INTRODUCTION

The *Movement Disorders Prescriber's Guide to Parkinson's Disease* provides a comprehensive and succinct guide for all clinicians and health professionals involved in the treatment of people with Parkinson's disease. The guide provides practical information for use by clinicians and healthcare practitioners at all levels.

The chapters are alphabetical and follow the same format to enable quick retrieval of required information. Clinical experience of place in therapy and practice vignettes are included in each chapter.

General Notes

- All provided information applies to adult and not paediatric populations.
- 'Usual dosage range' under the section of 'Dosing and Use' refers to total daily dose, unless otherwise stated.
- Provided information applies for drug use in the context of Parkinson's disease (not other drugs indications), unless stated otherwise.
- The sections of drug-to-drug interactions refer to the most commonly used drugs in routine clinical practice; in case of doubt, consider consulting the marketed product provided information.
- In case of overdose always consult the relevant (local) poison control centre for the most up-to-date information.
- Provided costs only apply in the UK.

AMANTADINE

Therapeutics

Chemical Name and Structure

Amantadine (tricyclo[3.3.1.1]decan-1-amine, 1-adamantanamine, 1-aminoadamantane) is a white or nearly white crystalline, odourless, and bitter-tasting powder, with a molecular weight of 151.25 and an empirical formula of $C_{10}H_{17}N$. Amantadine is a tricyclic amine with two available preparations, amantadine hydrochloride, which is given orally, and the salt amantadine sulphate, which is administered either orally or IV.

Brand Names

- **Actison**, **Ampakine** (*Argentina*); **Amandin** (*Hong Kong*); **Amantex** (*Tunisia*); **Amantix** (*Poland*); **Amantrel** (*India*); **Atenegine** (*Japan*); **Amantix** (*Poland*); **Amantin** (*Ukraine*).
- **Enzil** (*Hong Kong*).
- **Gocovri** (*USA*).
- **Hofcomant** (*Greece*).
- **Kinestrel** (*Mexico*).
- **Lysovir** (*UK*).*
- **Mantadan** (*Italy*); **Mantadix** (*France*); **Mantidan** (*Brazil*); **Midantan** (*Russian Federation*).
- **Neomidantan** (*Russian Federation*, *Ukraine*).
- **Osmolex** (*USA*).
- **Parkadina** (*Portugal*); **PK-Merz** (*Austria*, *Czech Republic*, *Estonia*, *Germany*, *Hong Kong*, *Hungary*, *Israel*, *Lithuania*, *Malaysia*, *Mexico*, *Philippines*, *Russian Federation*, *Switzerland*, *Turkey*, *Ukraine*); **Prayanol** (*Chile*).
- **Symadin** (*South Africa*); **Symmetrel** (*Australia*, *Greece*, *Hong Kong*, *Japan*, *Netherlands*, *New Zealand*, *Singapore*, *South Africa*, *Switzerland*, *UK*).
- **Tregor** (*Germany*); **Trilasym** (*UK*).
- **Viregyt-K** (*Czech Republic*, *Hungary*, *Poland*).

*Not licensed for Parkinson's disease.

Generics Available

- Yes.

Licensed Indications for Parkinson's Disease

- Idiopathic Parkinson's disease, either as monotherapy or as an add-on to standard preparations (FDA, EMA, EMC), anti-dyskinetic action and used to manage levodopa-induced dyskinesias.

Licensed Indications for Other Conditions

- Post-encephalitic parkinsonism, symptomatic parkinsonism following CNS injury by carbon monoxide intoxication (FDA-only for immediate release tablet/capsule or syrup), drug-induced parkinsonism (FDA), parkinsonism cases (FDA, EMA).

- Herpes zoster, in elderly or debilitated patients at risk of developing a severe and painful rash in order to manage long-duration pain (EMC).
- Influenza A virus infection (prophylaxis, treatment) (FDA-only for immediate release tablet/capsule or syrup).*

*No longer recommended due to resistance (Centers for Disease Control and Prevention (CDC)).

Non-licensed Use for Parkinson's Disease
- Levodopa-induced peak dose and diphasic dyskinesias.

Non-licensed Use for Other Conditions
- Creutzfeldt–Jacob disease (limited early evidence).
- Triple therapy of amantadine, ribavirin, and interferon in chronic hepatitis C patients previously unresponsive to therapy.
- Intractable hiccups.
- Fatigue in multiple sclerosis.
- Fatigue in Parkinson's disease (investigational).

Ineffective
- Depression.
- Huntington's disease.
- Essential tremor.
- Tardive dyskinesia.
- Chronic hepatitis C patients, who are treatment-naïve or experience relapses.

Mechanism of Action
- Although the precise mechanism by which amantadine exerts anti-parkinsonian effects is poorly understood, it has been proposed to be due to increased dopamine release, prevention of dopamine reuptake and a direct, mild anticholinergic effect.
- Amantadine is a weak, non-competitive antagonist of NMDA glutamate receptors. Its anti-glutamatergic properties may explain the anti-dyskinetic efficacy.
- The antiviral mechanism seems to be unrelated to the amantadine effect in the context of Parkinson's disease.

Efficacy Profile
- The goal of amantadine therapy is to achieve better control of parkinsonian symptoms/signs, including levodopa-induced dyskinesias, plus minimizing adverse effects produced by increased levodopa dosage and improving patients' quality of life.
- According to the MDS EBM Committee:
  - amantadine is 'likely efficacious' and 'possibly useful', as an early monotherapy in Parkinson's disease;
  - amantadine is 'efficacious' and 'clinically useful' in treating dyskinesias.
  - there is 'insufficient evidence' to support amantadine use in the management of Parkinson's disease-related ICDs and related disorders.

- The beneficial effect of IR amantadine preparations has been demonstrated in numerous high-quality studies, while a multi-centre, double-blind RCT has shown that wash-out of amantadine in dyskinetic Parkinson's disease patients significantly worsened LID.
- Long-term efficacy of IR amantadine preparations (≥1 year) has been demonstrated in one RCT and one double-blind, placebo-controlled, non-randomized study.
- Three double-blind RCTs have demonstrated the efficacy of ER amantadine preparations on LID in Parkinson's disease patients, while an open-label extension study has found no long-term safety and tolerability issues for a 2-year follow-up period (EASE LID 1, 2 & 3, ALLAY-LID 2). A secondary benefit of reduction in OFF time was also noted.
- A double-blind crossover study with an open follow-up period has found that a small sample of Parkinson's disease patients abolished or reduced pathological gambling with amantadine use. Interestingly, a retrospective analysis of a large cross-sectional study (DOMINION) of ICDs in Parkinson's disease has shown that amantadine use was associated with occurrence of ICDs, including pathological gambling.
- According to a retrospective study, a longer duration of amantadine treatment may decrease the rate of FoG. Another small retrospective study has found a patient-reported subjective improvement in FoG after initiating amantadine, although this effect was transient on some occasions.
- Amantadine is less effective than levodopa in treating parkinsonian motor symptoms.
- It is probably equally effective to anticholinergic agents in treating parkinsonian symptoms. Addition of amantadine to anticholinergic agents might produce further improvement, although this is not a commonly encountered or recommended as a combination due to significant safety issues.
- Addition of amantadine to levodopa is expected to produce greater reduction in parkinsonian symptoms than amantadine or levodopa alone (in patients who cannot tolerate high levodopa doses).
- Amantadine's anti-dyskinetic action is expected to appear about 48 h after ingestion. In some countries (e.g. Austria) Amantadine is occasionally given IV to counter severe dyskinesias.
- Preliminary evidence based on primary cultures (neurons, microglia, and astroglia) has suggested a neuroprotective role of amantadine on dopamine neurons via an anti-inflammatory effect mediated by microglia and an enhanced expression of GDNF in astroglia.

Pharmacokinetics

Absorption and Distribution

- Oral bioavailability: 86–90%.
- Food co-ingestion: neither delays the rate, nor reduces the extent of absorption.

- Tmax: 2–4 h (IR preparations) and 12 h (ER preparations).
- Time to steady state: within 3 days.
- Pharmacokinetics: linear for doses up to 200 mg/day, higher doses may result in greater than proportional increase in maximum plasma concentrations.
- Protein binding: 67%.
- Volume of distribution: 1.5–6.1 l/kg (oral preparations).

Metabolism
- Metabolized to a minor extent, mostly by N-acetylation (5–15%). At least eight metabolites have been identified in the urine (unknown clinical significance).

Elimination
- Half-life in healthy adults is about 16 h (10–31 h).
  - Half-life may be at least two- or three-fold prolonged in impaired renal function (CrCl<40 ml/min/1.73 m^2).
- Amantadine is mostly (~80–90%) excreted unchanged in the urine after 4–5 days.
  - Urine acidification (including urine-acidifying drugs) may increase amantadine excretion, while an increased pH in the urine might have the opposite effect.

Drug Interaction Profile

Pharmacokinetic Drug Interactions
- Urine-acidifying drugs (e.g. *acetazolamide*) may decrease levels and effects of amantadine due to increasing its excretion rate.
- *Quinidine*, *sulfamethoxazole*, and *triamterene* may increase levels and effects of amantadine by decreasing renal clearance.

Pharmacodynamic Drug Interactions
- Co-medication with *abobotulinumtoxinA*, *onabotulinumtoxinA*, tricyclic antidepressants, neuroleptics, antimuscarinic agents used for overactive bladder (e.g. *solifenacin*, *oxybutynin*), antihistamines, MAOIs, and other agents with anticholinergic properties (e.g. *trazodone*) may enhance potential systemic anticholinergic effects (synergistic action), particularly in terms of inhibiting GI motility.
  - Co-administration with anticholinergic antiparkinsonian agents may provide additional therapeutic benefit in marginally treated patients compared to either agent alone, but may lead to adverse anticholinergic effects, including nightmares, confusion, and acute psychotic reactions.
- Co-administration with opiates may lead to anticholinergic-like effects (usually in opiate abuse, not in usual doses).
- Co-administration with alcohol might increase potential CNS effects, such as dizziness, somnolence, light-headedness, orthostatic hypotension and confusion.

- Co-administration with CNS stimulants may result in additive CNS stimulation, causing nervousness, irritability, insomnia, or even seizures or arrhythmias.
- Co-administration with *thioridazine* has been reported to worsen tremor in elderly Parkinson's disease patients.
- Co-medication with drugs causing electrolyte imbalance or increasing QT interval, such as Class IA and III anti-arrhythmics, antipsychotics (e.g. *haloperidol*, *phenothiazine derivatives*, *pimozide*), tricyclic antidepressants, certain antimicrobial agents (e.g. *moxifloxacin*, *erythromycin*), certain antihistamines (e.g. *astemizole*, *mizolastine*),, and others may lead to potentially fatal Torsade de Pointes arrhythmias and is considered a risk factor for sudden cardiac death.
- Co-medication with serotonergic agents, including SSRIs/SNRIs, tricyclic antidepressants, opioids, *lithium*, *buspirone*, amphetamines, MAOIs, and triptans may increase the risk of a potentially life-threatening serotonin syndrome.
- Co-administration with *bupropion* or *memantine* may lead to pharmacodynamic synergism and increased adverse effects from the CNS (e.g. agitation, dizziness).

Adverse Effects

How Drug Causes Adverse Effects

- The exact mechanism by which amantadine causes adverse effects has not been established, although acute toxicity may be attributable to its anticholinergic effects.
- It is generally well-tolerated with more side effects occurring with higher doses.
- Side effects usually appear within the first 2–4 days of treatment initiation and disappear 24–48 h after amantadine discontinuation.

Common Adverse Effects

- Very common (≥1/10):
  - IR preparations: oedema of ankles, livedo reticularis.
  - ER preparations: hallucinations, dizziness, dry mouth, peripheral oedema, constipation, falls, orthostatic hypotension, urinary tract infections.
- Common (≥1/100 to <1/10):
  - Neuropsychiatric: anxiety, elevation of mood, light-headedness, headache, lethargy, hallucinations, nightmares, ataxia, slurred speech, loss of concentration, nervousness, depression, insomnia, myalgia, hallucinations, confusion, nightmares.
  - Cardiovascular: palpitations, orthostatic hypotension.
  - GI: dry mouth, anorexia, nausea, vomiting, constipation.
  - Skin: diaphoresis.

- Uncommon (≥1/1,000 to <1/100):
  - Eye/ear: blurred vision.

Life-Threatening or Dangerous Adverse Effects
- Rare (≥1/10,000 to <1/1,000):
  - Suicidality.
  - Neuroleptic malignant-like syndrome.
  - Convulsions.
  - Psychosis.
  - Heart failure.
  - Urinary retention.
- Very rare (<1/10,000):
  - Leukopenia.
- Unknown frequency:
  - Delirium.

Rare and Not Life-Threatening Adverse Effects
- Corneal oedema
- Reversible elevation of liver enzymes.
- ICDs.
- Tremor, dyskinesia.
- Diarrhoea.
- Exanthema, photosensitization.
- Urinary incontinence.

Weight Change
- Not reported.

What to Do About Adverse Effects
- Discuss common adverse effects with patients or caregivers before starting medication, including symptoms that should be reported to the physician.
- In some cases, adverse effects subside after the first week of continued therapy.
- Some adverse events (especially CNS-related) are dose-dependent, so consider lowering the dose to 200 mg or 100 mg daily. If adverse effects are still troublesome or persist, consider withdrawing therapy completely.
- In case of newly developing adverse effects, consider excluding renal impairment or interactions with newly introduced medications.
- If patients on amantadine experience excessive drowsiness, somnolence, and/or episodes of sudden-onset sleep during activities that require active participation, they should refrain from driving or operating machines and inform their treating physician. Therapy discontinuation is generally advised.
  - Patients should be particularly vigilant, as they may not have any warning signs and they may feel alert just prior to falling asleep.

A

AMANTADINE

Dosing and Use

Usual Dosage Range

- IR: 100–400 mg daily (a dose of 400 mg/day should not be exceeded).
- ER: 137–274 mg daily (Gocovril).
- ER: 129–322 mg daily (Osmolex ER).

Available Formulations

- Capsules: 100 mg.
- Oral solution: 50 mg/5 ml.
- Capsules, ER: 68.5 mg, 137 mg (Gocovril).
- Tablets, ER: 129 mg, 193 mg, 258 mg (Osmolex ER).

How to Dose

- IR: 100 mg daily for at least one week; may increase to 100 mg twice daily and titrate accordingly against signs and symptoms without exceeding 400 mg/day in divided doses (gradual dose increase at intervals of at least 1 week).
- ER (Gocovril): 137 mg once at bedtime; increase to 274 mg once at bedtime after one week.
- ER (Osmolex): 129 mg once in the morning: may increase dose in weekly intervals up to 322 mg/day (one 129 mg + one 193 mg tablet).

Dosing Tips

- Amantadine IR or ER products are not interchangeable.
- Direct switching from conventional amantadine to ER preparations was found to be efficacious and well-tolerated.
- Doses exceeding 200 mg/day may provide some additional relief but have been associated with increased neuropsychiatric side effects.
- Amantadine may appear to lose efficacy within a few months of continuous treatment; effectiveness may be prolonged by withdrawal for 3–4 weeks.
- Avoid evening or bedtime dosing of amantadine to prevent insomnia, confusion, or hallucinations, especially among the elderly.
- Administer daily doses in two divided doses to decrease adverse CNS effects.
- No additional benefit is expected from amantadine therapy where optimized therapeutic doses of levodopa are administered.

How to Withdraw Drug

- Amantadine should be withdrawn gradually, e.g. half the dose at weekly intervals, in order to lower the risk of withdrawal symptoms.
  - Osmolex ER: gradually reduce dose from higher doses to 129 mg daily for 1–2 weeks before discontinuation.
  - Gocovri: to stop therapy in patients who have been on the drug for more than 4 weeks, the dose should be reduced by half if possible for their final week of dosing.

- Withdrawal symptoms may present as aggravation of parkinsonian features, delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression, or slurred speech.
  - Parkinsonian crises, manifesting as confusion, marked rigidity, urinary retention, and bulbar palsy, have been reported within 3 days after an abrupt amantadine discontinuation, even in the absence of apparent clinical efficacy of amantadine.
- In case of amantadine titration or discontinuation, close patient monitoring is advised; cases of NMS have been reported, especially in patients treated with neuroleptics.

Overdose

- May be fatal; the lowest reported acute lethal dose was 1000 mg.
- It can present as:
  - Cardiovascular: arrhythmia, tachycardia, hypertension, heart failure/arrest.
  - Respiratory: hyperventilation, pulmonary oedema, respiratory distress, ARDS.
  - Renal: urine retention, decreased CrCl, renal insufficiency.
  - CNS: hyperreflexia, restlessness, convulsions, torsion spasms, dystonic posturing, dilated pupils, dysphagia, confusion, disorientation, delirium, hallucinations, acute psychosis, myoclonus, lethargy, hyperthermia, coma.
  - Gastrointestinal: dry mouth, nausea, vomiting.
- There is no specific antidote. Close monitoring is advised.
- Vomiting induction and/or gastric aspiration (and lavage in conscious patients), administration of activated charcoal, or saline cathartic may be used according to clinical judgement.
  - Haemodialysis does not remove significant amounts of amantadine (~4%), possibly due to extensive tissue binding.
- In case of convulsions and/or excessive motor restlessness, consider administering anticonvulsants, such as diazepam IV, paraldehyde IM or per rectum, or phenobarbital IM.
- In case of acute psychotic symptoms, delirium, dystonic posturing, or myoclonus, consider administering physostigmine by slow IV infusion (1 mg in adults). Repeat as applicable.
- In case of urine retention, consider placing an indwelling bladder catheter, which can be maintained for the time required.

Tests and Therapeutic Drug Monitoring

- Assessment of renal function is advised at baseline and at regular intervals, especially in the case of new adverse events.
- Periodic monitoring for melanoma development is advised.

Other Warnings/Precautions

- Close monitoring is advised in patients with known cardiovascular disorders (including orthostatic hypotension, peripheral oedema, and

congestive heart failure) or eczematoid dermatitis, as amantadine may aggravate these conditions.
- Close monitoring is advised in patients with known psychiatric disorders, as amantadine may exacerbate psychosis (particularly the ER preparations), especially at initiation and after dose increases. An alternative therapeutic option should be used, if possible.
- Close monitoring is advised in case of conditions (including pharmacological agents) that alter the urine pH to more acidic or alkaline, as they will predispose to an increased or decreased excretion of amantadine, respectively. On the latter occasion, increased accumulation of amantadine may occur, increasing the possibility for adverse events.
- Co-administration with alcohol is not recommended. Alcohol may result in dose-dumping if co-administered with ER amantadine.
- Amantadine may be co-administered with the influenza virus vaccine, administered by intramuscular injection (inactivated vaccine), but not with the nasal flu vaccine (live attenuated vaccine).

Do Not Use (Contraindications)
- Known sensitivity to amantadine or to any of its excipients, including lactose.
  - Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose–galactose malabsorption.
- History of gastric ulceration.
- Untreated angle closure glaucoma.
- History of seizures.
- Cholinergic subtype of Parkinson's disease where use of anticholinergics can be hazardous owing to worsening cognitive function.

Special Populations

Renal Impairment
- Elimination is almost exclusively via urinary excretion, even in renal failure, and amantadine may persist in the plasma for several days, causing severe side effects in the case of accumulation.
- Amantadine dosage should be individualized according to CrCl:
  - UK:
    - CrCl>35 ml/min: 100 mg daily.
    - CrCl 15–35 ml/min: 100 mg every 2–3 days.
    - CrCl<15 ml/min: not recommended.
  - USA:
    - CrCl 30–50 ml/min: 200 mg on the first day; 100 mg daily afterwards.
    - CrCl 15–29 ml/min: 200 mg on the first day; 200 mg on alternate days afterwards.
    - CrCl<15 ml/min or patients on haemodialysis: 200 mg every 7 days.
    - ER preparations are contraindicated in end-stage renal disease (CrCl<15 ml/min).