Drug Class Monograph

Class: Antiparkinson Agents

Drugs: Apokyn (apomorphine injectable), Azilect (rasagiline), Cogentin (benztropine), Comtan (entacapone), Eldepryl (selegiline), Mirapex (pramipexole), Mirapex ER (pramipexole ER), Neupro (rotigotine transdermal patch), Requip (ropinirole), Requip XL (ropinirole XL), Rytary (carbidopa/levodopa ER), Sinemet (carbidopa/levodopa), Sinemet CR (carbidopa/levodopa ER), Tasmar (tolcapone)

Formulary medications: Comtan (entacapone), Eldepryl (selegiline), Mirapex (pramipexole), Requip (ropinirole), Sinemet (carbidopa-levodopa), Sinemet CR (carbidopa-levodopa ER)

Line of Business: Non-Medicare

Effective Date: August 17, 2016

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This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

Policy/Criteria:

1. Mirapex ER (pramipexole ER), Requip XL (ropinirole XL)
   a. Confirmed diagnosis of Parkinson’s disease
   b. Inadequate response or clinically significant adverse effects to one formulary dopamine agonist (e.g. pramipexole, ropinirole)
   c. Prescribed by a neurologist

2. Neupro (rotigotine transdermal patch)
   a. Confirmed diagnosis of Parkinson’s disease or Restless Leg Syndrome
   b. Failure or clinically significant adverse effects to two formulary dopamine agonists (e.g. pramipexole, ropinirole)
   c. Prescribed by a neurologist

3. Rytary (carbidopa, levodopa ER capsule)
   a. Confirmed diagnosis of Parkinson’s disease
   b. Inadequate response or clinically significant adverse effects to one formulary alternative: carbidopa-levodopa or carbidopa-levodopa ER
   c. Prescribed by a neurologist
4. **Tasmar (tolcapone)**
   a. Confirmed diagnosis of Parkinson’s disease
   b. Must use concurrently with carbidopa and levodopa
   c. Failure or clinically significant adverse effects to entacapone
   d. Prescribed by a neurologist

5. **Azilect (rasagiline)**
   a. Confirmed diagnosis of Parkinson’s disease
   b. Failure or clinically significant adverse effects to selegiline and one additional formulary alternative (e.g. carbidopa/levodopa, pramipexole, ropinirole, etc.)
   c. Prescribed by a neurologist

6. **Apokyn (apomorphine inj)**
   a. Confirmed diagnosis of Parkinson’s disease
   b. Documented concurrent treatment with at least one other anti-parkinson medication (e.g. carbidopa-levodopa, ropinirole, etc.)
   c. Documentation of hypomobility “off” episodes
   i. Note: Off episodes refer to the “wearing off” (worsening of Parkinson’s symptoms) at the end of levodopa dosing interval or unpredictable “on/off” episodes
   d. Prescribed by a neurologist

7. **Cogentin (benztropine)**
   a. DHCS carve-out

**Clinical Justification:**

*2010 European Federation of Neurological Societies (EFNS) and Movement Disorder Society –European Section (MDS-ES) Recommendations on Therapeutic Management of Parkinson’s Disease*

Practical Recommendations for the Treatment of Early Untreated PD

- The choice of drug depends on the impact of improving motor disability (better with levodopa) compared with the risk of motor complications (more common in younger patients, delayed by agonists) and neuropsychiatric complications (more common in older and cognitively impaired patients; greater with agonists)
- Therapeutic options include the following:
  - Levodopa is the most effective symptomatic drug (Level A)
    - Controlled-release formulations or adding entacapone is not effective in the delay of motor complications (Level A)
  - Oral or transdermal dopamine agonist
    - Pramipexole, ropinirole and rotigotine are effective (Level A)
    - Initial treatment with an agonist can be recommended in younger patients (GPP- Good Practice Point)
MAO-B inhibitor (selegiline, rasagiline) (Level A)
- Amantadine or an anticholinergic (Level B)
- Ergot derivatives are not recommended as first-line medication because of the risk of fibrotic reactions
- Rehabilitation: because of the lack of evidence in early-stage disease, a recommendation cannot be made

Practical Recommendation for the Adjustment of Initial Therapy in Patients without Motor Complications

- Patients on dopaminergic therapy
  - If on levodopa:
    - Increase the dose (GPP)
    - Add an agonist (GPP)
    - Add a COMT inhibitor (GPP)
  - If on dopamine agonist therapy:
    - Increase the dose (GPP)
    - Switch between agonist (Level C)
    - Add levodopa (GPP)
- Patients not on dopaminergic therapy
  - A stage will come when there is a requirement for adding levodopa or a dopamine agonist (GPP)
- Patients with disabling tremor
  - If significant tremor persists:
    - Anticholinergics (GPP)
    - Clozapine (Level B)
    - Beta-blocker (propranolol)
    - Deep brain stimulation

Recommendations for the Treatment of Motor Complications in PD

- Wearing-off (end-of-dose akinesia, predictable ON-OFF)
  - Adjust levodopa dosing; adjustments in the frequency of dosing may attenuate wearing-off (GPP)
  - CR levodopa may improve wearing-off (Level C) and night time akinesia (GPP)
  - Add COMT or MAO-B inhibitors
    - Tolcapone, although more effective than entacapone, is potentially hepatotoxic and only recommend in patients failing on other medications
  - Add dopamine agonists
    - Non-ergot dopamine agonists are first-line
    - None has proven superior, but switching one agonist to another can be helpful (Level B/C)
  - Add amantadine or an anticholinergic
    - Addition of an anticholinergic (in younger patients) or amantadine may improve symptoms
• Severe motor fluctuation
  o Subcutaneous apomorphine (Level A) or pump (Level C)
  o Intrajejunal levodopa/carbidopa enteric gel (Level C)
  o Deep brain stimulation (Level A) for patients below the age of 70 without psychiatric or cognitive problem due to the risk of adverse events

• Dyskinesia
  o Reduce levodopa dose, at the risk of increasing OFF. The latter can be compensated for by increasing the number of doses or a dopamine agonist (Level C)
  o Discontinue or reduce MAO-B or COMT inhibitors (GPP), at the risk of worsening wearing-off
  o Amantadine (Level A) (200-400mg/day)
  o Add atypical antipsychotics: clozapine (Level C) or quetiapine (Level C). Clozapine is associated with potential serious adverse events (agranulocytosis, myocarditis).
  o Deep brain stimulation

• Please refer to the EFNS/MDS-ES guideline for more information

2002 American Academy of Neurology (AAN) Practice Parameter: Initiation of Treatment for Parkinson’s Disease

• What is the role of selegiline in the treatment of early PD?
  o Selegiline has mild symptomatic benefit (Class II)
  o No convincing clinical evidence for neuroprotective benefit (Class II)
  o No convincing clinical evidence for increased mortality with selegiline whether it is given in combination with levodopa or as monotherapy (Class II)

• Recommendations for patients with PD who require symptomatic treatment
  o Initial symptomatic treatment of patients with PD with selegiline in order to confer mild, symptomatic benefit prior to the institution of dopaminergic therapy may be considered (Level A, Class II)

  o Initiating dopaminergic therapy
    ▪ Either levodopa or a dopamine agonist may be used. The choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each individual patient with PD (Level A, Class I and II)
    ▪ For patients with PD in whom levodopa treatment is being instituted, either an immediate-release or sustained-release preparation may be considered (Level B, Class II)
Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor and ADL disability in patients with PD who require dopaminergic therapy
Levodopa is more effective than cabergoline, ropinirole and pramipexole in treating the motor and ADL features of PD

2006 American Academy of Neurology (AAN) Practice Parameter: Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia

- Which medications reduce off time?
  - Entacapone and rasagiline should be offered to reduce off time (Level A)
  - Pergolide, pramipexole, ropinirole and tolcapone should be considered to reduce off time (Level B). Tolcapone (hepatotoxicity) and pergolide (valvular fibrosis) should be used with caution and require monitoring.
  - Apomorphine, cabergoline and selegiline may be considered to reduce off time (Level C)
  - Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C)

- What is the relative efficacy of medications in reducing off time?
  - There is insufficient evidence to recommend one agent over another (Level U)
  - Ropinirole may be chosen over bromocriptine for reducing off time (Level C)

- Which medications reduce dyskinesia?
  - Amantadine may be considered for patients with PD with motor fluctuations in reducing dyskinesia (Level C)
  - There is insufficient evidence to support or refute the efficacy of clozapine in reducing dyskinesia (Level U)

- Please refer to the AAN guideline for more information

References: