# Dosulepin (Prothiaden®): Guidance on withdrawal

**Indication:** Dosulpein is a tricyclic antidepressant (TCA) indicated in the treatment of depressive illness, especially where sedation is required. [i]

**Formulary status**: Non formulary (but some patients may have been initiated and maintained historically). Note: When an antidepressant is to be prescribed, TCAs are no longer considered first line treatment for depression due to their side effect profile. SSRIs are equally effective as other antidepressants and have a favourable risk-benefit ratio.[ii] Dosulepin is effective but known to be particularly dangerous in overdose and now not recommended for treatment of depression.

**Dose**: In the treatment of depression, the usual initial dose is 75 mg daily in divided doses *or* as a single dose at bedtime, increased if necessary to 150 daily. Doses can be increased gradually up to 225mg daily in some circumstances (e.g. hospital use). The recommended initial dose for the elderly in the UK is 50-75 mg daily which should be increased with caution under close supervision.

**Unlicensed uses:** Neuropathic pain/chronic pain, insomnia, anxiety.

**Mode of action:** Serotonin and noradrenaline reuptake inhibitor.

- **Anticholinergic activity** may cause dry mouth, constipation and blurred vision.
- **H1 blockade** may cause sedation.
- **Adrenergic αlpha 1 receptor blockade** may cause dizziness, sedation and hypotension.
- **Ion channel blockade** may cause cardiac arrhythmias and seizures especially in overdose**.**[iii]

**Reasons for caution:** Reports of cardiac arrhythmias, QTc prolongation, sinus tachycardia orthostatic hypotension. Drug interactions. High rate of fatality in overdose.

**Side effects:**

- As listed above

**Guidance and recommendations:**

- No new patients should be prescribed dosulepin.
- Patients currently prescribed dosulepin should be identified and have their treatment history reviewed. Where possible dosulepin should be gradually withdrawn and stopped if no longer clinically indicated.
- Suitable alternatives may include an SSRI such as sertraline, mirtazapine (if a sedative antidepressant is required), imipramine or lofepramine if an alternative TCA is required. Individual product literature for each of these medicines is available from www.medicines.org.uk
- TCAs should not be terminated abruptly (unless a serious adverse event has occurred e.g. cardiac arrhythmia), instead gradually taper down the daily dose in weekly/two weekly decrements[iv] over **at least** 4 **weeks** to avoid withdrawal effects. [v]
- For patients who have been taking dosulepin for long term maintenance treatment (>1 year), more gradual tapering may be appropriate, in the region of at least 6 months. [v]
- Even with a gradual dose reduction some withdrawal symptoms may appear within the first 5 days.[v] As with all swaps in medication tailor the withdrawal process to the individual patient, monitoring patient tolerability.
- In patients taking a split daily dose, the morning dose should ideally be completely reduced first before withdrawing the night time dose to minimise the change in effects on night-time sedation.

**Few studies have specifically examined the best strategy for switching between antidepressants. The following advice is based on available information, theoretical concerns and clinical experience. It is intended for general guidance only.**[iii]

**Suggested withdrawal and crossover to mirtazapine schedule**
(E.g. where sedative action required)

| Drug | Current dose | Week 1 | Week 3 | Week 5 | Week 7 |
|---|---|---|---|---|---|
| **Dosulepin** | 75mg/day | 50mg/day | 25mg/day | 25mg/ alternate days | STOP |
| **Mirtazapine** | Nil | Nil | 15mg/day (at night) | 30mg/day (at night) | Further dose ↑ based on response |

**Suggested withdrawal and crossover to imipramine/lofepramine schedule**[iv v]
(E.g. where anxiolytic action required)

| Drug | Current dose | Week 1 | Week 3 | Week 5 | Week 7 |
|---|---|---|---|---|---|
| **Dosulepin** | 75mg/day | 50mg/day | 25mg/day | 25mg/ alternate days | STOP |
| **Imipramine*** *Recommended elderly doses[iv] | Nil | Nil | 10mg/day (at night) | 20mg/day (at night) | Further dose ↑ based on response |
| **Lofepramine** | Nil | Nil | 70mg twice daily | 70mg twice daily | Further dose ↑ based on response |

**Practical considerations:**

- Issue 7 day scripts for safety reasons and to reduce waste.
- Dosulepin is available as 25mg capsules and 75mg tablets. Limit the prescribing for safety reasons and to make regimes simpler whilst reducing doses.
- Tailor the withdrawal and cross over process to the individual patient based on efficacy and tolerability.
- If the patient experiences any withdrawal effects then return to the previous dose of dosulepin and continue with the cross over at a slower pace using smaller decrements.
- Information on good sleep hygiene and non-pharmacological techniques may be found at www.nhs.uk/conditions/insomnia.

**References:**

[i] Dosulepin SPC. MHRA.gov.uk [Accessed 26/11/2017]
[ii] CG90. Published date: October 2009. Last updated: April 2016. https://www.nice.org.uk/guidance/cg90
[iii] Maudsley Prescribing Guidelines Antidepressants. 12th Edition
[iv] https://www.sps.nhs.uk/articles/how-do-you-switch-between-tricyclic-ssri-and-related-antidepressants/ [Accessed: 26/11/2017]
[v] Joint Formulary Committee. British National Formulary [Online] London: BMJ Group and Pharmaceutical Press Available: http://www.medicinescomplete.com [Accessed: 26/11/2017]

# Guidance for patients
# Dosulepin for depression and insomnia

**Why should I stop dosulepin?**
Dosulepin is an old medicine that is unsafe when taken in large doses. Accidentally taking too much has led to deaths across the country. National regulatory bodies now suggest that all dosulepin prescriptions should be reviewed over concerns of the likelihood of harm to patients. Dosulepin should be slowly reduced to prevent any adverse effects.

**Will I get any effects on stopping dosulepin?**
Dosulepin is an antidepressant, which can be used for anxiety, depression or insomnia. On stopping antidepressants 'discontinuation' symptoms can occur. These symptoms are usually mild and are lessened by slowly lowering the dose in small steps. These symptoms include: excessive saliva production, runny nose, diarrhoea or abdominal cramps. Doses used for insomnia are usually low and may be less likely to cause 'discontinuation' symptoms.

**Is dosulepin addictive?**
Dosulepin is not addictive, it does not cause tolerance (meaning a higher dose is needed to get the same effect) or craving (a feeling of the need or urge to take it).

**What if I've been taking dosulepin to manage low mood/depression?**
The first thing you and your GP need to consider is if you still need to take an antidepressant. As a guide the following is the recommended time to take anti-depressants for:

- For a first episode of major depression or anxiety, your chances of becoming unwell again are much lower if you keep taking the antidepressant for six months after you have recovered. This will be longer if you have risk factors for becoming depressed again such as remaining symptoms or if you have experienced stressful or traumatic life events.
- For a second episode of depression, your chances of becoming depressed again are lower if you keep taking the antidepressant for one or two years after you have got better.
- For depression that keeps coming back, continuing to take an antidepressant longer term has been shown to have a protective effect for at least five years.

**If needed is there another medicine I can take to treat my low mood/depression?**
There are a number of different antidepressants available which your GP can discuss with you. When choosing the right antidepressant for you the GP will consider your depressive (target) symptoms, side-effects of the antidepressant, interaction(s) with other prescribed medicines and any physical conditions you may have.
A handy chart which can help you compare the different medicines used to treat depression is available at: https://www.choiceandmedication.org/swlstg-tr/generate/handychartdepression.pdf

**How will my GP stop dosulepin completely or switch to another antidepressant?**
If you and your GP decide it is appropriate for you to stop dosulepin, then this will be done gradually and cautiously to prevent discontinuation symptoms such as anxiety, flu-like symptoms and insomnia. The rate at which the dose of dosulepin is reduced will depend on your current dose, how long you have been taking dosulepin and if you experience any discontinuation symptoms. The dose is usually reduced weekly over a period of at least 4 weeks or in some cases much longer. You will be reviewed regularly by your GP during this time.

If switching antidepressants is thought to be the most appropriate option for you; your GP will tailor the switch specifically to your needs. How your GP carries out the switch will depend on which antidepressant you are switching to and the nature of your depression. It is ideal to completely withdraw dosulepin before starting a new antidepressant; however, a cross-over period is often necessary to ensure that your symptoms of depression continue to be treated. During the cross-over period the dose of dosulepin is reduced and the new antidepressant is started at a low dose. As the dose of the new antidepressant is increased the dosulepin is gradually stopped.

**Is there anything I can do to improve my sleep?**
Sleep hygiene aims to make you more aware of the different factors that may affect sleep. Your GP may advise you to:

- Establish fixed times for going to bed and waking up (and avoid sleeping in after a poor night's sleep).
- Try to relax before going to bed.
- Maintain a comfortable sleeping environment (not too hot, cold, noisy or bright).
- Avoid napping during the day.
- Avoid caffeine, nicotine and alcohol within six hours of going to bed.
- Avoid exercise within four hours of bedtime (although exercise earlier in the day is beneficial).
- Avoid eating a heavy meal late at night.
- Avoid watching or checking the clock throughout the night.
- Avoid using the bedroom for anything other than sleep and sex.
- Keep a sleep diary to monitor the progress of treatment, noting duration of sleep, diet and exercise.

Further information on good sleep hygiene and non-pharmacological techniques may be found at www.nhs.uk/conditions/insomnia

**Is there another medicine I can take to help my sleep?**
Sleeping tablets (hypnotics) are medications that encourage sleep. They may be considered if your symptoms are particularly severe, to ease short-term insomnia or if the sleep hygiene methods have not helped. However, it is not normally recommended to prescribe this type of medication as although they can provide short-term relief of symptoms they do not treat the underlying cause of your insomnia, they can also be addictive. If you have long term insomnia, sleeping tablets are unlikely to help. Your GP may consider referring you to a clinical psychologist to discuss other approaches to treatment.

**What if I decide to stay on dosulepin?**
Your doctor will need to record your decision in your patient notes. You must ensure that you keep to the prescribed dose. You should immediately seek advice and help from a doctor if you take more than the dose prescribed by your doctor. Your medicines must be kept away from children and others to help prevent someone accidently taking them. Your GP may also reduce the quantity you get on each prescription. Your GP will continue to review your medicines with you over time.

**References:**
MHRA Drug Safety Update. Dosulepin: Measures to reduce the risk of accidental fatal overdose. December 2007
R G CUMMING, J PHILIP MILLER, J L KELSEY, P DAVIS, C L ARFKEN, S J BIRGE and W A PECK. Medications and Multiple Falls in Elderly People: The St Louis OASIS Study. Age Ageing (1991) 20 (6): 455-461.
Pomara, Nunzio et al. Increased sensitivity of the elderly to the central depressant effects of diazepam. Journal of Clinical Psychiatry, Vol 46(5), May 1985, 185-187.
Viukari M & Miettinen P: Diazepam, promethazine and propiomazine as hypnotics in elderly inpatients. Neuropsychobiology 1984; 12:134-137.
Bazire S. Psychotropic Drug Directory. 2016
Taylor D et al. Maudsley Prescribing Guideline in Psychiatry, 12th