gested that the rate of major malformations in all 3 groups was not greater than the baseline rate of 1 to 3%.

1. Einarson A, *et al.* A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry* 2003; **48:** 106–10.

Interactions

Nefazodone should not be given to patients receiving MAOIs or for at least 14 days after they are stopped; it has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping nefazodone therapy. For further details on the combined use of antidepressants, see Antidepressants under Interactions of Phenelzine, p.418.

Orthostatic hypotension can be a problem with nefazodone, and therefore caution is required for any patient also on antihypertensive therapy.

Nefazodone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 responsible for the metabolism of some benzodiazepines, and consequently it may produce clinically important increases in their plasma concentrations. Use with astemizole, cisapride, pimozide, and terfenadine (which are metabolised by the same isoenzyme) is best avoided because the potential also exists for increased plasma concentrations of these drugs, with the risk of inducing ventricular arrhythmias. Other substrates for this isoenzyme may also interact with nefazodone: atorvastatin, lovastatin, and simvastatin should be used with caution with nefazodone since there have been rare reports of rhabdomyolysis with such combinations. Increased serum concentrations of ciclosporin or tacrolimus, both substrates for CYP3A4, have been reported in patients also receiving nefazodone. Monitoring of serum ciclosporin or tacrolimus levels is recommended when either of these two drugs is given with nefazodone.

Plasma concentrations of digoxin are increased by nefazodone, and because of digoxin's narrow therapeutic index, plasma concentrations of digoxin should be monitored if use with nefazodone is necessary.

Caution should be exercised when haloperidol is given with nefazodone as the clearance of haloperidol may be reduced. Plasma concentrations of carbamazepine are also increased when used with nefazodone. More importantly, carbamazepine may reduce nefazodone plasma concentrations to subtherapeutic levels and therefore use together is not recommended. Giving buspirone with nefazodone significantly increases the serum concentrations of buspirone; the manufacturers of nefazodone recommend that the initial dose of buspirone is reduced if these drugs are given together.

The potential for interaction between nefazodone and general anaesthetics exists and the manufacturer recommends that nefazodone should be stopped before elective surgery for as long as clinically feasible.

Benzodiazepines. For further details of interactions between nefazodone and benzodiazepines, see Diazepam, p.990.

Pharmacokinetics

Nefazodone is readily absorbed from the gastrointestinal tract and peak plasma concentrations have been obtained within about 2 hours after oral doses. Absorption is delayed and reduced by food but this is not considered to be clinically significant. Nefazodone undergoes extensive first-pass metabolism and is more than 99% bound to plasma proteins; it is widely distributed. It is extensively metabolised by *N*-dealkylation and hydroxylation in the liver to several metabolites, two of which, hydroxynefazodone and *m*-chlorophenylpiperazine, are known to be pharmacologically active. Excretion is mainly as metabolites via the urine (about 55%) and the faeces (20 to 30%). The plasma elimination half-life is 2 to 4 hours. Pharmacokinetic parameters are reported to be non-linear with increasing doses. Nefazodone is distributed in small amounts into breast milk (see Breast Feeding, above).

◊ Reviews.

1. Greene DS, Barbhaiya RH. Clinical pharmacokinetics of nefazodone. *Clin Pharmacokinet* 1997; **33:** 260–75.

Uses and Administration

Nefazodone is a phenylpiperazine antidepressant structurally related to trazodone (see p.424). It blocks the reuptake of serotonin at presynaptic neurones and is an antagonist at postsynaptic 5-HT_2 receptors. Unlike trazodone, nefazodone inhibits the reuptake of noradrenaline. It blocks α_1-adrenoceptors but has no apparent effect on dopamine receptors. Nefazodone does not appear to have very significant antimuscarinic properties compared with tricyclic antidepressants.

Nefazodone hydrochloride has been given for the treatment of depression. One manufacturer (*Bristol-Myers Squibb*) has withdrawn nefazodone worldwide (see also Effects on the Liver, above); however, nefazodone remains available in the USA, and possibly some other countries, as a generic preparation. The usual initial oral dose is 100 mg twice daily increased if necessary, in increments of 100 to 200 mg at intervals of at least a week, to a maximum of 300 mg twice daily. Doses are restricted in elderly patients: a recommended initial dose is 50 mg twice daily.

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

Nefazodone has been tried in anxiety disorders, but other drugs may now be preferred.

Preparations

USP 31: Nefazodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Deprefax†; ***Austral.:*** Serzone†; ***Braz.:*** Serzone†; ***Cz.:*** Serzone†; ***Gr.:*** Nefirel†; ***Hong Kong:*** Serzone†; ***Israel:*** Serzonil†; ***Mex.:*** Serzone†; ***NZ:*** Serzone†; ***S.Afr.:*** Serzone†; ***Singapore:*** Serzone†; ***USA:*** Serzone†.

Nortriptyline Hydrochloride

(BANM, USAN, rINNM)

38489; Hidrocloruro de nortriptilina; Nortriptilin-hidroklorid; Nortriptilino hidrochloridas; Nortriptyliinihydrokloridi; Nortriptyline, chlorhydrate de; Nortriptylin-hydrochlorid; Nortriptylinhydroklorid; Nortriptylini hydrochloridum; Nortryptyliny chlorowodorek. 3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene) propyl(methyl)amine hydrochloride.

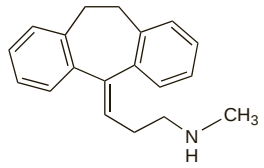
Нортриптилина Гидрохлорид

$C_{19}H_{21}N,HCl$ = 299.8.

CAS — 72-69-5 (nortriptyline); 894-71-3 (nortriptyline hydrochloride).

ATC — N06AA10.

ATC Vet — QN06AA10.



(nortriptyline)

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

Ph. Eur. 6.2 (Nortriptyline Hydrochloride). A white or almost white powder. Sparingly soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Nortriptyline Hydrochloride). A white to off-white powder having a slight characteristic odour. Soluble 1 in 90 of water, 1 in 30 of alcohol, 1 in 20 of chloroform, and 1 in 10 of methyl alcohol; practically insoluble in ether, in benzene, and in most other organic solvents. pH of a 1% solution in water is about 5. Store in airtight containers. 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 ventilation. Severe hyperventilation developed in a 61-year-old man with end-stage renal disease after receiving nortriptyline 125 mg daily;[1] mechanical ventilation was necessary to correct severe respiratory alkalosis.

1. Sunderrajan S, *et al.* Nortriptyline-induced severe hyperventilation. *Arch Intern Med* 1985; **145:** 746–7.

Porphyria. Nortriptyline is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

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

Pharmacokinetics

Nortriptyline is the principal active metabolite of amitriptyline (p.381). Nortriptyline has been reported to have a longer plasma half-life than amitriptyline. Nortriptyline is subject to extensive first-pass metabolism in the liver to 10-hydroxynortriptyline, which is active.

Metabolism. Individuals with a poor debrisoquine hydroxylation phenotype may be at greater risk of confusional states when taking nortriptyline.[1] This was thought to be because the polymorphic hydroxylation of debrisoquine and nortriptyline are mediated by similar enzymatic mechanisms [the cytochrome P450 isoenzyme CYP2D6], with poor oxidisers having higher plasma nortriptyline concentrations.[2,3] A nonlinear (dose-dependent) relationship between dose and plasma-nortriptyline concentrations has been observed during therapeutic drug monitoring[4] in subjects who were considered to be extensive metabolisers of debrisoquine; nonlinearity did not appear to occur in poor metabolisers. There was no significant correlation between hydroxylation phenotype and amitriptyline concentrations, suggesting that demethylation and hydroxylation of tricyclic antidepressants are mediated by different cytochrome P450 isoenzymes.[5]

The pharmacokinetics and pharmacological actions of 10-hydroxynortriptyline, the major active metabolite of nortriptyline, have been reviewed.[3]

1. Park BK, Kitteringham NR. Adverse reactions and drug metabolism. *Adverse Drug React Bull* 1987; **122:** 456–9.
2. Nordin C, *et al.* Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients—relationship to the debrisoquine hydroxylation metabolic ratio. *Br J Clin Pharmacol* 1985; **19:** 832–5.
3. Nordin C, Bertilsson L. Active hydroxymetabolites of antidepressants: emphasis on E-10-hydroxy-nortriptyline. *Clin Pharmacokinet* 1995; **28:** 26–40.
4. Jerling M, Alván G. Nonlinear kinetics of nortriptyline in relation to nortriptyline clearance as observed during therapeutic drug monitoring. *Eur J Clin Pharmacol* 1994; **46:** 67–70.
5. Bertilsson L, *et al.* Metabolism of various drugs in subjects with different debrisoquine and sparteine oxidation phenotypes. *Br J Clin Pharmacol* 1982; **14:** 602P.

Therapeutic plasma concentrations. Nortriptyline appears to have an optimum antidepressant effect at plasma concentrations between 50 and 150 nanograms/mL. Outside this range, there is a poor clinical response. Plasma concentration measurements are unequivocally useful in problem patients who do not respond to usual oral doses or in high-risk patients for whom, because of age or medical illness, it is especially important to use the lowest possible effective dose of the drug.[1]

It has been suggested[2] that within this window of total nortriptyline concentrations there is a probability of an antidepressant response of 68% or more with free concentrations of 7 to 10 nanograms/mL.

For reference to dose-dependent kinetics of nortriptyline observed in individuals with an extensive debrisoquine hydroxylation phenotype, see under Metabolism, above.

1. Task Force on the Use of Laboratory Tests in Psychiatry. Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry* 1985; **142:** 155–62.
2. Perry PJ, *et al.* The relationship of free nortriptyline levels to antidepressant response. *Drug Intell Clin Pharm* 1984; **18:** 510.

Uses and Administration

Nortriptyline is a dibenzocycloheptadiene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is the principal active metabolite of amitriptyline. Nortriptyline is one of the less sedating tricyclics and its antimuscarinic effects are mild.

Nortriptyline is given orally as the hydrochloride although doses are expressed in terms of the base; nortriptyline hydrochloride 113.8 mg is equivalent to about 100 mg of nortriptyline. In the treatment of **depression** a low starting dose is given gradually increasing to the equivalent of 75 to 100 mg daily in 3 or 4 divided doses. Up to a maximum of 150 mg daily may be required in patients with severe depression. Licensed drug information recommends that plasma concentrations of nortriptyline should be monitored when doses above 100 mg daily are given; however, the *BNF* considers that the evidence of any practical value is uncertain. Adolescents and the elderly may be given 30 to 50 mg daily in divided doses. Since nortriptyline has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

Nortriptyline is also used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home; tricyclic antidepressants are not recommended in children under 6 years of age (the *BNF* recommends that they should not be given until 7 years of age). Suggested doses are:

- 10 mg for children aged 6 to 7 years (20 to 25 kg)
- 10 to 20 mg for children aged 8 to 11 years (25 to 35 kg)
- 25 to 35 mg for children aged over 11 years (35 to 54 kg)

The dose should be given 30 minutes before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

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

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2). Nortriptyline has also been tried and may produce fewer adverse effects than amitriptyline. An initial oral dose of 10 to 25 mg at night has been suggested by the *BNF* for the management of **neuropathic pain**.

References to the use of nortriptyline.

1. Atkinson JH, *et al.* A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. *Pain* 1998; **76:** 287–96.
2. Watson CP, *et al.* Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology* 1998; **51:** 1166–71.

Smoking cessation. For reference to the use of nortriptyline in management of smoking cessation, see under Amitriptyline, p.382.

Preparations

BP 2008: Nortriptyline Capsules; Nortriptyline Tablets;
USP 31: Nortriptyline Hydrochloride Capsules; Nortriptyline Hydrochloride Oral Solution.

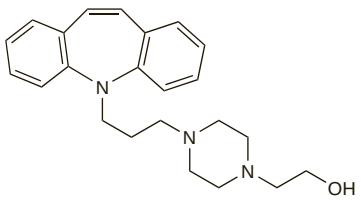
Proprietary Preparations (details are given in Part 3)
Arg.: Ateben†; ***Austral.:*** Allegron; ***Austria:*** Nortrilen; ***Belg.:*** Nortrilen; ***Braz.:*** Nortrip; Pamelor; ***Canad.:*** Aventyl; Norventyl†; ***Cz.:*** Nortrilen; ***Denm.:*** Noritren; ***Fin.:*** Noritren; ***Ger.:*** Nortrilen; ***Gr.:*** Nortrilen; ***Hong Kong:*** Nortrilen; ***India:*** Sensival; ***Israel:*** Nortylin; ***Ital.:*** Noritren; ***Neth.:*** Nortrilen; ***Norw.:*** Noritren; ***NZ:*** Norpress; ***Port.:*** Norterol; ***Spain:*** Norfenazin; Paxtibi; ***Swed.:*** Sensaval; ***Switz.:*** Nortrilen; ***Thai.:*** Norline; Nortrilen; Nortyline; Ortrip; ***UK:*** Allegron; ***USA:*** Aventyl; Pamelor.

Multi-ingredient: ***Arg.:*** Karile; ***Chile:*** Motitrel; ***Indon.:*** Motival; ***Irl.:*** Motival; ***Ital.:*** Dominans; ***Mex.:*** Motival; ***S.Afr.:*** Motival; ***Spain:*** Tropargal; ***Thai.:*** Cetavol; ***UK:*** Motival†.

Opipramol Hydrochloride *(BANM, USAN, rINNM)*

G-33040; Hidrocloruro de opipramol; Opipramol, Chlorhydrate d'; Opipramol Hidroklorür; Opipramoli Dihydrochloridum; Opipramoli Hydrochloridum; Opipramolu dichlorowodorek. 2-[4-(3-5*H*-Dibenz[*b,f*]azepin-5-ylpropyl)piperazin-1-yl]ethanol dihydrochloride.

Опипрамола Гидрохлорид
$C_{23}H_{29}N_3O,2HCl$ = 436.4.
CAS — 315-72-0 (opipramol); 909-39-7 (opipramol dihydrochloride).
ATC — N06AA05.
ATC Vet — QN06AA05.



(opipramol)

Pharmacopoeias. In *Pol.*

Profile

Opipramol hydrochloride is a dibenzazepine tricyclic antidepressant (see Amitriptyline, p.376) given in oral doses of 50 to 300 mg daily in the treatment of depression.

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

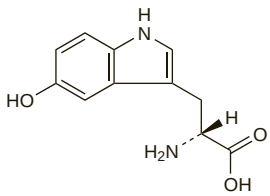
Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Insidon; ***Ger.:*** Insidon; ***Israel:*** Oprimol; ***Pol.:*** Pramolan; ***Switz.:*** Insidon; ***Turk.:*** Deprenil; Insidon; Insomin; Inzeton; Opridon; Oprimol.

Oxitriptan *(rINN)*

5-HTP; L-5-Hydroxytryptophan; Oxitriptán; Oxitriptanum; Ro-0783/B. L-2-Amino-3-(5-hydroxy-1*H*-indol-3-yl)propionic acid.

Окситриптан
$C_{11}H_{12}N_2O_3$ = 220.2.
CAS — 4350-09-8 (oxitriptan); 56-69-9 (DL-5-hydroxytryptophan).
ATC — N06AX01.
ATC Vet — QN06AX01.



Profile

Oxitriptan is the L form of 5-hydroxytryptophan, a precursor of serotonin. Like tryptophan (p.427) it is used in the treatment of depression; it is given in oral doses of up to 600 mg daily.

Oxitriptan is also used in doses of up to 1 g daily in myoclonic disorders, especially posthypoxic myoclonus (p.470). It has also been used in neurological conditions including migraine, pain syndromes, and sleep disorders, and as an adjunct in epilepsy and parkinsonism.

DL-Oxitriptan has also been used as an antidepressant.

Preparations

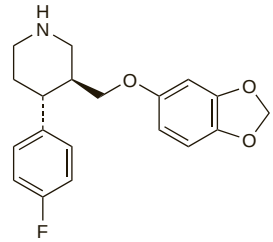
Proprietary Preparations (details are given in Part 3)
Cz.: Tript-OH; ***Fr.:*** Levotonine; ***Ger.:*** Levothym†; ***Ital.:*** Tript-OH; ***Port.:*** Cincofarm; ***Spain:*** Cincofarm; ***Switz.:*** Tript-OH.

Multi-ingredient: ***Indon.:*** Deprex; Menose.

Paroxetine *(BAN, USAN, rINN)*

BRL-29060; FG-7051; Paroksetiini; Paroxetin; Paroxetina; Paroxétine; Paroxetinum. (−)-*trans*-5-(4-*p*-Fluorophenyl-3-piperidylmethoxy)-1,3-benzodioxole.

Пароксетин
$C_{19}H_{20}FNO_3$ = 329.4.
CAS — 61869-08-7.
ATC — N06AB05.
ATC Vet — QN06AB05.



Paroxetine Hydrochloride *(BANM, rINNM)*

BRL-29060A; Hidrocloruro de paroxetina; Paroksetiinihydrokloridihemihydraatti; Paroksetin Hidroklorür; Paroksetino hidrochloridas hemihidratas; Paroksetyny chlorowodorek; Paroxetin hydrochlorid; Paroxétine, chlorhydrate de; Paroxétine (chlorhydrate de) hémihydraté; Paroxetine Hydrochloride Hemihydrate; Paroxetinhydrokloridhemihydrat; Paroxetini hydrochloridum; Paroxetini hydrochloridum hemihydricum.

Пароксетина Гидрохлорид
$C_{19}H_{20}FNO_3,HCl, ½H_2O$ = 374.8.
CAS — 78246-49-8 (anhydrous paroxetine hydrochloride); 110429-35-1 (paroxetine hydrochloride hemihydrate).

Pharmacopoeias. In *Eur.* (see p.vii) and *US*, which permit the anhydrous and hemihydrate forms.
Ph. Eur. 6.2 (Paroxetine Hydrochloride, Anhydrous). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Store in airtight containers at a temperature not exceeding 25°.
Ph. Eur. 6.2 (Paroxetine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. It exhibits pseudopolymorphism. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.
USP 31 (Paroxetine Hydrochloride). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white solid. Slightly soluble in water; soluble in alcohol and in methyl alcohol. Store the anhydrous form in airtight containers.

Paroxetine Mesilate *(BANM, rINNM)*

Mesilato de paroxetina; Paroxétine, Mésilate de; Paroxetine Mesylate *(USAN)*; Paroxetini Mesilas.

Пароксетина Мезилат
$C_{19}H_{20}FNO_3,CH_4O_3S$ = 425.5.
CAS — 217797-14-3.
ATC — N06AB05.
ATC Vet — QN06AB05.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391).

Extrapyramidal reactions (including orofacial dystonias) and withdrawal symptoms associated with paroxetine have been reported to the UK CSM more commonly than with other SSRIs. For further details, see Extrapyramidal Effects under Adverse Effects of Fluoxetine, p.393 and Withdrawal under Precautions, p.396.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p.394.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Pregnancy. For discussion of the risks of SSRIs during pregnancy, and whether paroxetine is associated with a greater teratogenic risk than other SSRIs, see under Fluoxetine, p.395.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p.396.

Pharmacokinetics

Paroxetine is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring within about 5 hours of ingestion. It undergoes extensive first-pass metabolism in the liver. The main metabolic pathway is oxidation followed by methylation and formation of glucuronide and sulfate conjugates. The cytochrome P450 isoenzyme CYP2D6 is partly responsible for the metabolism of paroxetine. Paroxetine is widely distributed throughout body tissues and is about 95% bound to plasma proteins. The elimination half-life of paroxetine is reported to be about 21 hours. Excretion is via the urine (about 64%) and the faeces (about 36%), mainly as metabolites in both cases. Paroxetine is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p.394).

◊ References.

1. Dalhoff K, *et al.* Pharmacokinetics of paroxetine in patients with cirrhosis. *Eur J Clin Pharmacol* 1991; **41:** 351–4.
2. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

Uses and Administration

Paroxetine, a phenylpiperidine derivative, is an SSRI with actions and uses similar to those of fluoxetine (p.397). It is given orally usually as paroxetine hydrochloride, as a single dose in the morning; it is also given as the mesilate. Doses are expressed in terms of the base; paroxetine hydrochloride 22.8 mg or paroxetine mesilate 25.8 mg are each equivalent to about 20 mg of paroxetine. The doses given below refer to preparations containing paroxetine hydrochloride; similar doses are also used when paroxetine is given as the mesilate.

In the treatment of **depression**, the usual dose of paroxetine is 20 mg daily, increased gradually, if necessary, in weekly increments of 10 mg to a maximum of 50 mg daily (but see Administration, below).

In the treatment of **generalised anxiety disorder**, the initial dose is 20 mg daily; further increases in increments of 10 mg at intervals of at least one week to a maximum of 50 mg have been given (but see Administration, below).

The initial dose in **obsessive-compulsive disorder** is 20 mg daily increased weekly in 10-mg increments to a usual maintenance dose of 40 mg daily; some patients may require up to 60 mg daily (but see Administration, below).

In the treatment of **panic disorder** with or without agoraphobia, the initial dose is 10 mg daily increased weekly in 10-mg increments according to response; the usual recommended maintenance dose is 40 mg daily, although some patients may benefit from 60 mg daily (but see Administration, below).

The recommended starting dose for the treatment of **post-traumatic stress disorder** is 20 mg daily. If necessary this may be increased in increments of 10 mg at intervals of at least one week to a maximum of 50 mg daily (but see Administration, below).

The initial dose for the treatment of **social anxiety disorder** is 20 mg daily increased after several weeks, if necessary, by increments of 10 mg to a maximum of 50 or 60 mg daily (but see Administration, below).