Pramipexole

Traffic light classification- Amber 2
Information sheet for Primary Care Prescribers

Key points/interactions

- Nausea is a common early side effect but usually responds to domperidone (10mg tds, or lowest effective dose – see MHRA advice)
- Ropinirole MR is first line dopamine agonist. Pramipexole MR should be reserved for patients in whom this is not suitable- see formulary.
- Dopamine agonists may cause compulsive/addictive behaviours such as gambling, compulsive shopping and hyper sexuality. Patients rarely recognise such changes as side effects and rarely report them unless specifically asked.

CLINICAL INFORMATION

Licensed Indications

Treatment of idiopathic Parkinson's disease. Pramipexole may be used alone (without levodopa) or in combination with levodopa throughout the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on-off” fluctuations).

Therapeutic Summary

As per the licensed indication.

NICE recommendations for the use of Pramipexole in Parkinson’s disease are:

- Consider a choice of dopamine agonists, levodopa or monoamine oxidase B (MAO-B) inhibitors for people in the early stages of Parkinson's disease whose motor symptoms do not impact their quality of life. Do not offer ergot-derived dopamine agonists as first-line treatment for Parkinson's disease.

- Offer a choice of dopamine agonists, MAO-B inhibitors or catechol-O-methyltransferase (COMT) inhibitors as an adjunct to levodopa for people with Parkinson's disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy, after discussing:
  - the person's clinical circumstances, for example, their Parkinson's disease symptoms, comorbidities and risks from polypharmacy
  - the person's lifestyle circumstances, preferences, needs and goals
  - the potential benefits and harms of the different medicine classes

- Choose a non-ergot-derived dopamine agonist in most cases, because of the monitoring that is needed with ergot-derived dopamine agonists. Only consider an ergot-derived dopamine agonist as an adjunct to levodopa for people with Parkinson's disease:
  - who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy **and**
  - whose symptoms are not adequately controlled with a non-ergot-derived dopamine agonist.

- When treating nocturnal akinesia, consider levodopa or oral dopamine agonists. If the selected option is not effective or not tolerated, offer the other instead.

Medicines Initiation

Consultant neurologist/specialist experienced in the management of PD. Modified Release preparations are preferred in order to avoid fluctuations in plasma levels. Pramipexole MR should be reserved for patients in whom ropinirole MR is not suitable.

Dose Regimen

NB: The tablet strengths for pramipexole are set out in the BNF and on the product packaging both in base and salt form. Either can be used, but both are given here for clarity.

Modified Release tablets are preferred in order to avoid fluctuations in plasma levels. Doses should be increased gradually from a starting dose of 0.26mg of base (0.375mg of salt) per day and then increased every 5-7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending dose schedule of Pramipexole prolonged-release tablets		
Week	Daily dose (mg of base)	Daily dose (mg of salt)
1	0.26	0.375
2	0.52	0.75
3	1.05	1.5

If a further dose increase is necessary the daily dose should be increased by 0.52mg (0.75mg salt) at weekly intervals up to a maximum dose of 3.15mg (4.5mg salt) per day.
Dose adjustments should be done based on the clinical response and the occurrence of undesirable effects. Dose adjustments will usually be recommended in secondary care; either to take place immediately or prior to the next clinic visit if necessary. The clinical nurse specialists (in liaison with hospital consultants) will also recommend dose changes between hospital visits if appropriate

For dosing advice on the immediate release, preparation see BNF or Summary of Product Characteristics(SPC).

Duration of treatment

Pramipexole is a treatment for chronic disease and therefore course length can be many years. Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome. See precautions section for discontinuation advice.

Missed dose

When the intake of a dose is missed, Pramipexole **modified-release tablets** should be taken within 12 hours after the regularly scheduled time. After 12 hours, the missed dose should be left out and the next dose should be taken on the following day at the next regularly scheduled time.

Contraindications

- Hypersensitivity to Pramipexole or any of the excipients

Precautions

- Renal impairment: for **modified release tablets** dosage adjustment required if CrCl between 30 and 50ml/min, not recommended in patients with CrCl <30ml/min. Dose adjustments for renal impairment are different for immediate release tablets, please refer to the SPC
- Severe cardiovascular disease (blood pressure monitoring required- see monitoring requirements)
- Psychotic disorders
- Risk of visual disorders (ophthalmological testing recommended- see monitoring requirements)
- If treatment discontinuation is necessary, pramipexole should be tapered off at a rate of 0.52 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.52 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.264 mg of base (0.375 mg of salt) per day.

Dopamine agonist withdrawal syndrome could still appear while tapering and a temporary increase of the dose could be necessary before resuming tapering

Monitoring

- Ask about the development of impulse control disorders (such as gambling, increased libido, hypersexuality, compulsive spending/buying, and binge eating). Patients may deny such symptoms when first asked about them.
- Ophthalmologic monitoring is recommended via a community optician or optometrist annually or biannually or if vision abnormalities occur.
- In severe cardiovascular disease, it is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy.
- Risk of postural hypotension (especially on initiation) - monitor blood pressure.

Adverse Effects

Side Effects	Action
Abdominal pain, dyspepsia, constipation	Usually transient. If persists discuss with neurologist/PD nurse specialist (PDNS)
Weight decrease, including decreased appetite	Usually transient. If persists discuss with neurologist/PDNS
Nausea & vomiting	Usually transient but may be quite severe. Unless very minor, prescribe Domperidone 10mg TDS (or lowest effective dose- see MHRA) during dose titration; this can usually be stopped within a few weeks.
Sedation	Usually transient. Advise patients not to drive/operate machinery if affected. If persists discuss with a neurologist. Incidence increases at doses >1.05mg MR per day (1.5mg of IR)
Orthostatic hypotension	Usually transient. If persists discuss with neurologist/PDNS
Light-headedness, dizziness	Usually transient. If persists discuss with neurologist/PDNS
Leg oedema	Rarely a major problem. Discuss with a neurologist if no other explanation identified
Hallucinations, confusion	Discuss with neurologist/PDNS
Psychotic reactions (other than hallucinations), including delusion, paranoia, delirium.	Discuss with neurologist/PDNS
'Dopamine dysregulation syndrome' Manifests as a change in behaviour, typically with an obsessional, risk-taking, sexual or financial axis.	Discuss with neurologist/PDNS
Hypersensitivity reactions including urticaria, rash, angioedema.	Discontinue and discuss with neurologist/PDNS
Visual disorders	Ophthalmological testing. Discuss with neurologist/PDNS/ ophthalmalogist
Raised hepatic enzymes	Discuss with neurologist/PDNS

Clinically relevant medicine interactions and their management

Patients selected for treatment with Pramipexole are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of Pramipexole therapy, the patient should be monitored for unusual side-effects or signs of potentiation of effect.

- **Neuroleptic medicinal products and other centrally acting dopamine antagonists** e.g. Sulpiride, Metoclopramide - may have an antagonistic effect if used with Pramipexole. Avoid concomitant use.
- **Inhibitors of active renal elimination pathway** e.g. cimetidine - may lead to increased levels of pramipexole.
- **Antihypertensives**– increased hypotensive effect
- **Memantine** - enhanced effect.

For further information on contraindications, precautions, adverse effects and interactions refer to the BNF or *Summary of Product Characteristics.*

Information given to the patient

Patients (and their family members and carers) should be given information on the following:

- The risk of excessive daytime sleepiness and sudden onset of sleep and the need to exercise caution when driving or operating machinery. If affected patients should refrain from driving or operating machinery until these effects have stopped occurring.
- The increased risk of developing impulse control disorders when taking dopamine agonist therapy and that these may be concealed by the person affected. Advice should be given about whom to contact if impulse control disorders develop.
- The risk of psychotic symptoms (hallucinations and delusions) with all Parkinson's disease treatments (and the higher risk with dopamine agonists).

Products available

Pramipexole tablets and Prolonged Release tablets

An estimate of the potential medicine costs (and any additional costs) to primary care
Pramipexole MR 0.26mg OD £13.00 x 30 tablets
Pramipexole 0.88mg tds £4.74 for 30 days (£1.58 per pack of 30 tablets)

REFERENCES

British National Formulary via NICE. Pramipexole. [Accessed 23/05/2024].
Summary of Product Characteristics. Pramiprexole Kkka 0.26mg prolonged release tabletsLast updated 30 Mar 2023. [Accessed 23/05/2024
NICE NG71 Parkinson's Disease in adults July 2017. [Accessed 23/05/2024]
MHRA Drug Safety Update: Domperidone: risks of cardiac side effects, May 2014 [Accessed 23/04/2024].
Drug tariff [Accessed 23/05/2024]