Depot Antipsychotics

Traffic light classification - Amber 2
Information sheet for Primary Care Healthcare Professionals

Scope

These guidelines are to support primary care healthcare professionals who are already prescribing and/or administering depot antipsychotics or those who wish to start.

Licensed Indications¹
Long-acting intramuscular (IM) depot antipsychotic injections are licensed for the maintenance treatment of schizophrenia and other psychoses.

Exclusions
See contraindications and precautions sections.

Olanzapine embonate (ZypAdhera®) is a RED drug on the traffic-lights classification. Patients prescribed “high-doses” of antipsychotics would be classified as RED i.e. prescribing would be the responsibility of the consultant psychiatrist. “High-dose” is defined as either a single antipsychotic prescribed at a dose higher than the BNF recommended maximum, or where more than one antipsychotic is prescribed, the combined dose, expressed as a percentage, is greater than 100%.

For example:
Olanzapine 15mg/day + flupentixol decanoate 200mg/week
= 15/20⁸ + 200/400⁹ = 75% + 50% = 125% BNF limit

Therapeutic Summary
Depot antipsychotic injections are a useful option when compliance with oral antipsychotic treatment is unreliable.²

Advantages of long-acting injections
- Assured compliance, avoid covert non-adherence
- Steady plasma levels compared to oral medication
- Reduction in relapses, rehospitalisation and severity of the relapse
- Bioavailability problems may be less (less first-pass metabolism for some people)
- Stable therapeutic effects
- Better downward titration to minimise side-effects

Disadvantages of long-acting injections
- Following a change of dose it can take weeks to achieve steady state plasma levels of drug
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- Drug cannot be quickly removed if side-effects develop (dystonia, extrapyramidal side-effects (EPSE), neuroleptic malignant syndrome (NMS))
- Perception by the patient of "being controlled", or feeling less in control of their treatment
- Pain at the site of injection. Over time hard plaques or nodules may form, which will reduce the ease of administration as well as causing discomfort
- Loss of dignity with the gluteal route

Medicines Initiation
Depot antipsychotics should be initiated by specialist secondary care mental health services.

A small test dose (see table below) is given initially and the patient observed for side-effects. If there have not been any problems 4-7 days following the test dose the dose can be gradually titrated to the lowest effective maintenance dose.

In the case of aripiprazole, paliperidone and risperidone long-acting injections there are no injectable test doses so patients are given a small dose of the oral antipsychotic to assess tolerability. Paliperidone is an active metabolite of risperidone. For further information refer to the aripiprazole, risperidone and paliperidone (AMBER 2) Information Sheets for Primary Care Prescribers.

Dosages and Route of Administration

Typical antipsychotic depots
Flupentixol decanoate, fluphenazine decanoate, haloperidol decanoate and zuclopenthixol decanoate are all oil-based injections where the drug is linked to a long-chain hydrocarbon and dissolved in either sesame oil or fractionated coconut oil. These depots are only licensed for administration by deep IM injection into the gluteal muscle.

Atypical antipsychotic depots
Aripiprazole, olanzapine, paliperidone and risperidone have been formulated as long-acting depot injections.

Aripiprazole (Abilify Maintena®) injection is given as a deep IM injection of 400mg once every calendar month into the deltoid or gluteal muscle using the correct size needle provided in the pack. Oral aripiprazole should be continued for at least two weeks after the first injection before tapering off. Aripiprazole Maintena® requires reconstitution with the solvent provided. The dose may need to be reduced if co-prescribed with strong CYP3A4 or CYP2D6 inhibitors. Please contact your local Mental Health Trust Pharmacist for advice.

Paliperidone palmitate (Xeplion®) injection is given as a deep IM injection into the deltoid or gluteal muscle using the correct size needle provided in the pack. A loading-dose of 150mg is given into the deltoid on day 1 followed by a second loading dose of 100mg into the deltoid on day 8. This is followed by monthly injections of 50-150mg into either the deltoid or gluteal muscle. It is available as a ready-prepared pre-filled syringe that does not require cold storage.

Paliperidone palmitate (Trevicta®) injection is given as a deep IM injection into the deltoid or gluteal muscle using the correct needle provided in the pack. It is a 3 monthly injection, indicated for the maintenance of schizophrenia in adult patients who are clinically stable on 1 monthly paliperidone injections (preferably for four
months or more), who do not require dose adjustments. The Trevicta® dose should be based on the previous 1-monthly paliperidone injectable dose using a 3.5-fold higher dose. A table for conversion of doses can be found on the paliperidone information sheet. There are no special storage conditions for Trevicta®.

Risperidone long-acting injection (Risperdal Consta®) is given as a deep IM injection into the deltoid or gluteal muscle every two weeks. It must be stored in a refrigerator at between +2 to +8°C and is only stable at room temperature for 7 days. The powder must be suspended in the diluent and administered using the correct size needle provided in the pack. Following an IM injection, the main release of risperidone starts from week 3 onwards, is maintained from weeks 4 to 6, and subsides by week 7. When switching to Consta®, other oral antipsychotics should be continued for at least three weeks after the first injection before being withdrawn. Please contact your local Mental Health Trust Pharmacist for advice.

Administration of Depot Injections
Practitioners must have the necessary knowledge, skills and competency to safely administer depot antipsychotic injections by deep intramuscular injection using the "z-track technique". Take particular care when selecting the needle gauge and length to ensure the drug is given into the muscle. For obese patients a longer 2-inch 20g/21g needle should be selected for gluteal administration and a 1.5-inch 22g needle for deltoid administration.

Reduction of local injection site reactions
- Use the lowest practical volume
- Inject less frequently if possible to prevent hard plaques of tissue forming.
- Use the Z-tracking technique to avoid extravasation
- Use a needle of the right length for the patient to ensure deep intramuscular administration (longer needles are required for people with a higher body mass index (BMI))
- Use alternate buttocks or arms (rotate injection sites) to allow time to heal

A very useful resource is;

Products Available
There are a range of long-acting depot antipsychotics available.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Formulations</th>
<th>Standard Adult Test Dose</th>
<th>Usual Maintenance Dose Range (wk=week)</th>
<th>Dosing Interval (weeks)</th>
<th>Average Cost per Year (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupentixol decanoate</td>
<td>Depixol®,</td>
<td>20mg/ml, 100mg/ml, 200mg/ml</td>
<td>20mg</td>
<td>50mg 4wk to 300mg 2wk (max. 400mg/wk)</td>
<td>2-4wk</td>
<td>£160 (100mg 2wk)</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Modecate ®</td>
<td>12.5mg/0.5ml, 25mg/ml, 50mg/0.5ml, 100mg/ml</td>
<td>12.5mg</td>
<td>12.5-100mg 2-5wk</td>
<td>2-5wk</td>
<td>£60 (25mg 2wk)</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>Haldol®</td>
<td>50mg/ml, 100mg/ml</td>
<td>50mg</td>
<td>50-300mg 4wk</td>
<td>4wk</td>
<td>£50 (50mg 4wk)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Zuclopenthixol decanoate</th>
<th>Clopixol® (see note below)</th>
<th>200mg/ml, 500mg/ml</th>
<th>100mg</th>
<th>200-500mg 1-4wk (max. 600mg/wk)</th>
<th>2-4wk</th>
<th>£80 (200mg 2wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone long-acting injection</td>
<td>Risperdal Consta®</td>
<td>25mg, 37.5mg, 50mg</td>
<td>Oral risperidone 2mg/d</td>
<td>25-50mg 2wk</td>
<td>2wk</td>
<td>£2900 (37.5mg 2wk)</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Xeplion® Trevicta®</td>
<td>50mg, 75mg, 100mg, 150mg, 175mg,263mg, 350mg, 525mg</td>
<td>Oral risperidone 2mg/d</td>
<td>50-150mg every month</td>
<td>Monthly</td>
<td>£3100 (75mg/ month)</td>
</tr>
<tr>
<td>Aripiprazole long-acting injection</td>
<td>Abilify Maintena®</td>
<td>400mg</td>
<td>Oral aripiprazole</td>
<td>400mg every month</td>
<td>Monthly</td>
<td>£2650 (400mg/ month)</td>
</tr>
</tbody>
</table>

**Note:** Do not confuse the slow and long-acting zuclopenthixol decanoate (Clopixol®, Clopixol Conc® depot with the faster, shorter-acting zuclopenthixol acetate (Clopixol Acuphase®) formulation which (although not recommended) is used for rapid tranquillisation. Errors have occurred when these products have been interchanged. The drug name and the packaging are very similar.

### Duration of Treatment
Following recovery from an acute episode of psychosis, the risk of relapse is high if antipsychotic medication is stopped within 1 to 2 years. If a patient has expressed a desire to stop their depot or if they have been stable on the depot for over five years they should be referred by the GP back to mental health services for advice and assessment.

### Explicit Criteria for Review and Discontinuation of the Depot
Withdrawal symptoms have been described after abrupt discontinuation of oral antipsychotics but are unlikely following the discontinuation of a depot injection as blood levels will fall slowly over some weeks after the last injection. It is however recommended any antipsychotic is discontinued gradually and that signs and symptoms of relapse are monitored for regularly (for at least 2 years after discontinuation).

### Monitoring Requirements and Responsibilities
During antipsychotic treatment, improvement in the patient's clinical condition may take several weeks. Attainment of peak plasma levels, therapeutic effect and steady state plasma levels are all delayed with depot medication. Sufficient time should be allowed between dose changes for steady state to be reached.

During titration to an effective maintenance dose the patient should be closely monitored. Suicidal behaviour is inherent in psychotic illnesses, and in some cases has been reported early after initiation or switch of antipsychotic therapy. High risk patients should be closely supervised during treatment.
### General Health Monitoring for All Patients

Ask about compliance and side effects at every consultation

**All patients should be offered an annual physical health check (more often if clinically indicated).** A copy should be sent to the care coordinator and psychiatrist and put in the secondary care notes.

**Particular attention should be given to:**

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Smoking, alcohol, substance misuse, diet, level of physical exercise, sexual health, contraceptive advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular risk factors</td>
<td>Blood pressure and lipids</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Hyperglycaemia/diabetes and hyperprolactinaemia</td>
</tr>
<tr>
<td>Injection site</td>
<td>Assess the injection site for signs of redness, swelling, nodules</td>
</tr>
<tr>
<td>Other side-effects</td>
<td>Such as weight gain (monitor BMI, waist circumference), sexual dysfunction, lethargy, extrapyramidal movement disorder side-effects (including tardive dyskinesia)</td>
</tr>
<tr>
<td></td>
<td>Two useful side-effect tools that can be completed by patients are the GASS (Glasgow Antipsychotic Side-effect Scale)(^5) and LUNSERS (Liverpool University Neuroleptic Side-Effect Rating Scale)(^4)</td>
</tr>
</tbody>
</table>

### Schedule for Physical Monitoring\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Initial Baseline Health Check &amp; during first year (by secondary care)</th>
<th>Annual Health Check (by GP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Function</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Liver Function</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Renal Function</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Full Blood Count</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td><strong>E.C.G.</strong></td>
<td>√ (if indicated)</td>
<td>(only if indicated)</td>
</tr>
<tr>
<td>Fasting Blood Plasma Glucose, HbA(_{1c})</td>
<td>√ (repeat at 3 months and 12 months)</td>
<td>√</td>
</tr>
</tbody>
</table>
### Side-Effects and their Management

<table>
<thead>
<tr>
<th>SIDE EFFECTS</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common (≥10%) – unless indicated</strong></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism, extrapyramidal symptoms</td>
<td>Consider a dose reduction. An anticholinergic (e.g. procyclidine) maybe helpful for symptoms of stiffness, tremor and dystonia.</td>
</tr>
<tr>
<td>Akathisia (may include physical &amp; /or psychological restlessness)</td>
<td>Refer to Psychiatrist. A reduction in dose, or change to an alternative antipsychotic maybe required.</td>
</tr>
<tr>
<td><strong>Common (≥1% and &lt;10%)</strong></td>
<td></td>
</tr>
<tr>
<td>Weight gain / increased appetite</td>
<td>Encourage a healthy balanced diet and regular exercise. Monitor and refer to a dietician and/or Psychiatrist if appropriate.</td>
</tr>
<tr>
<td>Somnolence / drowsiness / dizziness</td>
<td>Consider dose reduction. Advise patients not to drive/operate machinery if affected.</td>
</tr>
<tr>
<td>Raised prolactin (&gt;1000mU/L) – or if symptomatic</td>
<td>e.g. galactorrhoea, gynaecomastia, disturbances of menstrual cycle/amenorrhoea, sexual dysfunction. Dose-related. Consider dose-reduction or switching to an alternative antipsychotic. Refer to Psychiatrist.</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Monitor. Refer to Psychiatrist if appropriate.</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Consider dose reduction. Review need for co-prescribed anticholinergics (e.g. procyclidine).</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Consider dose reduction. Review need for co-prescribed anticholinergics (e.g. procyclidine).</td>
</tr>
<tr>
<td>Constipation</td>
<td>High fibre diet, good fluid intake, exercise, laxative.</td>
</tr>
<tr>
<td><strong>Others Uncommon (≥ 0.1% and &lt;1%)</strong></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Consider dose reduction. Advise patient to take time when standing up. Do not drive if affected.</td>
</tr>
</tbody>
</table>
Prolonged QTc interval, abnormal ECG

The upper limit of normal for the corrected QT interval (QTc) is 440msec for men and 470msec for women. If the QTc is above this limit but there is a genuine indication for the antipsychotic at this dose and there is no alternative then providing the patient has no symptoms (pre-syncpe or syncpe) the treatment can be continued and the patient monitored at regular intervals.

If the patient has symptoms of pre-syncpe/syncpe, a history of syncpe or torsades de points, or is co-prescribed any other medication that can prolong the QT interval (see below) then expert cardiology advice should be sought.

A QTc of >500msec is always abnormal and is at a level where arrhythmic complications get much more likely. A cardiology opinion should be sought immediately and the patient's drug regimen reviewed without delay.

Raised blood glucose, raised LFTs, fall in white cell count (WCC) or platelets

Monitor and refer if appropriate.

Others – frequency unknown

**Neuroleptic malignant syndrome (NMS) - hyperthermia, muscle rigidity, autonomic instability, altered consciousness, ↑ creatinine kinase (CK) levels**

Very rare. Discontinue ALL antipsychotic(s) immediately. If suspected refer to an acute hospital without delay. Recovery from NMS will be delayed if patient was on a depot. Depot antipsychotics should not be started. Refer to Psychiatrist.

**Tardive dyskinesia (TD)**

Refer to Psychiatrist. A reduction in dose or change to an alternative atypical antipsychotic maybe required. Review use of co-prescribed anticholinergics (e.g. procyclidine) as these can worsen tardive dyskinesia.

**Injection site problems**

Inspect the injection site each time. Rotate the injection sites. Ensure correct injection technique.

**Contraindications - see individual SPC for specific contraindications**

Patients with a known hypersensitivity to any ingredient.

**Precautions – Refer to Psychiatrist if Necessary**

- Antipsychotic use maybe associated with an increased risk of venous thromboembolic events (VTE). All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventative measures undertaken\(^3\).
- Consider carefully the risk of cerebrovascular events before treating any patient with a previous history of stroke or Transient Ischaemic Attack or high baseline risk of cerebrovascular disease (e.g. hypertension, diabetes, smoking, atrial fibrillation)
- Patients with dementia (particularly those who are dehydrated, co-prescribed furosemide, or have risk factors for stroke)
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- Patients with cardiovascular disease, including QT prolongation, congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia, and hypomagnesaemia
- Patients with Parkinson’s disease or dementia with Lewy bodies
- Patients with epilepsy or history of seizures
- Pregnancy, breast-feeding
- Patients with diabetes and patients at risk require appropriate clinical monitoring for hyperglycaemia and/or development or exacerbation of pre-existing diabetes
- Renal/ liver disease
- Narrow angle glaucoma
- Hyperthyroidism, phaeochromocytoma
- Myasthenia gravis
- Prostatic hypertrophy
- Severe respiratory disease
- Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect e.g. risperidone, paliperidone. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery.

Clinically Relevant Medicine Interactions and Their Management – Refer to Psychiatrist if Necessary

- Use with caution in those who consume alcohol or receive medicines that can cause central nervous system depression (e.g. opiate analgesics, benzodiazepines, z-hypnotics) due to increased risk of sedation
- Dopamine agonists / anti-Parkinsonian medicines – effects are antagonised
- Increased risk of extrapyramidal side-effects with metoclopramide, prochlorperazine
- Caution with other drugs known to prolong the QT interval due to increased risk of arrhythmias e.g. methadone, amiodarone, disopyramide, sotalol, moxifloxacin, some antimalarials (e.g. quinine), some antivirals (e.g. ritonavir, saquinavir)
- Increased risk of hypotension with antihypertensives e.g. ACE inhibitors, alpha-blockers, calcium channel blockers, diuretics
- Carbamazepine (and other CYP 3A4 inducers) may reduce plasma levels of risperidone and haloperidol. Doses may need to be reviewed on introduction or on withdrawal of carbamazepine.
- CYP2D6 inhibitors e.g. some SSRIs may increase plasma levels of haloperidol, zuclopenthixol, risperidone and fluphenazine. Antipsychotic doses may need to be reviewed on introduction of a CYP2D6 inhibitor.

For full details of contraindications, precautions and interactions, please consult the manufacturers Summary of Product Characteristics (SPC)¹ or BNF.

CRITERIA FOR TRANSFERRING CARE TO PRIMARY CARE

- The patient’s mental health is stable (this can mean stable but with some residual symptoms)
- The patient is tolerating and accepting a regular maintenance dose of depot antipsychotic and consistently attends for their depot injection
- The patient has been receiving the depot medication for at least 12 months.
- Suitable support arrangements for community care are in place
An agreed care plan is in place with respect to monitoring the patients' mental and physical health, assessing the effects and side-effects of medication, and actions required if the patient does not attend for their depot, shows signs of relapse or intolerable side-effects.

It should be clearly documented in correspondence who will be responsible for prescribing and carrying out the routine monitoring.

**PSYCHIATRIST RESPONSIBILITIES**

- To assess the patient, establish the diagnosis, determine a management strategy and devise a care plan in conjunction with the GP, other healthcare professionals and appropriate support agencies.
- To initiate the depot antipsychotic, titrate to the minimum effective maintenance dose, monitor response and assess/manage initial side-effects.
- When prescribing depot antipsychotics to specify the form, strength, dose and dosing interval between injections, and brand where appropriate.
- To provide the patient with written information about the illness and depot antipsychotic treatment.
- To provide the GP with a copy of the agreed care plan.
- The care plan should state who is responsible for monitoring the patients mental and physical health at the appropriate time intervals.
- To be available for advice and agree an action plan if the GP reports signs of relapse, side-effects, compliance problems or level of risk to self or others is increased.
- To have procedures in place for rapid referral by the GP where appropriate.
- To prescribe the depot antipsychotic until the GP takes over care.
- To notify the GP as soon as practical of any changes to drug treatment or care plan.
- For both the GP and the psychiatrist to receive a copy of any blood test results, the name and address of BOTH parties should be specified on the pathology blood sample form.
- To advise on dose adjustments and when it is appropriate to stop, and how to stop the depot.
- To discharge the patient to primary care when appropriate following agreement with the GP.

**GP RESPONSIBILITIES**

- To check that the patient engages with the practice and attends for their antipsychotic depot injection at the agreed times and to follow up the patient in cases on non-attendance.
- When prescribing depot antipsychotics to specify the form, strength, dose and dosing interval between injections, and brand where appropriate.
- To monitor at regular intervals the mental health, general health and well being of the patient, assess compliance, monitor and manage side-effects, in liaison with the psychiatrist if necessary.
- To ensure the patient has the necessary blood tests and to interpret the results, seeking advice where necessary.
For both the GP and the psychiatrist to receive a copy of any blood test results, the name and address of BOTH parties should be specified on the pathology blood sample form

To notify the psychiatrist as soon as practical of any test results or changes to drug treatment, if appropriate

To place the patient on the practice case register for schizophrenia or serious mental illness and undertake annual reviews as described above

PATIENT RESPONSIBILITIES

- Your mental health team will give you written information about your depot antipsychotic medication when you start the injections. A very useful information resource is the Choice and Medication website at http://www.choiceandmedication.org/nottinghamshirehealthcare/

- Another good on-line resource is the Royal College of Psychiatrists at http://www.rcpsych.ac.uk/mentalhealthinfoforall.aspx

- If you misplace this information or require further information about your treatment please ask your mental health team

- If you are unable to attend for your depot injection at the agreed appointment time please could you contact the clinic as soon as possible and make another appointment

- If you have questions about the possibility of changing your treatment or switching from a depot injection to an oral or tablet preparation, or you are thinking about stopping your treatment, please discuss this first with your GP who can then refer you back to specialist mental health services if necessary.

- If you would like to speak to a mental health pharmacist about your medication, please contact your local hospital pharmacy department (Monday to Friday, 9am to 5pm):
  - Wells Road Centre Pharmacy 01159 555 356
  - Highbury Hospital Pharmacy 0115 854 2247
  - Millbrook Mental Health Unit Pharmacy 01159 560 883
  - Rampton Hospital Pharmacy 01777 560 883
  - Medicines Information Email: MI@nottshc.nhs.uk

Author
John Lawton, Clinical Pharmacy Service Manager, Nottinghamshire Healthcare NHS Foundation Trust

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References
1. www.medicines.org.uk
2. NICE Clinical Guideline 178, Psychosis and schizophrenia in adults: treatment and management. February 2014
4. LUNERS rating scale.
5. GASS rating scale