2. Balant-Gorgia AE, *et al.* Clinical pharmacokinetics of clomipramine. *Clin Pharmacokinet* 1991; **20:** 447–62.
3. Nielsen KK, *et al.* Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. *Clin Pharmacol Ther* 1994; **55:** 518–27.
4. Herrera D, *et al.* Pharmacokinetics of a sustained-release dosage form of clomipramine. *J Clin Pharmacol* 2000; **40:** 1488–93.

## Uses and Administration

Clomipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It has antimuscarinic properties and is also a potent serotonin reuptake inhibitor. Clomipramine is one of the more sedating tricyclics. It is used as the hydrochloride.

In the treatment of **depression** in adults, clomipramine hydrochloride is given in oral doses of 10 mg daily initially, increasing gradually to 30 to 150 mg daily if required; up to 250 mg daily or higher may be given in severe cases. A suggested initial dose for the elderly is 10 mg daily increasing gradually over 10 days to 30 to 75 mg daily if required. Clomipramine may be given in divided doses throughout the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

In the treatment of **obsessive-compulsive disorder** and **phobias**, clomipramine hydrochloride may be given in an initial oral dose of 25 mg daily (or 10 mg daily for elderly patients or those sensitive to tricyclics) increased gradually over two weeks to 100 to 150 mg daily. In some countries, maximum doses of 250 mg daily have been used. Similar doses have also been used in the management of **panic disorder**. In some countries clomipramine hydrochloride is also used for the treatment of obsessive-compulsive disorder in children and adolescents aged 10 years and over (see below for doses).

In some countries clomipramine may be given for depression or obsessive-compulsive disorder by the intramuscular or intravenous routes if giving it orally is impracticable or inadvisable. The initial dose of clomipramine hydrochloride by intramuscular injection is 25 to 50 mg daily, increasing to a maximum of 100 to 150 mg daily; oral dosage should be substituted as soon as possible. Clomipramine hydrochloride may also be given by intravenous infusion in doses of 50 to 75 mg daily diluted in 250 to 500 mL of sodium chloride 0.9% or glucose 5% and infused over 1.5 to 3 hours. When a satisfactory response to parenteral doses has been obtained oral therapy should be substituted, initially giving double the parenteral dose by mouth and subsequently adjusting if necessary. Patients must be carefully supervised during intravenous infusion of clomipramine hydrochloride and the blood pressure carefully monitored owing to the risk of hypotension.

In the adjunctive treatment of **cataplexy associated with narcolepsy**, clomipramine hydrochloride is given in an initial oral dose of 10 mg daily and gradually increased until a satisfactory response occurs, usually within the range of 10 to 75 mg daily.

Clomipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

**Administration in children.** In the UK, the use of clomipramine in children under 18 years is not recommended in the treatment of depressive states, phobias, or cataplexy associated with narcolepsy. However, in some countries clomipramine hydrochloride is used for the treatment of *obsessive-compulsive disorder* in children and adolescents aged 10 years and over. Initial oral doses are 25 mg daily, increased gradually during the first 2 weeks to a maximum daily dose of 3 mg/kg or 100 mg, whichever is smaller, and given in divided doses. Further increases are permitted, over several weeks to a maximum daily dose of 3 mg/kg or 200 mg, whichever is smaller. Once titration has been achieved the dose may be given as a single dose at bedtime.

Clomipramine hydrochloride is also licensed for oral use in the management of *nocturnal enuresis* in some countries (for a discussion of tricyclic use in nocturnal enuresis see Micturition Disorders under Amitriptyline, p.381). The age ranges and licensed doses vary somewhat from country to country, however. For example, in *France*, use is licensed in children over 6 years of age, at a daily dose of 10 to 30 mg, or 0.5 to 1 mg/kg, whereas in *Austria* and *Switzerland* the licensed dose is: 6 to 8 years, 20 to 30 mg; 9 to 12 years, 25 to 50 mg; over 12 years, 25 to 75 mg.

**Anxiety disorders.** Tricyclic antidepressants that inhibit serotonin reuptake, such as clomipramine and imipramine, have been given in the management of anxiety disorders (p.952) including obsessive-compulsive disorder (p.952), panic disorder (p.952), post-traumatic stress disorder (p.953), and trichotillomania.

References.

1. Swedo SE, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). *N Engl J Med* 1989; **321:** 497–501.
2. McTavish D, Benfield P. Clomipramine: an overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs* 1990; **39:** 136–53.
3. Kelly MW, Myers CW. Clomipramine: a tricyclic antidepressant effective in obsessive compulsive disorder. *DICP Ann Pharmacother* 1990; **24:** 739–44.
4. Papp LA, *et al.* Clomipramine treatment of panic disorder: pros and cons. *J Clin Psychiatry* 1997; **58:** 423–5.
5. Fallon BA, *et al.* Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry* 1998; **55:** 918–24.
6. Sasson Y, *et al.* A double-blind crossover comparison of clomipramine and desipramine in the treatment of panic disorder. *Eur Neuropsychopharmacol* 1999; **9:** 191–6.

**Autism.** Clomipramine reduced adventitious movements when tried in 5 boys with autistic disorder.[1] However, in a small study in 7 children no improvement in symptoms was noted and adverse effects were common and serious.[2] In another study,[3] although clomipramine was found to be as effective as haloperidol in the treatment of some autistic symptoms, patients on clomipramine were significantly less likely to complete the trial for reasons that included the onset of adverse effects.

1. Brasic JR, *et al.* Clomipramine ameliorates adventitious movements and compulsions in prepubertal boys with autistic disorder and severe mental retardation. *Neurology* 1994; **44:** 1309–12.
2. Sanchez LE, *et al.* A pilot study of clomipramine in young autistic children. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 537–44.
3. Remington G, *et al.* Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol* 2001; **21:** 440–4.

**Micturition disorders.** In some countries, clomipramine is used in children for the treatment of nocturnal enuresis; for further details, see Administration in Children, above.

**Pain.** Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2). In a number of countries, clomipramine hydrochloride is licensed for the treatment of chronic pain; oral doses range from 10 to 150 mg daily. Parenteral doses are licensed in some countries.

**Premenstrual syndrome.** Clomipramine reduced premenstrual irritability and depressed mood when given during the luteal phase;[1] doses of clomipramine ranged from 25 to 75 mg daily. It was postulated that the efficacy of clomipramine in relieving premenstrual symptoms is related to its serotonin reuptake inhibitor activity. For the overall management of premenstrual syndrome, see p.2099.

1. Sundblad C, *et al.* Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. *Neuropsychopharmacology* 1993; **9:** 133–45.

**Sexual dysfunction.** Clomipramine has been used for its inhibitory effect on ejaculation in the management of premature ejaculation[1-5] (p.2181). In some men with very short latencies (less than 1 minute) continuous therapy with a low daily dose of clomipramine, typically 20 or 30 mg, may be more effective than taking 25 mg as required.[5] Any benefits may relate to its effect as a serotonin reuptake inhibitor; other antidepressants with serotonin reuptake inhibiting actions, such as fluoxetine and sertraline, have also been tried in this condition.[4]

1. Hawton K. Erectile dysfunction and premature ejaculation. *Br J Hosp Med* 1988; **40:** 428–36.
2. Althof SE, *et al.* A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *J Clin Psychiatry* 1995; **56:** 402–7.
3. Haensel SM, *et al.* Clomipramine and sexual function in men with premature ejaculation and controls. *J Urol (Baltimore)* 1996; **156:** 1310–15.
4. Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. *J Urol (Baltimore)* 1998; **159:** 425–7.
5. Rowland DL, *et al.* Effective daily treatment with clomipramine in men with premature ejaculation when 25 mg (as required) is ineffective. *BJU Int* 2001; **87:** 357–60.

**Stuttering.** Clomipramine was of modest success in a controlled study[1] of 17 patients with developmental stuttering (p.1001). It was suggested that its efficacy may be related to its serotonin reuptake inhibitor activity.

1. Gordon CT, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of developmental stuttering. *J Clin Psychiatry* 1995; **56:** 238–42.

## Preparations

***BP 2008:*** Clomipramine Capsules;
***USP 31:*** Clomipramine Hydrochloride Capsules.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Anafranil; Clomipram†; ***Austral.:*** Anafranil; Clopram; Placil; ***Austria:*** Anafranil; ***Belg.:*** Anafranil; ***Braz.:*** Anafranil; Clo; Clomipran; ***Canad.:*** Anafranil; Novo-Clopamine†; ***Chile:*** Anafranil; Atenual; Ausentron; Deprelin; ***Cz.:*** Anafranil; Hydiphen†; ***Denm.:*** Anafranil; ***Fin.:*** Anafranil; ***Fr.:*** Anafranil; ***Ger.:*** Anafranil; Hydiphen†; ***Gr.:*** Anafranil; ***Hong Kong:*** Anafranil; Zoiral; ***Hung.:*** Anafranil; ***India:*** Anafranil; ***Indon.:*** Anafranil; ***Irl.:*** Anafranil; ***Israel:*** Anafranil; Maronil; ***Ital.:*** Anafranil; ***Malaysia:*** Anafranil; Clopress†; ***Mex.:*** Anafranil; ***Neth.:*** Anafranil; ***Norw.:*** Anafranil†; Clopress; ***Philipp.:*** Anafranil; ***Pol.:*** Anafranil; Hydiphen; ***Port.:*** Anafranil; ***Rus.:*** Anafranil (Анафранил); Clofranil (Клофранил); ***S.Afr.:*** Anafranil; Clomidep; Equinorm; ***Singapore:*** Anafranil†; ***Spain:*** Anafranil; ***Swed.:*** Anafranil; ***Switz.:*** Anafranil; ***Thai.:*** Anafranil; Clofranil†; ***Turk.:*** Anafranil; ***UK:*** Anafranil; ***USA:*** Anafranil; ***Venez.:*** Anafranil.

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## Desipramine Hydrochloride *(BANM, USAN, rINNM)*

Desipramiinihydrokloridi; Désipramine, chlorhydrate de; Desipramin-hydrochlorid; Desipraminhydroklorid; Desipramini hydrochloridum; Desmethylimipramine Hydrochloride; Dezipramin-hidroklorid; Dezipramino hidrocloridas; Dezypraminy chlorowodorek; DMI; EX-4355; G-35020; Hidrocloruro de desipramina; JB-8181; NSC-114901; RMI-9384A. 3-(10,11-Dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyl(methyl)amine hydrochloride.

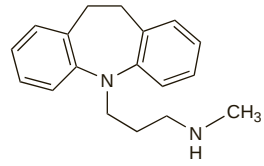
Дезипрамина Гидрохлорид

$C_{18}H_{22}N_2.HCl = 302.8$.

*CAS — 50-47-5 (desipramine); 58-28-6 (desipramine hydrochloride).*

*ATC — N06AA01.*

*ATC Vet — QN06AA01.*



*(desipramine)*

**Pharmacopoeias.** In *Eur.* (see p.vii) and *US.*

**Ph. Eur. 6.2** (Desipramine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. Protect from light.

**USP 31** (Desipramine Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 12 of water, 1 in 14 of alcohol, and 1 in 3.5 of chloroform; insoluble in ether; freely soluble in methyl alcohol. Store in airtight containers.

### Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

**Breast feeding.** For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

### Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

### Pharmacokinetics

Desipramine is the principal active metabolite of imipramine (p.400).

### Uses and Administration

Desipramine, the principal active metabolite of imipramine (p.400), is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is one of the less sedating tricyclics and its antimuscarinic effects are mild. Desipramine is used as the hydrochloride.

In the treatment of depression, desipramine hydrochloride is given orally in daily doses of 100 to 200 mg; higher doses of up to 300 mg daily may be required in severely depressed patients in hospital. Lower doses should be used in adolescents and the elderly and are usually 25 to 100 mg daily; up to 150 mg daily may be required for severe depression. Initial doses should be low and gradually increased according to tolerance and clinical response. Therapy may initially be given as a single daily dose or in divided doses; maintenance therapy may be given as a single daily dose usually at night.

Desipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

**Cocaine dependence.** Since dopamine depletion may be the cause of the depression often associated with cocaine craving and with relapse, drugs such as desipramine that interact with dopaminergic systems have been tried in managing cocaine

withdrawal symptoms (p.1860). However, a systematic review[1] was unable to find evidence to support the use of antidepressants in the treatment of cocaine dependence although the efficacy of desipramine was suggested in some individual studies.

1. Lima MS, *et al.* Antidepressants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 24/11/05).

**Hyperactivity.** When drug therapy is required for attention deficit hyperactivity disorder (see p.2148) tricyclic antidepressants such as imipramine or desipramine[1-4] are usually reserved for patients who fail to respond to, or who are intolerant of, stimulants. They may also be of use for selected patients with co-existing disorders such as Tourette's syndrome, anxiety, and enuresis.

1. Rapport MD, *et al.* Methylphenidate and desipramine in hospitalized children: I. separate and combined effects on cognitive function. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 333–42.
2. Pataki CS, *et al.* Side effects of methylphenidate and desipramine alone and in combination in children. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1065–72.
3. Singer HS, *et al.* The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 1995; **95:** 74–81.
4. Spencer T, *et al.* A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2002; **59:** 649–56.

**Pain.** Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2) when given in subantidepressant doses.

References to the use of desipramine.

1. Kishore-Kumar R, *et al.* Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47:** 305–12.
2. Max MB, *et al.* Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; **326:** 1250–6.
3. Coquoz D, *et al.* Central analgesic effects of desipramine, fluvoxamine, and moclobemide after single oral dosing: a study in healthy volunteers. *Clin Pharmacol Ther* 1993; **54:** 339–44.
4. Gordon NC, *et al.* Temporal factors in the enhancement of morphine analgesia by desipramine. *Pain* 1993; **53:** 273–6.

### Preparations

***BP 2008:*** Desipramine Tablets;
***USP 31:*** Desipramine Hydrochloride Tablets.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Nebril†; ***Austria:*** Pertofran; ***Belg.:*** Pertofran†; ***Canad.:*** Norpramin; ***Chile:*** Distonal; ***Fr.:*** Pertofran†; ***Ger.:*** Pertofran†; Petylyl; ***Israel:*** Deprexan; ***Ital.:*** Nortimil; ***Mex.:*** Norpramin†; ***NZ:*** Pertofran†; ***Pol.:*** Petylyl; ***USA:*** Norpramin.

**Multi-ingredient:** ***Arg.:*** Plafonyl†.

## Desvenlafaxine Succinate *(BANM, USAN, rINNM)*

*O*-Desmethylvenlafaxine succinate; Dèsvenlafaxine, Succinate de; Desvenlafaxini Succinas; DVS-233 (base or succinate); Succinato de desvenlafaxina; Wy-45233. 1-[(1*RS*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol hydrogen butanedioate monohydrate.

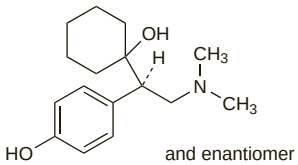
Десвенлафаксина Суксинат

$C_{16}H_{25}NO_2.C_4H_6O_4.H_2O$ = 399.5.

*CAS — 93413-62-8 (desvenlafaxine); 386750-22-7 (desvenlafaxine succinate).*

*ATC — N06AX23.*

*ATC Vet — QN06AX23.*




*(desvenlafaxine)*

### Profile

Desvenlafaxine, the major active metabolite of venlafaxine, is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p.427). It is given orally as the succinate but doses are expressed in terms of the base; desvenlafaxine succinate 75.8 mg is equivalent to about 50 mg of desvenlafaxine. The succinate is given in the treatment of depression (p.373) as a modified-release preparation providing a dose equivalent to desvenlafaxine 50 mg once daily. Higher doses of up to 400 mg daily have been studied, but provide no additional benefit and are associated with more frequent adverse effects. The dose may need to be reduced in patients with renal impairment (see below).

Desvenlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Desvenlafaxine is under investigation in the management of menopausal vasomotor symptoms, neuropathic pain, and fibromyalgia.

◊ References.

1. DeMartinis NA, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry* 2007; **68:** 677–88.
2. Septien-Velez L, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol* 2007; **22:** 338–47.
3. Liebowitz MR, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry* 2007; **68:** 1663–72.

**Administration in renal impairment.** The usual desvenlafaxine oral dose of 50 mg daily may be given to patients with mild to moderate renal impairment. In severe impairment (creatinine clearance less than 30 mL/minute) a dose of 50 mg may be given on alternate days. Supplemental doses should not be given after dialysis.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***USA:*** Pristiq.

## Dibenzepin Hydrochloride *(BANM, USAN, rINNM)*

Dibenzépine, Chlorhydrate de; Dibenzepini Hydrochloridum; HF-1927; Hidrocloruro de dibenzepina. 10-(2-Dimethylaminoethyl)-5,10-dihydro-5-methyl-dibenzo[*b*,*e*][1,4]diazepin-11-one hydrochloride.

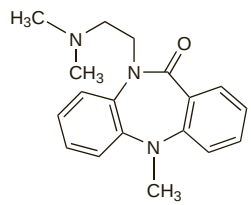
Дибензепина Гидрохлорид

$C_{18}H_{21}N_3O.HCl$ = 331.8.

*CAS — 4498-32-2 (dibenzepin); 315-80-0 (dibenzepin hydrochloride).*

*ATC — N06AA08.*

*ATC Vet — QN06AA08.*




*(dibenzepin)*

### Profile

Dibenzepin hydrochloride is a tricyclic antidepressant (see Amitriptyline, p.376).

In the treatment of depression dibenzepin hydrochloride is given in oral doses of 480 mg daily; higher doses of up to 720 mg daily may be required in some patients with severe depression. Elderly patients should be given reduced doses of 240 mg daily initially, increased to a maximum of 480 mg daily if required.

Dibenzepin hydrochloride has also been given by intravenous infusion.

In some countries it has also been used for nocturnal enuresis.

Dibenzepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

◊ References.

1. Wirtheim E, Bloch Y. Dibenzepin overdose causing pulmonary edema. *Ann Pharmacother* 1996; **30:** 789–90.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Austria:*** Noveril; ***Cz.:*** Noveril; ***Ger.:*** Noveril†; ***Hung.:*** Noveril; ***Israel:*** Noveril; Victoril†; ***Pol.:*** Noveril; ***Switz.:*** Noveril.

## Dosulepin Hydrochloride *(BANM, rINNM)*

Dosulepiinihydrokloridi; Dosulépine, chlorhydrate de; Dosulepin-hydrochlorid; Dosulepinhydroklorid; Dosulepini hydrochloridum; Dosulepino hidrochloridas; Doszulepin-hidroklorid; Dothiepin Hydrochloride *(USAN)*; Hidrocloruro de dosulepina. 3-(Dibenzo[*b*,*e*]thiepin-11-ylidene)propyldimethylamine hydrochloride.

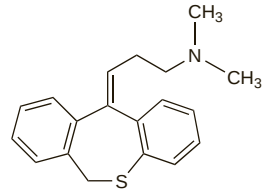
Досулепина Гидрохлорид

$C_{19}H_{21}NS.HCl$ = 331.9.

*CAS — 113-53-1 (dosulepin); 897-15-4 (dosulepin hydrochloride).*

*ATC — N06AA16.*

*ATC Vet — QN06AA16.*




*(dosulepin)*

**Pharmacopoeias.** In *Eur.* (see p.vii).
**Ph. Eur. 6.2** (Dosulepin Hydrochloride). A white or faintly yellow crystalline powder. It consists chiefly of the *E*-isomer. Freely soluble in water, in alcohol, and in dichloromethane. A 10% solution in water has a pH of 4.2 to 5.2. Protect from light.

### Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

**Breast feeding.** For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

**Effects on the cardiovascular system.** For reference to an increased risk of ischaemic heart disease in patients treated with dosulepin, see under Amitriptyline, p.376.

**Overdosage.** After an overdose of 1 g of dosulepin, the ECG of a 41-year-old man showed cardiac abnormalities mimicking an acute myocardial infarction.[1] However, as cardiac enzymes did not confirm an ischaemic event, the abnormalities were thought to be due to either the quinidine-like effect of dosulepin or changes in potassium membrane permeability.

1. Steeds RP, Muthusamy R. Abnormal ventricular conduction following dothiepin overdose simulating acute myocardial infarction. *Heart* 2000; **83:** 289.

**Porphyria.** Dosulepin hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

### Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

### Pharmacokinetics

Dosulepin hydrochloride is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldothiepin (also termed northiaden). Paths of metabolism also include *S*-oxidation.

Dosulepin is excreted in the urine, mainly in the form of its metabolites; small amounts are also excreted in the faeces. Elimination half-lives of about 14 to 24 and 23 to 46 hours have been reported for dosulepin and its metabolites, respectively.

Dosulepin is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p.378).

◊ References.

1. Maguire KP, *et al.* Clinical pharmacokinetics of dothiepin: single-dose kinetics in patients and prediction of steady-state concentrations. *Clin Pharmacokinet* 1983; **8:** 179–85.
2. Yu DK, *et al.* Pharmacokinetics of dothiepin in humans: a single dose dose-proportionality study. *J Pharm Sci* 1986; **75:** 582–5.
3. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; **33:** 635–9.

### Uses and Administration

Dosulepin hydrochloride is a tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is one of the more sedating tricyclics. In the UK, the MHRA suggests that the use of dosulepin for depression should be limited, because of the small margin of safety between the maximum therapeutic dose and potentially fatal overdose. It advises that treatment should only be started by a specialist-care prescriber, and that the quantity issued per prescription should be limited. In patients with increased risk factors for suicide at the start of treatment, during dose adjustment, and until improvement occurs, the MHRA suggests a maximum supply equivalent to 2 weeks of treatment with 75 mg daily.

In the treatment of depression, dosulepin hydrochloride is given in oral doses of 25 mg three times daily initially, gradually increased to 50 mg three times daily if necessary; alternatively a single dose at night may be given. Higher doses of up to 225 mg daily have been given to severely depressed patients in hospital. The recommended initial dose for the elderly is 50 to 75 mg daily.

Dosulepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.