aimed at comparing two therapeutic strategies in persons with newly diagnosed PD: early initiation with levodopa or initiation with a DA or a MAOBI. Starting treatment with levodopa warrants a better symptom control, but the risk of motor complications in the long term is higher than with a levodopa-sparing approach that, allowing a delayed introduction of levodopa, may achieve a better symptomatic control in the long term. Nevertheless, DAs and MAOBIIs are associated with disabling non-motor side effects (confusion, hallucinations, nausea, impulse control disorders, etc.) and are more expensive than levodopa.

The trial was designed to answer a question that is commonly faced by clinicians and that is still subject to debate, since robust data from large samples, with adequate follow up length and with clinically meaningful outcomes (related to quality of life, rather than to specific motor or non-motor sets of symptoms) are still lacking. The PD MED compared 632 patients with early PD randomized to DAs with 528 patients randomized to levodopa, followed up for a median of 3 years (range 0-9; analysis on continuous outcomes performed on an observation time of 7 years). More than 80% of patients randomized to DAs received ropinirole or pramipexole. Over 7 years, quality of life, assessed by means of the 39-item Parkinson’s Disease Questionnaire (PDQ-39), mobility subscale, showed no significant difference between the levodopa arm and the DA arm at any time point, but the average score was constantly better among patients treated with levodopa, as was the average scores relative to the activities of daily living (ADL) subscales. Such patient-rated scores related to quality of life showed a better improvement in the early-levodopa arm than in the levodopa-sparing arm, in particular: 1.8 points on the mobility subscale (95%CI 0.5 to 3.0, P=0.005), 1.9 on the ADL subscale (95%CI (0.7 to 3.0, P=0.002) and 1.0 point (95%CI 0.3 to 1.7, P=0.008) on the summary index score, expressing overall PDQ-39 score. Also the EQ-5D utility score, derived from the EuroQol EQ-5D instrument, shows a difference expressed in quality–adjusted life-years in favour of the levodopa-based approach (0.03, 95%CI 0.01 to 0.05, P=0.0002). These differences were noted despite a higher proportion of patients suffering of levodopa-related dyskinesias (hazard ratio 1.52, 95%CI 1.16-2.0, P=0.003).

Treatment tolerability, assessed by discontinuation rates, was better among patients on levodopa, mainly because of side effects associated with the use of DAs. The proportion of persons that by the end of the follow up discontinued treatment because of side events was significantly lower among those that started treatment with levodopa than those that were allocated to an early treatment with DAs (2% vs. 28%, respectively, p<0.0001). Another interesting finding was that subgroup analyses on patients younger and older than 70 years showed no significant differences in terms of efficacy in the long term between the levodopa-sparing and the early-levodopa approach. This information could be useful in clinical practice since most people with early PD requiring pharmacological treatment are older than 60, and – as mentioned before – age is an important factor for clinicians when deciding what therapeutic strategy to start with (PD MED).

The quality of the study and a summary of findings are displayed in a table according to the GRADE method in Annex F.
These findings suggest that, among persons with early PD, DAs offer a substantial benefit when compared to placebo, but no significant benefit over levodopa, and therefore initiating treatment with a DA seems to offer no substantial benefit in the short term or long term.

Advanced PD

The quality of studies on DAs in advanced PD has been described in the SR by Stowe et al. (Stowe 2010), that found that of the 44 trials included in the SR 26 described the method of randomization, and only five provided details about allocation concealment. Despite most trials declared an intention-to-treat analysis, in many studies it was unclear how many patients were not included in the final analysis.

The Cochrane SR by Stowe et al. found that ergot and non-ergot DAs, when compared to placebo, significantly reduced “off” time (mean difference -1.54 hours; 95%CI -1.83 to -1.26), the levodopa dose (mean difference – 116.03mg/day 95%CI -134.45 to -97.61) and the UPDRS II, III and total scores (mean reductions: -2.05, 95%CI -2.58 to -1.51; -4.86, 95%CI -5.90 to -3.82; -10.01, -12.76 to -7.26, respectively) (Stowe 2010).

The authors of the SR state that no conclusions can be made about which class of add-on treatment is more efficacious than another in advanced PD. Available evidence about differences in terms of efficacy between DAs and other classes of drugs (COMT and MAOBI) is largely based on indirect comparisons, since the SR identified only three small, open-label RCTs, with a short follow-up (8 to 12 weeks) comparing DAs with COMT, as add-on treatment to levodopa in persons with advanced PD (Deuschl 2007; Tolcapone Study Group 1999, Koller 2001). None of the three studies gave significant results.

One study compared entacapone (N=82) with cabergoline (N=79), with the aim of demonstrating non-inferiority (non-inferiority margin of 30 minutes) between the two drugs, added to levodopa, in reducing the total daily “off” time in persons with advanced PD. The study failed to demonstrate the non-inferiority, although a trend in favour of the entacapone was shown. (Deuschl 2007). Notably, the minimal clinically important change for a reduction in “off” time has been defined as 1 hour (Hauser 2011).

The second trial compared tolcapone (N=72) with bromocriptine (N=74), showing no significant differences were seen between the two groups in changes in “on/off” time or UPDRS Subscales II (ADL) and III (motor function) scores. (Tolcapone Study Group 1999)

The third trial assessed the efficacy of tolcapone (N=101) compared to pergolide (N=102) by means of the UPDRS II and III subscores, and failed to show significant differences between the two treatments (Koller 2001).

The network metaanalysis on non-ergot DAs by Thorlund et al. (Thorlund 2013) found that, similarly to what has been described for early PD, in persons with advanced PD DAs vs. placebo yielded statistically significant mean differences for all outcomes (UPDRS II, III and “off” time) at all time points (11 to 16 and 24 to 48 weeks).

Mean differences in the UPDRS II score (ADL) were similar at 11-16 weeks and at 24-48 weeks, ranging from -1.84 (95%CI -3.22 to -0.44) to -2.20 (95%CI -3.24 to -1.14) for ropinirole vs. placebo and from -2.03 (95%CI -2.69 to -1.37) to -2.18 for pramipexole (95%CI -2.96 to -1.42) vs. placebo. The UPDRS III mean differences and mean reductions in “off” time showed similar point estimates with largely overlapping CIs both at 11-16 and at 24-48 weeks for pramipexole and ropinirole: UPDRS mean reductions ranged from -4.22 (95%CI -6.31 to -2.37) for pramipexole vs placebo at 24-48 weeks, to – 5.03 (95%CI -6.73 to -3.39) for pramipexole vs placebo at 11-16 weeks. “Off” time reductions ranged from – 1.17 hours (95%CI -2.49 to -0.31) for ropinirole vs placebo at 24 to 48 weeks, to -1.60 hours (95%CI -3.27 to -0.59) for pramipexole vs. placebo at 24-48 weeks.

However, similarly to what has been noted about early PD, when compared to levodopa neither of the DAs showed significant differences for any outcome, at any time point.

Long-acting non-ergot DAs

Two SRs by Zhou et al. (Zhou 2014; Zhou 2014A) focused on the efficacy and safety of non-ergot long-acting DA preparations: extended release (ER) pramipexole, ropinirole prolonged release (PR) and transdermal rotigotine.

One SR (Zhou 2014) compared non-ergot long-acting DAs with placebo. Two of the nine RCTs included in this review investigated ER pramipexole, one in early and one in advanced PD. One study was on ropinirole PR in advanced PD. Efficacy results were expressed by means of the UPDRS II (activities of daily living) and III
(motor score) subscales. Overall differences included both oral and non-oral preparations, and no subanalysis were provided for oral DAs. However, all three trials on long-acting DAs consistently showed a significant benefit over placebo both in early as well as in advanced PD, regardless of the outcome considered (UPDRS II, III or II+III). Point estimates expressed as mean difference in UPDRS scores showed an advantage over placebo ranging from −1.20 (95%CI -2.20 to -0.20) in advanced PD to -7.0 (95%CI -9.26 to -4.74) in early PD for ER pramipexole (considering the ADL and the cumulative ADL + motor UPDRS subscores, respectively), and from -2.60 (95%CI -3.69 to -1.51) to -4.80 (95%CI -7.32 to -2.28) in the only RCT testing ropinirole PR in advanced PD. Long-acting DAs provided also a significant reduction in “off” time as compared with placebo (WMD -1.29, 05%C -1.64 to -0.93).

Another SR (Zhou 2014A) compared long-acting DAs with standard preparations, expressing their efficacy in terms of UPDRS II+III subscores in early PD, and of UPDRS II+III and of reduction of “off” time in advanced PD with motor fluctuations. No statistically significant difference was observed in any of the comparisons, both for early and advanced PD (Zhou 2014A).

11. Summary of comparative evidence on safety

All DAs (ergot and non ergot) may give neurologic and psychiatric AEs related to their dopaminergic action on different types of dopamine receptors, also within normal-range dosages. Dopamine dysregulation syndrome is including hypersexuality, pathological gambling and stereotypic motor acts. This syndrome may be difficult to manage. (NICE 2006)

The most prominent safety issues related to ergot DAs are related to the risk of developing fibrosis, namely cardiac valvular fibrosis, leading to valvular regurgitation and its subsequent effects on cardiac function, and retroperitoneal fibrosis. These events, although rare, may cause severe clinical consequences, and lead to withdrawal from the market of lisuride and pergolide. Also cabergoline has been withdrawn in some developed countries. Because of these risks, the clinical use of ergot DAs has been progressively decreasing.

The risk of developing dyskinesia and non-motor complications (particularly nausea, dizziness, somnolence and hallucinations) is significantly increased among patients taking DAs as compared to placebo and to levodopa alone. These findings are reported in SRs considering DAs as a class as well as those investigating only one substance, regardless of the stage of the disease.

A SR cumulating the results of 4 RCTs (N=1,062 patients) reports an increased relative risk of dyskinesia of 2.71 (95% CI 1.74, 4.21) among patients treated with ropinirole, as compared with patients in placebo arms, regardless of the stage of PD. (Kulisevsky 2010)

Early PD (see also Annex A, Update of the Cochrane systematic review of dopamine agonist therapy in early Parkinson’s disease)

Among motor complications, DAs (given with or without associated levodopa) show a lower incidence of dyskinesia (OR 0.51, 95% CI 0.43 to 0.59; P < 0.00001), dystonia (OR 0.64, 95% CI 0.51 to 0.81; P = 0.0002) and motor fluctuations (OR 0.75, 95% CI 0.63 to 0.90; P = 0.002) when compared to levodopa alone. Oedema, somnolence, constipation, dizziness, hallucinations and nausea are the non motor complication showing significant differences among persons with early PD treated with DAs, when compared to levodopa alone. Among patients with early PD, the frequency of headache, vomiting, hypotension, anxiety and depression, shows no significant differences between DAs compared to placebo or to levodopa. (Stowe 2008).

No significant difference has been observed in terms of mortality between DAs and placebo, neither among different DAs nor between ergot and non ergot DAs. (Stowe 2008)

The RS by Zhou et al (Zhou 2014) found that long-acting non-ergot DAs show a higher withdrawal rate than placebo among persons with early PD. Namely, the RS included only one trial comparing ER pramipexole with placebo, with a Mantel-Haenszel risk ratio of 2.77 (95%CI 0.99 to 7.78). Although not statistically significant, this point estimate was consistent with the values associated with the use of transdermal DAs. Also dizziness, constipation and insomnia showed a higher frequency among persons with early PD, while nausea, dyskinesia and hallucinations showed a higher frequency than placebo both in early and in advanced PD persons.

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Nevertheless, it has to be noted that this SR does not provide results relative to oral long-acting DAs only, and data included in the metanalysis regarding early PD treated with oral DAs are provided by only one trial.

**Advanced PD**

One SR included data relative to 8,436 patients with advanced PD treated with adjuvant therapies associated to levodopa. Of the 44 studies eligible for inclusion in the metanalysis, 20 were on DAs (cabergoline, pergolide, bromocriptine, ropinirole and pramipexole). The SR found that the use of DAs was associated to a higher overall frequency of side effects than placebo (OR 1.52, 95% CI 1.22 to 1.90) (Stowe 2010).

A significantly increased risk of dyskinesia as compared with placebo (OR 2.67, 95% CI 2.25, 3.17) was observed among patients treated with DAs in the metanalysis by Stowe et al. (Stowe 2010).

Among persons with advanced PD, dizziness is more frequently associated with DAs than placebo (OR 1.44 95%CI 1.15 to 1.80), as well as hallucinations (OR 2.65 95%CI 1.97 to 3.56), postural hypotension (OR 1.46 95%CI 1.15 to 1.84), nausea (OR 1.63 95%CI 1.34 to 1.99), somnolence (OR 1.82 95%CI 1.27 to 2.61), dyspnoea (OR 3.18 95%CI 1.20 to 8.44) (although there was a low number of events in both arms).

The frequency of constipation, dry mouth, insomnia, vomiting, abdominal pain, headache, agitation, anorexia, anxiety, ataxia, confusion, depression, diarrhoea, dyspepsia, show no difference as compared to placebo among patients with advanced PD. (Stowe 2010)

No significant difference in mortality has been observed among patients with advanced PD treated with DAs as compared with placebo, although most of the studies reporting mortality among the outcomes show zero events in at least one of the treatment arms (Stowe 2010).

**Overall withdrawals** were significantly less common among persons with advanced PD treated with DAs (OR 0.56, 95%CI 0.46 to 0.66), while patient withdrawal due to AEs was not significantly higher than placebo (Stowe 2010).

The metanalysis by Zhou et al. showed that in advanced PD the risk of withdrawal due to AEs associated with use of long-acting non-ergot DAs is not significantly different from that of placebo. (Zhou 2014) Although this metanalysis does not provide data relative to oral preparations only, its results suggest that long-acting DAs may give a higher rate of withdrawals due to AEs among persons with early PD, as previously mentioned. The higher relative risk values as compared to placebo among persons with advanced PD were observed relative to hallucinations, dyskinesia and nausea, when considering all (oral and non-oral) long-acting non-ergot DAs. No differences between long-acting and standard preparations of DAs were observed in relation to withdrawals due to AEs (Zhou 2014A).

**SRs of observational studies**

Three SRs of observational studies assessed the risk of valvular regurgitation among persons affected by PD and treated with DAs.

One SR, including both ergot and non-ergot DAs, did not report how retrieved studies were selected, and the quality of studies included in the metanalysis was not assessed. The SR found that the use of non-ergoline DAs in persons with PD is not associated with a risk of valvular regurgitation (Rasmussen 2011).

A more recent SR by De Vecchis et al. focused on cabergoline included 9 observational studies on persons affected by early or advanced PD, among which all the references of the SR by Rasmussen et al. The metanalysis showed that valvular regurgitation occurs at a significantly higher frequency in patients with PD treated with cabergoline than in control patients (OR 7.25, 95%CI 3.71 to 14.18), with a dose-response gradient (the mean cumulative cabergoline dose in PD patients is positively related with the dimension size, i.e., with the odds ratio concerning valve regurgitation of any degree at the level of one or more cardiac valves) (De Vecchis 2013).

In the SR by Steiger et al. no metanalysis was performed, due to the variability in the design of the included studies and in the reporting of the outcomes (the grading of cardiac valve regurgitation was often subjective, with possible inter-study and inter-examiner variability). However, the authors found that in 11 of the 14 studies
included there was a significant increase in cardiac valve regurgitation frequency and severity in the ergot vs the
non-ergot control group (Steiger 2009).

11.1 Estimate of total patient exposure to date

No data were retrieved about the number of persons with PD exposed to treatment with DAs

11.2 Description of adverse effects/reactions

Ergot and non-ergot derivative DAs share neurologic AEs: asthenia, excess daytime sleepiness, headache and
dizziness. The most recent non-ergot derivatives pramipexole and ropinirole might cause specific AEs related to
mental function (confusion, hallucinations, sleep attacks and compulsive behavior disorders). Adverse effects
impairing mental function may limit their use particularly in the elderly.

Table – Adverse effects of ergot derivative DAs (Martindale 2009, Micromedex)
Summary of Product Characteristics (SPC) available on FDA website: http://www.fda.gov/Drugs/default.htm
[accessed on December 1, 2014])

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Adverse effects reported/frequency</th>
</tr>
</thead>
</table>
| Bromocriptine    | Neurologic: asthenia 12.5% to 18.9% of patients with type 2 diabetes treated; dizziness (hyperprolactinemic indications: 17%; type 2 diabetes indication: 11.9% to 14.8%), headache (hyperprolactinemic indications, 19%; type 2 diabetes, 11.4% to 16.8%), somnolence (3% to 6.6%, any indication)
Neurologic rare AE: cerebrovascular accident, seizure
Gastrointestinal: constipation (acromegaly indication, 14%; hyperprolactinemic indications, 3%; type 2 diabetes indication, 5.8% to 11.3%); diarrhea (hyperprolactinemic indications, 3%; type 2 diabetes, 8.1% to 8.8%), indigestion (acromegaly indication, 4%; type 2 diabetes, 7.5%), nausea (acromegaly indication, 18%; hyperprolactinemic indications, 49%; type 2 diabetes, 25.4% to 32.5%), vomiting (acromegaly indication, 2%; hyperprolactinemic indications, 5%; type 2 diabetes, 5.3% to 8.1%)
Cardiovascular: Hypotension (type 2 diabetes indication, 2.2%), Raynaud's phenomenon, syncope, vasospasm (digital); coronary artery thrombosis (rare), Heart valve disorder (rare), Myocardial infarction (very rare), Pericardial effusion (rare), stroke (very rare)
Ophthalmic: Amblyopia (type 2 diabetes indication, 5.3% to 7.5%); blurred vision and diplopia (reports)
Respiratory: rhinitis (type 2 diabetes indication, 10.7% to 13.8%), sinusitis (type 2 diabetes indication, 7.4% to 10%)
Fatigue (hyperprolactinemia indications, 7%; type 2 diabetes, 13.9%)
Psychiatric (rare): hallucinations, psychotic disorder |
| Cabergoline      | Gastrointestinal: Constipation (7% to 10%), Nausea (27% to 29%)
Neurologic: Dizziness (9% to 17%), Headache (9% to 30%)
Fatigue (5% to 10%)
Frequency not reported:
Cardiovascular: Congestive heart failure, Disorder of pericardium, Heart valve disorder
Gastrointestinal: Retroperitoneal fibrosis |
### Pergolide

Cardiovascular adverse events: up to 1.1%; chest pain: 3.7%; Edema of face 1.1%; Hypertension 1.6%; Hypotension 1.1% up to 20% (orthostatic hypotension in 1 study); Pulitations 2.1%; pericarditis / pericardial effusion have also been described; Peripheral edema 7.4%; syncope 2.1%; Raynaud's phenomenon (rare);

Dermatologic Effects: Erythromelalgia (several case reports); rash 3.2%;

Endocrine/Metabolic Effects: neuroleptic malignant syndrome: rapid dose decreases, change in therapy or abrupt withdrawal of pergolide or other antiparkinsonian agents has been associated with signs and symptoms resembling neuroleptic malignant syndrome (e.g. elevated temperature, muscular rigidity, altered consciousness, and autonomic instability); Weight gain: 1.6%

Gastrointestinal Effects: Abdominal pain 1.6%; Constipation 10.6%; Diarrhea 6.4%; Disorder of taste 1.6%; Indigestion 6.4%; Loss of appetite 4.8%; Nausea 24.3%; Vomiting 2.7%; Xerostomia 3.7%

Hematologic Effects: Anemia 1.1%

Musculoskeletal Effects: Arthralgia 1.6%; Backache 1.6%; Bursitis 1.6%; Myalgia 1.1%; Neck pain 2.7%

Neurologic Effects: Asthenia 4.2%; Confusion 11.1%; Dizziness 19.1%; Dyskinesia 62.4%; Dystonia 11.6%; Insomnia 7.9%; Somnolence 10.1%; Tremor 4.2%; headache 5.3%

Ophthalmic Effects: Abnormal vision 5.8%; Diplopia 2.1%;

Psychiatric Effects: Akathisia 1.6%; Anxiety 6.4%; depression 3.2%; vivid dreams/delusion have been reported; Extrapyramidal syndrome 1.6%; Hallucinations 13.8%; Personality disorder/Psychotic disorder 2.1% each;

Renal Effects: hematuria 1.1%

### Dihydroergocryptine Mesilate

Not found

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**Table – Adverse effects of non-ergot derivative DAs**

Martindale, UpToDate, FDA

SPC available on FDA website: http://www.fda.gov/Drugs/default.htm [accessed on December 1, 2014]

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Adverse event/frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>Cardiovascular: Orthostatic hypotension (dose related; • 53%), Edema (2% to 8%), chest pain (3%)</td>
</tr>
<tr>
<td></td>
<td>Central nervous system: Somnolence (dose related; 6% to 36%), extrapyramidal syndrome (28%), insomnia (4% to 27%), dizziness (2% to 26%), hallucinations (5% to 17%), abnormal dreams (1% to 11%), headache (4% to 16%), Confusion (4% to 10%), dystonia (2% to 8%), fatigue (3% to 9%), amnesia (dose related; 4% to 6%), sudden onset of sleep (3% to 6%), vertigo (2% to 4%), hypesthesia (3%), abnormal thinking (2% to 3%), akathisia (2% to 3%), malaise (2% to 3%), paranoia (2%), sleep disorder (1% to 3%), depression (• 2%), delusions (1%), fever (1%), myoclonus (1%)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal: Nausea (dose related; 11% to 28%), constipation (dose related; 4% to 14%); Xerostomia (4% to 7%), anorexia (1% to 5%), vomiting (4%), Diarrhea</td>
</tr>
</tbody>
</table>
(1% to 7%), abdominal discomfort/pain (1% to 4%), dyspepsia (3%), xerostomia (3%), appetite increased (2% to 3%), dysphagia (2%), weight loss (2%), salivary hypersecretion (2%), diarrhea (1% to 2%)

Neuromuscular / skeletal: Dyskinesia (17% to 47%), weakness (1% to 14%), Gait abnormalities (7%), hypertonia (7%), limb pain (3% to 7%), muscle spasm (3% to 5%), falls (4%), arthritis (3%), tremor (3%), back pain (2% to 3%), bursitis (2%), muscle twitching (2%), balance abnormalities (2%), CPK increased (1%), myasthenia (1%)

Genitourinary: Urinary frequency (6%), urinary tract infection (4%), impotence (2%), urinary incontinence (2%)

Accidental injury (17%)

Endocrine & metabolic: Libido decreased (1%)

Ocular: Accommodation abnormalities (4%), vision abnormalities (3%), diplopia (1%)

Respiratory: Dyspnea (4%), cough (3%), rhinitis (3%), pneumonia (2%) Relevant, postmarketing reported: impulsive/compulsive behaviors (eg, binge eating, hypersexuality, pathological gambling, shopping), libido increased.

Ropinirole Cardiovascular: Hypotension (2% to 25%), Orthostatic hypotension (Parkinson's disease, 5%; restless legs syndrome, 0.8%), Sinus node dysfunction, Syncope (1% to 11.5%), hypertension (5%), chest pain (4%), flushing (3%), palpitations (3%), peripheral ischemia (3%), atrial fibrillation (2%), extrasystoles (2%), peripheral edema (2%), lower extremity edema (7%), tachycardia (2%)

Gastrointestinal: Abdominal pain (6% to 7%), Constipation (4% to 5%), Nausea (11% to 60%), Vomiting (7% to 12%), dyspepsia (4% to 10%), abdominal pain (3% to 7%), xerostomia (3% to 5%), diarrhea (5%), anorexia (4%), flatulence (3%)

Neurologic: Dizziness (Parkinson's disease, 6% to 40%; restless legs syndrome, 11%), Dyskinesia, dose-related: 13%, Headache 6%, Somnolence 7% to 40%, Drowsiness (11% to 40%), fatigue (including weakness, malaise; 9% to 16%), confusion (5%), hallucination (5%; dose related), hypoesthesia (4%), amnesia (3%), paresthesia (3%), yawning (3%), lack of concentration (2%), vertigo (2%), insomnia

Fatigue (8% to 11%)

Psychiatric: Hallucinations (5% to 15%), sudden onset sleep

Dermatologic: Diaphoresis (6%), hyperhidrosis (3%)

Genitourinary: Urinary tract infection (5%), impotence (3%), urinary incontinence (2%)

Neuromuscular & skeletal: Arthralgia (4%), limb pain (3%), muscle cramps (3%), hyperkinesia (2%), muscle spasm, myalgia

Ophthalmic: Visual disturbance (6%), eye disease (3%), xerophthalmia (2%)

Endocrine & metabolic: Weight loss (2%)

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Drug-specific adverse effects

Ergot dopamine agonists and fibrosis

In 2002 a causal association between ergot derivative pergolide and valvular regurgitation has been postulated (Pritchett 2002). Since then many case reports and observational studies have supported this suspicion, and concerns about possible cardiac valve damage exist also for cabergoline. On 26 June 2008, the European Medicines Agency (EMA) has completed a review of the safety of the ergot-derived dopamine agonists. The review focused on the risk of fibrosis in patients taking these medicines for long periods, particularly cardiac fibrosis, and it was carried out under an ‘Article 31’ referral. For cabergoline and pergolide, the Committee for Medicinal Products for Human Use (CHMP) noted that the risk of fibrosis of the heart valves is well established, that the prescribing information for both products already includes contraindications stating that patients with evidence of heart valve problems should not take them, and that the medicines should only be used for PD in patients who have already taken or cannot take other treatments. Therefore, the CHMP recommended that the prescribing information for these two medicines should be updated to include:

- a warning stating that patients must be monitored for signs of fibrosis with echocardiography before treatment is started and regularly during treatment;
- a reduction of the maximum recommended dose to 3 mg per day;
- ‘cardiac fibrosis’ as a ‘very common’ side effect (seen in more than 1 patient in 10 taking either medicine).

In contrast, there is not enough evidence to determine whether there is an increased risk of fibrosis of the heart valves in patients taking bromocriptine, dihydroergocryptine or lisuride. However, since such a risk cannot completely be excluded, the Committee recommended that warnings on the possible risk of fibrosis in patients taking these medicines at high doses for long periods should be included in their prescribing information. The dose of bromocriptine should also be limited to 30 mg a day. In addition, the CHMP recommended that a contraindication for patients with pre-existing valve problems should be included in the prescribing information for bromocriptine and dihydroergocryptine-containing medicines (EMA ergot safety).

In the US cabergoline and pergolide are no more available for the treatment of PD. Pergolide drug products were voluntarily removed from the market by the manufacturer on March 29, 2007 due to safety concerns of an increased risk for serious heart valve damage in patients taking pergolide for PD (FDA pergolide). Cabergoline is only available as 0.5 mg tablets that have the following indication: “treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas” (FDA drugs@fda)

Non-ergot dopamine agonists and effects on mental function

Sudden onset sleep

Pramipexole and ropinirole have been associated with attacks of sudden onset of sleep, sometimes without any prior feeling of drowsiness, that can occur at any time during treatment, and that may result in road traffic accidents. The Summary of Product Characteristics (SPC) of licensed pramipexole containing products states that the incidence of daytime somnolence is increased at daily doses of pramipexole hydrochloride higher than 1.5 mg. A retrospective analysis of data to evaluate the incidence and nature of somnolence in patients receiving pramipexole in clinical studies showed that for patients with moderate or severe somnolence, the onset of worst-reported somnolence occurred at a mean daily dose of around 4 mg (range: 0.75 to 4.5 mg). (FDA drugs@fda, EMA Mirapex).

The SPC of licensed ropinirole containing products states that “in controlled clinical trials, somnolence was commonly reported in patients receiving the drug and was more frequent in Parkinson's disease (up to 40% vs 6% placebo) than in Restless Legs Syndrome (12% vs 6% placebo). It has been reported that falling asleep
while engaged in activities of daily living usually occurs in a setting of preexisting somnolence, although patients may not give such a history and for this reason, prescribers should reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.” (FDA drugs@fda) The SPC states that there is insufficient information to establish if a dose reduction will prevent episodes of sudden sleep while engaged in activities of daily living. Therefore patients have to be advised of possible additive effects when taking other sedating medications, alcohol, or other central nervous system depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with ropinirole, or when taking a concomitant medication (e.g., ciprofloxacin) that increases its plasma levels.

Pathological gambling and other impulse control disorders

Dopamine agonist therapy is associated with an increased risk of impulse control disorders including pathologic gambling, compulsive sexual behavior, or compulsive buying. Both SPCs of licensed pramipexole and ropinirole containing products state that “case reports and the results of a cross-sectional study (pramipexole) suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, binge eating, and/or other intense urges and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson’s disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with pramipexole or ropinirole. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking pramipexole [or ropinirole].” (FDA drugs@fda)

11.3 Identification of variation in safety due to health systems and patient factors

According to the RS by Stowe et al. the mean age of participants in trials in advanced PD is 63 years. Although in this SR it was not possible to investigate differences in terms of safety by age by means of a metaanalysis including published data, it is probable that older persons with PD may not tolerate adjuvant therapy with DAs as well as younger patients (Stowe 2010). Therefore the elderly (which represent the majority of persons with PD in clinical practice) may be considered a population particularly at risk of safety issues when using DAs.

11.4 Summary of comparative safety against comparators

**DAs vs. levodopa (early PD)**

The main advantage of DAs over levodopa in terms of safety is the lower occurrence of motor fluctuations, particularly dyskinesia.

The risk of developing dyskinesia among patients with early PD treated with DAs is significantly lower than that of patients taking levodopa (OR 0.45, 95% CI 0.37 to 0.54), as well as the risk of developing motor fluctuations (OR 0.71, 95% CI 0.58 to 0.87) or dystonia (OR 0.64, 95% CI 0.50 to 0.81) (Stowe 2008).

Among patients with early PD, non-motor side-effects are more frequent with DAs compared to levodopa, with clinically significant increases in the risk of oedema (OR 3.68, 95% CI 2.62 to 5.18), somnolence (OR 1.49, 95% CI 1.12 to 2.00), constipation (OR 1.59, 95% CI 1.11 to 2.28), dizziness (OR 1.45, 95% CI 1.09 to 1.92), hallucinations (OR 1.69, 95% CI 1.13 to 2.52) and nausea (OR 1.32, 95% CI 1.05 to 1.66). Comparisons with placebo gave consistent results, similar to those observed vs. placebo, but with stronger associations (Stowe 2008).
Among patients with early PD, the frequency of insomnia, headache, vomiting, hypotension, anxiety and depression, shows no significant differences between DAs (with or without levodopa) compared to levodopa (Stowe 2008).

In trials comparing a DA with levodopa overall patient withdrawal was significantly more common among persons with advanced PD treated with levodopa (OR 2.02, 95% CI 1.70 to 2.40), but heterogeneity was high and explained mainly by the differences in trial design (open, single- or double-blind). Withdrawals due to AEs and to lack of efficacy were more frequent among persons treated with DAs in the trials that compared DAs with levodopa (OR 2.47 95%CI 1.96 to 3.11, and OR 2.93 95%CI 1.94 to 4.42, respectively) (Stowe 2008).

A lower risk of developing dyskinesia among patients with early PD treated with ergot and non-ergot DAs, compared with those treated with levodopa, was found by a SR including 10 RCTs. The metanalysis showed that in persons with early PD, monotherapy with a DA results in an overall 87% lower risk of dyskinesia compared to treatment with levodopa (OR=0.13, 95% CI 0.09 to 0.19). The authors of the SR excluded from this analysis patients when they had received open-label levodopa during the study; this choice might have introduced a selection bias, since 400 of the 1,171 patients assigned to DA therapy added levodopa at some point. However, the analysis on the total incidence of dyskinesia in the DA group (regardless of whether it occurred before or after the introduction of open-label levodopa) still showed a difference in favor of DAs (OR = 0.21, 95% CI 0.14 to 0.34; P < 0.001).

Point estimates from individual trials show a consistently lower risk, with ORs ranging from 0.04 (95% CI 0.00, 0.78) to 0.25 (95%CI 0.09, 0.19) in the seven trials with results significantly in favor of DAs. The risk for dyskinesia was independent of the use of an ergot rather than a non ergot derivative and of the duration of treatment.

A potential source of bias in this study was the possibility of a publication bias favoring the publication of studies with significant results; the authors did not formally assess such risk. The directness of the results might have hampered by the fact that the definition of dyskinesia, its severity and the way of its assessment across studies were not appraised, and only the occurrence of dyskinesia – regardless of its entity- was considered in the SR. Mild dyskinesia may be better tolerated, particularly among relatively young persons affected by early PD (mean age in the included studies was around 60 years), therefore the crude number of dyskinesia episodes may be scarcely informative when considering global health status of persons with early PD (Chondrogiorgi 2014).

**DAs vs. each other or vs. other adjuvant therapies (advanced PD)**

Very few RCTs make direct comparisons between two DAs in advanced PD, therefore inferences about safety between DAs are mainly based on indirect comparisons.

The SR by Stowe et al. evaluated the overall risk of AEs in 1,166 persons with advanced PD treated with DAs, 1,237 treated with COMTIs and 494 treated with MAOBIs. The metanalysis shows that the overall frequency of AEs was significantly higher than placebo in the groups treated with DAs (OR 1.52, 95% CI 1.22 to 1.90) and with COMTIs (OR 2.00, CI 1.62 to 2.47; P<0.00001), while MAOBIs did not show a statistically significant difference (OR 1.32, CI 0.95 to 1.84, P=0.1) (Stowe 2010).

Considering individual substances of the class of DAs, side effects were significantly more commonly associated with the use of cabergoline (OR 2.08, 95% CI 1.01 to 4.29; P=0.05) and pramipexole (OR 1.67, 95%CI 1.16 to 2.39; P=0.005) than with placebo. (Stowe 2010)

The use of bromocriptine and ropinirole did not show significant differences with placebo (OR 1.25, 95%CI 0.77 to 2.03; P=0.36; OR 1.44, 95%CI 0.99 to 2.09; P=0.05, respectively).

**Mortality** was considered in 7 placebo-controlled studies on DAs, 6 of which had zero events in at least one of the allocation arms, therefore – although the cumulative difference observed in the metanalysis is not statistically significant - it is difficult to draw conclusions about this particular outcome (Stowe 2010).

According to the SR by Stowe et al., withdrawal from treatment due to adverse AEs showed no difference among patients with advanced PD treated with DAs in respect to placebo (OR 1.05 95%CI 0.82 to 1.35; P=0.69), unlike persons receiving COMTIs, showing a significantly higher odds of withdrawal (OR 1.46, CI 1.13 to 1.90; P=0.004).

There is no strong evidence suggesting differences between DAs and other classes of adjuvant treatments in persons with advanced PD, nor between different compounds among DAs . Withdrawal due to lack of efficacy
was significantly lower for patients on DAs than those in the placebo arms, but 6 of the 12 trials considering this outcome had zero events in at least one of the allocation groups, and heterogeneity was detected between trials. **Quality of life** was assessed in only one study on ropinirole prolonged release (EASE-PD study), showing significant differences in favour of ropinirole in the mobility, ADL, emotional well-being, stigma and communication domains of the PDQ-39 rating scale (Stowe 2010).

### 12. Summary of available data on comparative costs and cost-effectiveness

We used the *International Drug Price Indicator Guide* to summarize the comparative cost effectiveness, taking levodopa (the main drug treatment in PD, which is already include in the EML) as a reference to DAs. Among DAs, only bromocriptine mesilate 2.5 mg 30 tab-cap is included in the *International Drug Price Indicator Guide*. The Defined Daily Dose (DDD) of bromocriptine is 40mg; the DDD of levodopa is 600 mg, the unit price of bromocriptine ranges from 0.0396 USD in Sudan to 0.3077 USD in South Africa, with a median price of 0.1616 USD and a high/low ratio of 7.76 (see table).

<table>
<thead>
<tr>
<th>Drug</th>
<th>DDD</th>
<th>High/Low Ratio</th>
<th>Price (US $)</th>
<th>Price DDD (US $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine mesilate 2.5 mg tab-cap (PO)</td>
<td>40 mg</td>
<td>3.46</td>
<td>0.4066/tab-cap (median)</td>
<td>6.50</td>
</tr>
<tr>
<td>Supplier Number of Prices=2</td>
<td></td>
<td>7.76</td>
<td>0.1616/tab-cap (median)</td>
<td>2.58</td>
</tr>
<tr>
<td>Buyer Number of Prices=6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levodopa+ carbidopa 100mg +10 mg tab-cap (PO)</td>
<td>0.6 g</td>
<td>0.0715/tab-cap</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Buyer Number of Prices=1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levodopa+ carbidopa 100mg +25 mg tab-cap (PO)</td>
<td>0.6 g</td>
<td>1.03</td>
<td>0.0824/tab-cap (median)</td>
<td>0.49</td>
</tr>
<tr>
<td>Buyer Number of Prices=2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levodopa+ carbidopa 250mg +25 mg tab-cap (PO)</td>
<td>0.6 g</td>
<td>1.32</td>
<td>0.1347/tab-cap (median)</td>
<td>0.32</td>
</tr>
<tr>
<td>Supplier Number of Prices=3</td>
<td></td>
<td>3.84</td>
<td>0.1180/tab-cap (median)</td>
<td>0.28</td>
</tr>
<tr>
<td>Buyer Number of Prices=5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The information about pricing in developed countries has been retrieved from the *National Price Sources of the Health Action International* (HAI).

The price of DAs available from on-line databases vary: some databases (such as the Common European Drugs Database, CEDD) provide wholesale price, some others (such as the Italian Farmadati and the US Center for Medicare and Medicaid Services, CMS) the retail price and some others (such as the UK Prescription Services) the reimbursement price. This makes it difficult to make comparisons between the cost of medicines in different countries. When available we reported the retail price, since the wholesale price and reimbursement price may be influenced by local agreements, rules and negotiations.

### 12.1 Range of cost of the proposed medicine

In the tables that follow, prices (for branded and non proprietary products, when available) are expressed in EUR, with a currency exchange rate as of December 1, 2014 from GBP and USD.

In developed countries the price of DAs varies considerably. Branded drugs are generally more expensive. Ergot DAs are less expensive than non-ergot DAs.

The price of **bromocriptine** 5 mg capsules varies from **0.48 EUR** (=0.38 GBP, reimbursement price in the UK) to **0.58 EUR** (maximum wholesale brand price range in EU countries). The price of **cabergoline** 1 mg tablets varies from **0.72 EUR** (non-proprietary pharmacy retail price in Italy) to **4.04 EUR** (=3.19 GBP, reimbursement price in the UK).
The price of ropinirole 2mg tablets varies from 0.12 EUR (=0.10 GBP, reimbursement price in the UK) to 2.31 EUR (=2.86 USD, reimbursement price in the US).
The price of pramipexole 0.75 mg tablets varies from 0.07 EUR (=0.09 USD, non-proprietary reimbursement price in the US) to 10.31 EUR (=13.06 USD, brand reimbursement price in the US).

Table - UK reimbursement price for DAs (http://www.ppa.org.uk/ppa/edt_intro.htm [accessed on November 14, 2014])

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
<th>Basic Price</th>
<th>Unit Price</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine 10mg capsules</td>
<td>100</td>
<td>6950</td>
<td>0.70</td>
<td>X</td>
</tr>
<tr>
<td>Bromocriptine 1mg tablets</td>
<td>100</td>
<td>6010</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine 2.5mg tablets</td>
<td>30</td>
<td>7136</td>
<td>2.38</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine 5mg capsules</td>
<td>100</td>
<td>3757</td>
<td>0.38</td>
<td>X</td>
</tr>
<tr>
<td>Pergolide 1mg tablets</td>
<td>100</td>
<td>13070</td>
<td>1.31</td>
<td></td>
</tr>
<tr>
<td>Pergolide 250mcg tablets</td>
<td>100</td>
<td>3577</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Pergolide 50mcg tablets</td>
<td>100</td>
<td>3254</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 1mg tablets</td>
<td>84</td>
<td>303</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 250 mg tablets</td>
<td>12</td>
<td>166</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 2mg modified-release tablets</td>
<td>28</td>
<td>1254</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 2mg tablets</td>
<td>28</td>
<td>286</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 4mg modified-release tablets</td>
<td>28</td>
<td>2509</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 500mcg tablets</td>
<td>28</td>
<td>224</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 5mg tablets</td>
<td>84</td>
<td>1641</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Ropinirole 8mg modified-release tablets</td>
<td>28</td>
<td>4211</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>Pramipexole 1.05mg modified release tablets</td>
<td>30</td>
<td>12966</td>
<td>4.32</td>
<td>X</td>
</tr>
<tr>
<td>Pramipexole 1.57mg modified release tablets</td>
<td>30</td>
<td>20236</td>
<td>6.75</td>
<td>X</td>
</tr>
<tr>
<td>Pramipexole 180mcg tablets</td>
<td>30</td>
<td>244</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Pramipexole 2.1mg modified release tablets</td>
<td>30</td>
<td>25991</td>
<td>8.66</td>
<td>X</td>
</tr>
<tr>
<td>Pramipexole 2.62mg modified release tablets</td>
<td>30</td>
<td>33727</td>
<td>11.24</td>
<td>X</td>
</tr>
<tr>
<td>Pramipexole 260mcg modified release tablets</td>
<td>30</td>
<td>3249</td>
<td>1.08</td>
<td>X</td>
</tr>
<tr>
<td>Pramipexole 3.15mg modified release tablets</td>
<td>30</td>
<td>38987</td>
<td>13.00</td>
<td>X</td>
</tr>
<tr>
<td>Product Description</td>
<td>NDC</td>
<td>NADAC * Per Unit (US $)</td>
<td>Effective Date</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----</td>
<td>-------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Pramipexole 350mcg tablets</td>
<td>30</td>
<td>1572</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Pramipexole 520mcg modified release</td>
<td>30</td>
<td>6498</td>
<td>2.17</td>
<td></td>
</tr>
<tr>
<td>Pramipexole 700mcg tablets</td>
<td>30</td>
<td>427</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Pramipexole 88mcg tablets</td>
<td>30</td>
<td>219</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Cabergoline 1mg tablets</td>
<td>20</td>
<td>6377</td>
<td>3.19</td>
<td></td>
</tr>
<tr>
<td>Cabergoline 2mg tablets</td>
<td>20</td>
<td>7257</td>
<td>3.63</td>
<td></td>
</tr>
<tr>
<td>Cabergoline 500mcg tablets</td>
<td>8</td>
<td>3472</td>
<td>4.34</td>
<td></td>
</tr>
</tbody>
</table>

**Table - CMS US - Weekly NADAC Reference File (as of 11/05/2014). Retail community pharmacy price for DAs.**

(http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Pharmacy-Pricing.html) [accessed on November 28, 2014]
Table - European wholesales price (http://cedd.oep.hu/) and Italy pharmacy retail price (http://www.farmadati.it/ [accessed on December 1, 2014]) for DAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>NPP Unit Price range (€)</th>
<th>Brand Unit Price range (€)</th>
<th>NPP Unit Price (€)</th>
<th>Brand Unit Price (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine 10mg capsules</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0,73</td>
</tr>
<tr>
<td>Bromocriptine 2.5mg tablets</td>
<td>0,14</td>
<td>0,24</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bromocriptine 5mg capsules</td>
<td>-</td>
<td>0,46 - 0,58</td>
<td>-</td>
<td>0,38</td>
</tr>
<tr>
<td>Pergolide 1mg tablets</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pergolide 2.5mg tablets</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pergolide 5mg tablets</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ropinirole 1mg tablets</td>
<td>0,17 - 0,35</td>
<td>0,34 - 0,67</td>
<td>0,26</td>
<td>0,35</td>
</tr>
<tr>
<td>Ropinirole 0,25 mg tablets</td>
<td>0,05 - 0,09</td>
<td>0,09 a 0,26</td>
<td>0,11</td>
<td>0,17</td>
</tr>
<tr>
<td>Ropinirole 0,5 mg tablets</td>
<td>0,12 - 0,18</td>
<td>0,18 - 0,48</td>
<td>0,21</td>
<td>0,28</td>
</tr>
<tr>
<td>Ropinirole 2mg modified-release tablets</td>
<td>-</td>
<td>0,63 - 1,09</td>
<td>0,33</td>
<td>0,42</td>
</tr>
<tr>
<td>Ropinirole 2mg tablets</td>
<td>0,33 - 0,62</td>
<td>0,56 - 0,66</td>
<td>0,51</td>
<td>0,63</td>
</tr>
<tr>
<td>Ropinirole 4mg modified-release tablets</td>
<td>-</td>
<td>1,31 - 2,51</td>
<td>0,64</td>
<td>0,75</td>
</tr>
<tr>
<td>Ropinirole 5mg tablets</td>
<td>0,64 - 0,94</td>
<td>1,28 - 1,56</td>
<td>1,07</td>
<td>1,28</td>
</tr>
</tbody>
</table>

* NADAC Per Unit: The National Average Drug Acquisition Cost per unit, is the result of a survey of US retail prices, produced by Myers & Stauffer, L.C. NADAC files provide state Medicaid agencies covered outpatient drug information regarding retail prices for prescription drugs.
12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

*International Drug Price Indicator Guide*

It is difficult to estimate the cost-effectiveness of DAs in lower-middle-income countries, since also the information about the cost of PD for the patient, family and society is limited, and restricted to developed countries.

According to data from the US, prescription drugs account for about 5% of total costs, while outpatient care accounts for 7.5%, uncompensated care for 19%, and inpatient care for 20%. The most important share in the burden of PD is productivity loss, accounting for almost 50%.

The availability of antiparkinson drugs in primary care is variable: while in Europe it is 79.1%, in Africa it is only 12.5%. (WHO neurological disorders report 2006)

According to a study on 190 persons with PD followed up for one year in the province of Shangai (China) the overall mean annual cost for PD was approximately USD 925 (EUR 746), and these costs accounted for around half of the mean annual income. (Wang 2006)

In India the annual cost of DAs ranges from 109.4 (+/- 111.9 USD) for the earliest stages of the disease (Hoehn & Yahr stage I), to 128.1 USD (+/- 144 USD) for advanced stages (Hoehn & Yahr stage II and III), while the total cost for PD drugs ranges from 144.3 USD (+/- 144.3 USD) to 232.8 USD (+/- 158.3 USD). In India health insurance covers about 7% of health cost. The sample of patients surveyed in this study included 175 persons with PD accessing an outpatient neurological service in Bangalore (India), 73 of which (41%) had an annual income of less than 1,150 USD. (Ragothaman, 2006)
13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)
DAAs have been approved for use in Europe and in the US.


**Bromocriptine:**
US Pharmacopoeia (USP 31th revision)*: yes (as Bromocriptine mesylate)

**Pergolide**
US Pharmacopoeia (USP 31th revision)*: yes

**Cabergoline**

**Dihydroergocryptine Mesilate**
US Pharmacopoeia: (USP 31th revision 1): not found

**Pramipexole**
British Pharmacopoeia (BP 2014 ed.): yes (as Pramipexole Dihydrochloride Monohydrate)

**Ropinirole**
US Pharmacopoeia (USP 31th revision): no

* US Pharmacopoeia – On the US Pharmacopoeia web site is now available the 37th revision (2014)

15. Proposed (new/adapted) text for the WHO Model Formulary

The most effective treatment in PD is levodopa.
Dopamine agonists – like all other available treatments for PD, including levodopa – do not modify the course of the disease, and their action is symptomatic.
In recently diagnosed PD, when pharmacological therapy is deemed necessary, initiating treatment with DAs offers no clinically meaningful benefits over the choice of levodopa, which disadvantages in terms of motor side effects do not significantly impact quality of life in the long term.
The occurrence of motor complications after the first few years of treatment with levodopa can be managed by increasing the daily dose of levodopa, by changing its administration schedule, and by adding an adjunctive treatment to it.
Compared to placebo, add-on therapy with DAs significantly reduces the time spent in the “off” motor state, the required levodopa dose and improves overall disability scores by means of the UPDRS scores, but other side-effects (in particular non-motor) are increased with adjuvant therapy, especially in older patients.
No evidence supports the choice of one specific DA agent over the other, although non-ergot DAs are preferable because of the risk of rare but potentially severe long-term complications associated with the use of ergot derivatives.
Non-ergot DAs may be considered as an adjuvant therapy to levodopa in some, particularly younger, persons with advanced PD.
16. References (arranged alphabetically)

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