NHS
Dorset
Clinical Commissioning Group

SAFETY BULLETIN: DOSULEPIN PRESCRIBING

In December 2007, the Medicines and Healthcare Regulatory Agency (MHRA) issued safety advice around prescribing of dosulepin, related to the narrow margin between therapeutic doses and potentially fatal doses. Dosulepin is also included in the NHS England guidance on items not to be routinely prescribed in primary care. Nevertheless, dosulepin continues to be prescribed.

Prescribing has decreased in Dorset CCG but there is still work to do to ensure that, in line with national guidance, dosulepin in deprescribed for existing patients, and a suitable alternative antidepressant is offered.

The following points summarise the reasons that dosulepin is not recommended for prescribing nationally, and in Dorset:

- Dosulepin has a small margin of safety between the (maximum) therapeutic dose and potentially fatal doses.
- The NICE guideline on depression in adults recommends that dosulepin should not be prescribed for adults with depression because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.
- Dosulepin has also been used 'off label' in other indications such as fibromyalgia and neuropathic pain. However, the evidence for use in in this way is weak and is not recommended in either local or national guidance.
- The lethal dose of dosulepin is relatively low and can be potentiated by alcohol and other CNS depressants.
- Dosulepin overdose is associated with high mortality and can occur rapidly, even before hospital treatment can be received. Onset of toxicity occurs within 4-6 hours. Every year, up to 200 people in England and Wales fatally overdose with dosulepin. Of these about 20% are accidental. Doses of 750 mg in adults (ten 75mg tablets) have been associated with fatalities. The risk of overdose can also extend to others in the household of the person for whom the drug is prescribed.
- The risks associated with dosulepin are highest in patients who:
    - currently or have in the past been dependent on alcohol, or are known to binge drink
    - currently or have in the past been dependent on or used CNS depressants long term (e.g. analgesics, benzodiazepines)
    - have a history of attempted suicide or suicidal ideation
- Dosulepin has an established link with a number of adverse cardiovascular effects (cardiac arrhythmias, conduction disorders, hypotension, tachycardia/arrhythmia QTc prolongation, cardiac failure and circulatory collapse) especially in the elderly.
- Dosulepin has an anticholinergic burden score of 3 (ACB calculator online) and may be associated with increased risks of impaired cognition and falls in patients over the age of 65

Adapted with thanks from a document originally produced by Cheshire and Wirral Patnership NHS Foundation Trust (CWP)

years, particularly if being used with other medicines which in themselves increase the overall anticholinergic burden.

- Dosulepin is also included in the NHS England guidance on items not to be routinely prescribed in primary care, and is marked as 'less suitable for prescribing' in the British National Formulary (BNF) because relative incidence and severity of side effects is higher than other antidepressants, and risk of toxicity, and potential drug interactions

Dosulepin should be avoided in many conditions, for example patients with:

○ Diabetes	○ Epilepsy
○ Mania	○ Narrow-angle glaucoma
○ Parkinson's disease	○ Hepatic or renal impairment
○ Alzheimer's disease	○ Symptoms suggestive of prostatic hypertrophy
○ Cardiac disease	○ Undergoing electroconvulsive therapy
○ Thyroid disease	○ Urinary retention

- Dosulepin has many clinically relevant drug interactions, for example:
    - Dosulepin should not be given concurrently with a MAOI, nor within fourteen days of ceasing such treatment.
    - The concomitant administration of Dosulepin and SSRIs should be avoided since increases in plasma tricyclic antidepressant levels have been reported following the co-administration of some SSRIs.
    - Dosulepin may alter the pharmacological effect of some concurrently administered drugs including CNS depressants such as alcohol and narcotic analgesics; the effect of these will be potentiated as will be the effects of adrenaline and noradrenaline (some local anaesthetics contain these sympathomimetics).
    - There is an increased risk of postural hypotension when dosulepin is given with diuretics (class effect for all tricyclic antidepressants).
    - Dosulepin and other tricyclic antidepressants may also antagonise the anticonvulsant effect of antiepileptics (convulsive threshold decreased).
    - Barbiturates may decrease the serum concentration of dosulepin and thus affect its antidepressant action.
    - Methylphenidate may increase the serum concentration of dosulepin and thus affect its antidepressant action.
- Although often prescribed to aid sleep (unlicensed), it disrupts REM sleep and there is no evidence that it has sleep promoting effects.

Recommended actions

- Dosulepin still poses a significant risk to patients and prescribers should actively review all patients being prescribed this medicine and renew efforts to identify an alternative and safer antidepressant.

- Please refer to the sections below 'reducing and stopping dosulepin' and 'switching to another antidepressant' for advice about reducing and withdrawing dosulepin slowly, and where dosulepin has been prescribed in depression, the potential alternatives.
- As per NICE Clinical Guidance (CG90): Do not switch to, or start, dosulepin because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.

Reducing and stopping dosulepin

Dosulepin should not be stopped abruptly unless serious side effects have occurred. Slowly tapering the dose over 3 to 4 weeks can help prevent discontinuation symptoms, which may include anxiety, flu-like symptoms and insomnia. Some people may require a more gradual tapering of the dose if withdrawal symptoms occur. The doses selected and the speed at which they are reduced will need to be individualised for each patient. A suggested withdrawal regimen for dosulepin is:

Current dose	**Week 1**	**Week 2**	**Week 3**	**Week 4**
150 mg / day	100 mg / day	50 mg / day	25 mg / day	nil

Switching from dosulepin to another antidepressant

There should be very close monitoring of patients being switched from dosulepin to another antidepressant, as there are no published guidelines to determine exactly how the switch should take place. The switch will need to be tailored to each individual and carried out cautiously. The regimen will depend upon how severe the depression is, and which drug is being switched to. Gradual cross tapering is usually recommended but in some cases a washout period between drugs is required. Very general guidance on switching from dosulepin to another antidepressant is as follows:

Dosulepin to an SSRI	Gradually reduce the dosulepin dose to 25 to 50mg / day then add the SSRI at usual starting dose. Then slowly withdraw the remaining dosulepin over 5-7 days.
Dosulepin to mirtazapine	Cross taper cautiously
Dosulepin to venlafaxine	Cross taper cautiously starting with venlafaxine 37.5mg daily

The choice of antidepressant should be discussed with each individual patient. Considerations will include: relative side effects, current diagnoses and potential drug interactions with other prescribed medication.

Patient profile	**Suggested options and general guidance about switching**
In need of sedation	Mirtazapine (lower doses more sedating)
In need of activation	SSRI or venlafaxine
Cardiac disease	Mirtazapine or sertraline
Diabetes	SSRIs (most data supports fluoxetine)
Epilepsy	SSRIs

Hepatic impairment	Citalopram* (maximum dose 20mg/day)
Renal impairment	Citalopram* or sertraline
Parkinson's disease	SSRIs
Stroke	SSRIs (citalopram* if taking warfarin + consider Proton Pump Inhibitor (PPI) for gastric for gastric protection. Or mirtazapine (has a small effect on INR).

***Note:** Citalopram use is contraindicated in conjunction with antipsychotics*

Switching when dosulepin is being used off-label

Dosulepin should not be used for any unlicensed indication, seek specialist advice if needed. Contact the regional medicines information service in Southampton –by e-mailing medicinesadvice@uhs.nhs.uk or telephone **023 8120 6908** / **6909**.

Whilst moving to another antidepressant option, it would be prudent to provide only small supplies of dosulepin and/or the new drug and to review the patient often.

References

Dosulepin: measures to reduce risk of fatal overdose (MHRA Drug Safety Update – December 2007)
NICE Medicines Optimisation: Key therapeutic topics (February 2016)
NICE Clinical Guideline 90: Depression in adults: recognition and management (April 2016)
Summary of product characteristics for Dosulepin 75mg capsules (MHRA)
Cheshire and Wirral Partnership – Dosulepin advice (July 2015)
Items not to be routinely prescribed in primary care (NHS England, version 2, June 2019)