

**Porphyria.** Secobarbital has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

#### Interactions

As for Amobarbital, p.962.

#### Pharmacokinetics

Secobarbital is well absorbed from the gastrointestinal tract after oral doses and is reported to be about 46 to 70% bound to plasma proteins. The mean elimination half-life is reported to be 28 hours. It is metabolised in the liver, mainly by hydroxylation, and excreted in urine as metabolites and a small amount of unchanged drug.

#### Uses and Administration

Secobarbital is a barbiturate that has been used as a hypnotic and sedative. It has general properties similar to those of amobarbital (p.962). As a hypnotic in the short-term management of insomnia (p.957) it was usually given in an oral dose of 100 mg of the sodium salt at night, but barbiturates are no longer considered appropriate for such use.

Secobarbital sodium has also been given orally or by intramuscular or intravenous injection for premedication in anaesthetic procedures (p.1780) but barbiturates for pre-operative sedation have been replaced by other drugs.

#### Preparations

**USP 31:** Secobarbital Elixir; Secobarbital Sodium and Amobarbital Sodium Capsules; Secobarbital Sodium Capsules; Secobarbital Sodium for Injection; Secobarbital Sodium Injection.

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

**UK:** Seconal.

**Multi-ingredient:** **Port.:** Vesparax†; **UK:** Tuinal; **USA:** Tuinal.

#### Sertindole (BAN, USAN, rINN)

Lu-23-174; Sertindol; Sertindoli; Sertindolum. 1-(2-(4-[5-Chloro-1-(p-fluorophenyl)indol-3-yl]piperidino)ethyl)-2-imidazolidinone.

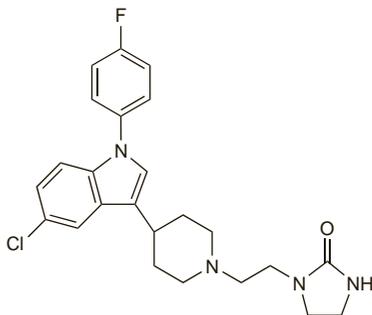
Сертиндол

$C_{24}H_{26}ClFN_4O = 440.9$ .

CAS — 106516-24-9.

ATC — N05AE03.

ATC Vet — QN05AE03.



#### Adverse Effects, Treatment, and Precautions

Although sertindole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Sertindole is associated with a low incidence of extrapyramidal adverse effects and does not appear to cause sedation. Prolactin elevation may be less frequent. The most common adverse effects with sertindole are peripheral oedema, rhinitis, dyspnoea, sexual dysfunction, dizziness, dry mouth, orthostatic hypotension, weight gain, and paraesthesia. Hyperglycaemia, convulsions, and tardive dyskinesia are uncommon.

Marketing of sertindole has been restricted because of cardiac arrhythmias and sudden cardiac deaths associated with its use (see below). Since sertindole has been associated with prolongation of the QT interval, usually during the first 3 to 6 weeks of treatment, it is recommended that patients should have an ECG before the start of therapy and periodically during treatment. Patients with pre-existing prolongation of the QT interval or a family history of congenital QT prolongation should not be given sertindole and sertindole should be stopped if such prolongation occurs during treatment. In addition, sertindole is contra-indicated in patients with a history of cardiovascular disease, heart failure, cardiac hypertrophy, arrhythmias, or bradycardia. Certain medications may also increase the risk (see Interactions, below). Sertindole should not be given to patients with uncorrected hypokalaemia or hypomagnesaemia. Baseline serum potassium and magnesium screening should be performed before starting sertindole therapy in patients who are at risk of significant electrolyte disturbances. Serum potassium should be monitored in patients with electrolyte disturbances, vomiting or diarrhoea, or receiving diuretics during sertindole treatment. It is also recommended that blood pressure should be monitored during dose titration and in early maintenance therapy.

Sertindole is contra-indicated in patients with severe hepatic impairment. It should be used with caution in the elderly and in patients with Parkinson's disease, mild to moderate hepatic impairment, or a history of seizures.

Sertindole may affect the performance of skilled tasks including driving.

Gradual withdrawal of sertindole is recommended because of the risk of withdrawal symptoms such as sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

**Dementia.** The FDA has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs in this class. See under Risperidone, p.1024.

**Effects on body-weight.** The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

**Effects on carbohydrate metabolism.** The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

**Effects on the cardiovascular system.** Prolongation of the QT interval is said by the manufacturer to be common in patients given sertindole, with the effect being greater at the upper end of the dose range. In addition, the QT interval is prolonged to a greater extent than that seen with some other antipsychotics. QT interval prolongation is a known risk factor for the development of serious arrhythmias such as torsade de pointes although such arrhythmias are uncommon with sertindole.

In evidence presented to the FDA it was reported that as of 1st June 1996 there had been 27 deaths, 16 due to adverse cardiac events, among the 2194 patients given sertindole in clinical studies.<sup>1</sup> By the end of November 1998, the UK CSM was aware of 36 suspected adverse drug reactions with a fatal outcome, 9 of which originated in the UK.<sup>2</sup> There had also been 13 reports of serious but non-fatal cardiac arrhythmias in the UK. Although not all the fatalities were related to sudden cardiac events, at the time the CSM considered that, given the number of serious arrhythmias and sudden cardiac deaths, the risk-benefit ratio of sertindole was no longer favourable. The drug was withdrawn from the market in the UK and subsequently in a number of other countries, although it remained available on a named-patient basis. However, in 2001, the issue was re-evaluated by the CSM and the European advisory body, the Committee on Proprietary Medicinal Products, and it was recommended that sertindole could be reintroduced in Europe under certain restrictions.<sup>3</sup> Initially sertindole should only be prescribed to patients enrolled in clinical studies to ensure that they are carefully selected and monitored. In the UK, sertindole was remarketed in September 2002.

1. Barnett AA. Safety concerns over antipsychotic drug, sertindole. *Lancet* 1996; **348**: 256.
2. CSM/MCA. Suspension of availability of sertindole (Serdolect). *Current Problems* 1999; **25**: 1. Also available at: [http://www.mhra.gov.uk/home/idcplg?IdcService=GET\\_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased](http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased) (accessed 16/05/06)
3. CSM/MCA. Restricted re-introduction of the atypical antipsychotic sertindole (Serdolect) (issued 10th September, 2002). Available at: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON1019523> (accessed 21/08/08)

**Effects on lipid metabolism.** The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

**Pregnancy.** For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p.983.

#### Interactions

The risk of arrhythmias with sertindole may be increased by other drugs that prolong the QT interval and use together should be avoided. Sertindole should be given with caution with drugs that produce electrolyte disturbances; monitoring of serum potassium is recommended if given with potassium-depleting diuretics. Sertindole may antagonise the effects of dopaminergics.

Sertindole is extensively metabolised by the cytochrome P450 isoenzymes of the group CYP3A and by CYP2D6. The use of potent inhibitors of CYP3A such as indinavir, itraconazole, and ketoconazole with sertindole is contra-indicated. Minor increases in sertindole plasma concentrations have been noted in patients also given macrolide antibacterials or calcium-channel blockers which also inhibit CYP3A; however, despite the small increase, the use of these CYP3A4 inhibitors with sertindole is not recommended. Fluoxetine and paroxetine, potent inhibitors of CYP2D6, have increased plasma concentrations of sertindole by a factor of 2 to 3 and lower maintenance doses of sertindole may be required. In contrast, enzyme inducers such as rifampicin, carbamazepine, phenytoin, and phenobarbital may decrease sertindole plasma levels by a factor of 2 to 3; in such cases, higher doses of sertindole may be required.

#### Pharmacokinetics

Sertindole is slowly absorbed with peak concentrations occurring about 10 hours after oral doses. It is about 99.5% bound to plasma proteins and readily crosses the placenta. Sertindole is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A. There is moderate interindividual variation in the pharmacokinetics of sertindole due to polymorphism in the isoenzyme CYP2D6. Poor metabolisers, deficient in this isoenzyme, may have plasma concentrations of sertindole 2 to 3 times higher than other patients. The two major metabolites, dehydrosertindole and norsertindole, appear to be inactive. Sertindole and its metabolites are excreted slowly, mainly in the faeces with a minor amount appearing in the urine. The mean terminal half-life is about 3 days.

#### Uses and Administration

Sertindole is an atypical antipsychotic that is an antagonist at central dopamine (D<sub>2</sub>), serotonin (5-HT<sub>2</sub>), and adrenergic (α<sub>1</sub>) receptors. It is used in the treatment of schizophrenia (p.955) in patients who are unable to tolerate at least one other antipsychotic. In addition, sertindole should only be prescribed to patients enrolled in clinical studies to ensure adequate monitoring, especially regular ECG measurements (see Adverse Effects, above).

Sertindole is given in an initial oral dose of 4 mg once daily, increased gradually in steps of 4 mg every 4 or 5 days to a usual maintenance dose of 12 to 20 mg once daily. The maximum dose is 24 mg daily. Slower dose titration and lower maintenance doses are advisable for the elderly and patients with mild to moderate hepatic impairment.

If therapy is interrupted for 1 week or more, the dose of sertindole should be re-titrated. An ECG should also be undertaken before re-starting sertindole.

#### References

1. Lewis R, et al. Sertindole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/05/06).

#### Preparations

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

**Austria:** Serdolect; **Cz.:** Serdolect; **Fr.:** Serdolect; **Gr.:** Serdolect; **Hung.:** Serdolect; **Neth.:** Serdolect; **Port.:** Serdolect; **Rus.:** Serdolect (Сердолект); **Switz.:** Serdolect; **UK:** Serdolect.

#### Sulpiride (BAN, USAN, rINN)

Sulpirid; Sulpirida; Sulpiridas; Sulpiridi; Sulpiridum; Sülprid; Szulpirid. N-(1-Ethylpyrrolidin-2-ylmethyl)-2-methoxy-5-sulphamoylbenzamide.

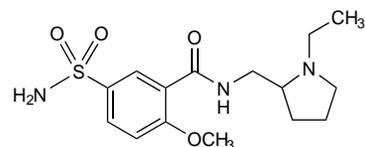
Сульпирид

$C_{15}H_{23}N_3O_4S = 341.4$ .

CAS — 15676-16-1 (sulpiride).

ATC — N05AL01.

ATC Vet — QN05AL01.



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

**Ph. Eur. 6.2** (Sulpiride). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in methyl alcohol. It dissolves in dilute solutions of mineral acids and in alkali hydroxides.

#### Levosulpiride (rINN)

Levosulpirida; Lévosulpiride; Levosulpiridum; Levosulpride; L-Sulpiride.

Левосульпирид

$C_{15}H_{23}N_3O_4S = 341.4$ .

CAS — 23672-07-3.

ATC — N05AL07.

ATC Vet — QN05AL07.

#### Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Sleep disturbances, overstimulation, and agitation may occur. Extrapyramidal effects appear to be as frequent as with chlorpromazine but have usually been mild. It has been suggested that sulpiride is less likely to cause tardive dyskinesia but good evidence of any important difference is lacking. Sulpiride is less likely to cause sedation than chlorpromazine and antimuscarinic ef-