

DATA SHEET

NAME OF MEDICINE

SERDOLECT®

Sertindole

4 mg, 12 mg, 16 mg, 20 mg tablets

PRESENTATION

Serdolect 4 mg tablets are oval, yellow, biconvex film-coated tablets marked with "S4" on one side.

Serdolect 12 mg tablets are oval, beige, biconvex film-coated tablets marked with "S12" on one side.

Serdolect 16 mg tablets are oval, rose, biconvex film-coated tablets marked with "S16" on one side.

Serdolect 20 mg tablets are oval, pink, biconvex film-coated tablets marked with "S20" on one side.

They contain the following excipients: starch - maize, lactose, hydroxypropylcellulose, cellulose - microcrystalline, croscarmellose sodium and magnesium stearate as well as a coating of hypromellose, titanium dioxide, macrogol 400 and

4 mg tablets: iron oxide yellow CI77492.

12 mg tablets: iron oxide yellow CI77492, iron oxide red CI77491.

16 mg tablets: iron oxide red CI77491.

20 mg tablets: iron oxide yellow CI77492, iron oxide red CI77491,
iron oxide black CI77499.

USES

Actions

Pharmacotherapeutic group: limbic selective antipsychotics, ATC-code: N05A E 03

It has been proposed that the neuropharmacological profile of sertindole, as an antipsychotic drug, is derived from its selective inhibitory effect on mesolimbic dopaminergic neurons and is due to balanced inhibitory effects on central dopamine D₂ and serotonin 5HT₂ receptors as well as on α_1 -adrenergic receptors.

In animal pharmacology studies, sertindole inhibited spontaneously active dopamine neurons in the mesolimbic ventral tegmental area (VTA) with a selectivity ratio of more than 100 compared to dopamine neurons in substantia nigra pars compacta (SNc). Inhibition of SNc activity is thought to be involved in movement side effects (EPS) associated with many antipsychotic drugs.

Antipsychotic drugs are known to increase serum prolactin levels through dopamine blockade. The prolactin levels in patients receiving sertindole remained within normal limits, both in short-term studies and during long-term treatment (1 year).

Sertindole has no effect on muscarinic and histaminic H₁ receptors. This is confirmed by the absence of anticholinergic and sedative effects related to those receptors.

Pharmacokinetics

Elimination of sertindole occurs via hepatic metabolism, with a mean terminal half-life of approximately 3 days. The clearance of sertindole decreases with multiple dosing to a mean around 14 L/h (females have approximately 20% lower apparent clearance than males, although lean-mass corrected clearances are comparable). Therefore, upon multiple dosing, accumulation is greater than predicted from a single dose, due to an increase in the systemic bioavailability. However, at steady state, clearance is dose independent and plasma concentrations are proportional to dose. There is moderate inter-subject variability in sertindole pharmacokinetics, due to the polymorphism in the cytochrome P450 2D6 (CYP2D6). Patients who are deficient in this hepatic enzyme have sertindole clearances that are ½ - ⅓ of those who are CYP2D6 extensive metabolisers. These poor metabolisers (up to 10% of the population) will therefore have plasma levels 2 - 3 times the normal. Sertindole concentration is not predictive of therapeutic effect for an individual patient; thus, dosing individualisation is best achieved by assessment of therapeutic effect and tolerability.

Absorption

Sertindole is well absorbed with a t_{max} of sertindole after oral administration of approximately 10 hours. Different dose strengths are bioequivalent. Food and aluminium-magnesium antacids have no clinically significant effect on the rate or the extent of sertindole absorption.

Distribution

The apparent volume of distribution (V_β/F) of sertindole after multiple dosing is approximately 20 L/kg. Sertindole is about 99.5% bound to plasma proteins, primarily to albumin and α₁-acid glycoprotein. In patients treated with recommended doses, 90% of the measured concentrations are below 140 ng/mL (~320 nmol/L). Sertindole penetrates into red blood cells with a 1.0 blood/plasma ratio. Sertindole readily penetrates the blood-brain and placental barriers.

Metabolism

Two metabolites have been identified in human plasma: dehydrosertindole (oxidation of the imidazolidinone ring) and norsertindole (N-dealkylation). Concentrations of dehydrosertindole and norsertindole are approximately 80% and 40%, respectively, of the parent compound at steady state. Sertindole activity is primarily due to the parent drug and the metabolites do not appear to have significant pharmacological effects in humans.

Elimination

Sertindole and its metabolites are eliminated very slowly, with a total recovery of 50 - 60% of a radiolabelled oral dose 14 days after administration. Approximately 4% of the dose is excreted into the urine as parent drug plus metabolites of which less than 1% is present as parent drug. Faecal excretion is the major route of excretion and accounts for the rest of the parent drug and metabolites.

Preclinical safety data

QT prolongation on the ECG, possibly due to inhibition of the delayed rectifier potassium channel (I_{Kr} , HERG), has been observed in animal studies. However, sertindole shows absence of early after-depolarisations in cardiac rabbit and dog Purkinje fibres. Early after-depolarisations are considered essential to trigger Torsade de Pointes. Sertindole did not induce Torsade de Pointes ventricular arrhythmias in atrio-ventricular node ablated rabbit hearts, despite experimental introduction of severe hypokalaemia (1.5 mmol) and bradycardia. However, the extrapolation of animal findings to humans with regard to QT prolongation and arrhythmia must be undertaken with caution as significant inter-species differences may exist.

The acute toxicity of sertindole is low. In chronic toxicity studies in the rat and dog (3 - 5 times clinical exposure), several effects were observed. These effects are in line with the pharmacological properties of the drug.

Indications

Sertindole is indicated for the treatment of schizophrenia.

Due to cardiovascular safety concerns, sertindole should only be used for patients intolerant to at least one other antipsychotic agent.

Sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients.

DOSAGE AND ADMINISTRATION

Note: ECG monitoring is required before and during treatment with sertindole; see PRECAUTIONS.

Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. Sertindole should therefore only be used for patients intolerant to at least one other antipsychotic agent.

Prescribing physicians should comply fully with the required safety measures; see CONTRAINDICATIONS and PRECAUTIONS.

Adults

Sertindole is administered orally once daily with or without meals. In patients where sedation is required, a benzodiazepine may be co-administered.

Titration

All patients should be started on sertindole 4 mg/day. The dose should be increased by increments of 4 mg after 4 - 5 days on each dose until the optimal daily maintenance dose, within the range of 12 - 20 mg, is reached. Due to the α_1 -blocking activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period. A starting dose of 8 mg or a rapid increase in dose carries a significantly increased risk of postural hypotension.

Maintenance

Dependent on individual patient response, the dose may be increased to 20 mg/day. Only in exceptional cases should the maximum dose of 24 mg be considered, as clinical trials have not demonstrated consistently improved efficacy above 20 mg and QT prolongation may be increased at the upper end of the dose range.

The blood pressure of the patients should be monitored during titration and early maintenance treatment.

Elderly patients

A pharmacokinetic study showed no difference between young and elderly subjects. However, only limited clinical trial data exist for patients greater than 65 years of age. Treatment should only be initiated after a thorough cardiovascular examination. Slower titration and lower maintenance doses may be appropriate in elderly patients (see PRECAUTIONS).

Reduced hepatic function

Patients with mild/moderate hepatic impairment require slower titration and a lower maintenance dose (see PRECAUTIONS).

Reduced renal function

Sertindole can be given at the usual dosage to patients with renal impairment. The pharmacokinetics of sertindole is not affected by haemodialysis.

Re-titration of sertindole in patients for whom treatment has previously been discontinued

When restarting sertindole treatment in patients who have had an interval of less than 1 week without sertindole, re-titration of sertindole is not required and their maintenance dose can be re-introduced. Otherwise, the recommended titration schedule should be followed. An ECG should be taken prior to re-titration of sertindole.

Switching from other antipsychotics

Treatment with sertindole can be initiated according to the recommended titration schedule concomitantly with cessation of other oral antipsychotics. For patients treated with depot antipsychotics, sertindole is initiated in place of the next depot injection.

CONTRAINDICATIONS

Hypersensitivity to sertindole or any of the excipients.

Sertindole is contraindicated in patients with known uncorrected hypokalaemia, and those with known uncorrected hypomagnesaemia.

Sertindole is contraindicated in patients with a history of clinically significant cardiovascular disease (e.g. recent acute myocardial infarction, and uncompensated heart failure), congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia (< 50 beats per minute).

Furthermore, sertindole should not be initiated in patients with congenital long QT syndrome or a family history of this disease, or in patients with a history of ventricular arrhythmia or Torsades de pointes or in patients with known acquired QT interval prolongation (QTc above 450 msec in males and 470 msec in females).

Sertindole is contraindicated in patients receiving drugs known to significantly prolong the QT interval. Relevant classes include:

- class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines (e.g. terfenadine, astemizole)
- some quinolone antibiotics (e.g. gatifloxacin, moxifloxacin)

The above list is not exhaustive and other individual drugs known to significantly increase QT interval (e.g. cisapride, lithium) are also contraindicated.

Co-administration of sertindole is contraindicated with drugs known to potently inhibit hepatic cytochrome P450 3A enzymes (see INTERACTIONS). Relevant classes include:

- systemic treatment with 'azole' antifungal agents (e.g. ketoconazole, itraconazole)
- some macrolide antibiotics (e.g. erythromycin, clarithromycin)
- HIV protease inhibitors (e.g. indinavir)
- some calcium channel blockers (e.g. diltiazem, verapamil)

The above list is not exhaustive and other individual drugs known to potently inhibit CYP3A enzymes (e.g. cimetidine) are also contraindicated.

Sertindole is contraindicated in patients with severe hepatic impairment.

WARNINGS AND PRECAUTIONS

Cardiovascular - Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Prolongation of the QTc interval in some drugs is associated with the ability to cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death.

However, clinical and non-clinical data have been unable to confirm whether sertindole is more arrhythmogenic than other antipsychotics. Sertindole should therefore only be used for patients intolerant to at least one other antipsychotic agent.

Prescribing physicians should comply fully with the required safety measures.

ECG monitoring:

- ECG monitoring is mandatory prior to and during treatment with sertindole.
- Sertindole is contraindicated if a QTc interval of more than 450 msec in males or 470 msec in females is observed at baseline.
- ECG monitoring should be conducted at baseline, upon reaching steady state after approximately 3 weeks or when reaching 16 mg and again after 3 months of treatment.
- During maintenance therapy the need for ECG monitoring should be assessed on an individual patient basis.
- During maintenance treatment, ECG measurements should take place prior to and after any increase in dose.
- An ECG is recommended after the addition or increase of dosage of concomitant medication that may increase the sertindole concentration (see INTERACTIONS).
- During treatment with sertindole, reduce dose if QT interval is prolonged and discontinue if QTc interval more than 500 msec is observed.
- For patients with symptoms such as palpitations, convulsions, or syncope that could indicate the occurrence of arrhythmias, the prescriber should initiate urgent evaluation, including an ECG.
- ECG monitoring is ideally conducted in the morning and the Fridericia formulae for calculating the QTc interval are preferred.

The risk of QT prolongation is increased in patients receiving concomitant treatment with drugs that prolong the QTc interval or drugs that inhibit sertindole metabolism (see CONTRAINDICATIONS).

Electrolyte disturbances - Baseline serum potassium and magnesium levels should be measured before commencing treatment with sertindole in patients at risk of significant electrolyte disturbances. Low serum potassium and magnesium should be corrected before proceeding with treatment. Monitoring of serum potassium is recommended for patients experiencing vomiting, diarrhoea, treatment with potassium-depleting diuretics, or other electrolyte disturbances.

Postural hypotension - Due to the α_1 -blocking activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period.

Parkinsonism - Antipsychotic drugs may inhibit the effects of dopamine agonists. Sertindole should be used cautiously in patients with Parkinson's disease.

SSRIs - Some SSRIs, like fluoxetine and paroxetine (potent CYP2D6 inhibitors), may increase the plasma levels of sertindole by a factor of 2 - 3. Sertindole should therefore only be used concomitantly with these drugs with extreme caution, and only if the potential benefit outweighs the risk. A lower maintenance dose of sertindole may be

needed and careful ECG monitoring should be undertaken before and after any dose adjustment of these drugs (see [INTERACTIONS](#)).

Poor CYP2D6 metabolisers - Sertindole should be used with caution in patients, who are known to be poor CYP2D6 metabolisers (see [INTERACTIONS](#)).

Reduced hepatic function - Patients with mild/moderate hepatic dysfunction should be closely observed. Slower titration and a lower maintenance dose are recommended.

Tardive dyskinesia - Tardive dyskinesia is thought to be caused by dopamine receptor hypersensitivity in the basal ganglia as a result of chronic receptor blockade by antipsychotics. A low incidence (comparable to that of placebo) of extrapyramidal symptoms during treatment with sertindole has been seen in clinical studies. However, long-term treatment with antipsychotic compounds (especially at high dosages) is associated with the risk of tardive dyskinesia. If signs of tardive dyskinesia appear, dosage reduction or drug discontinuation should be considered.

Seizures - Sertindole should be used with caution in patients with a history of seizures.

Neuroleptic Malignant Syndrome - A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. The management of NMS should include immediate discontinuation of antipsychotic drugs.

Withdrawal - Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movements disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Effects on ability to drive and use machines - Sertindole is not sedative, however, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Excipients - The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine.

Effects on fertility

Animal reproduction studies have not given evidence of teratogenic effects. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (0.2 mg/kg/day), and at higher dosages, a decreased pup survival in the early lactation period, reduced weight gain, and delayed development of pups in doses producing maternal toxicity.

Mating and fertility were affected in adult male rats at dosages of 0.14 mg/kg/day and above. The adult fertility impairment, which was reversible, was ascribed to the pharmacological profile of sertindole.

Use in pregnancy

Category B2

The safety of sertindole for use during pregnancy has not been established.

Sertindole was not teratogenic in animal reproduction studies. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (see Effects on fertility).

Consequently, sertindole should not be used during pregnancy.

Use in lactation

Studies in nursing mothers have not been performed, however, it is expected that sertindole will be excreted in breast milk.

If treatment with sertindole is considered necessary, discontinuation of breast-feeding should be considered.

Paediatric use

The safety and efficacy of sertindole in children and adolescents under the age of 18 have not been established.

Use in the elderly

In view of the increased risk of significant cardiovascular disease in the elderly, sertindole should be used with care in patients above 65 years of age. Treatment should only be initiated after a thorough cardiovascular examination (see DOSAGE AND ADMINISTRATION).

Carcinogenicity

Carcinogenicity studies conducted in the mouse and rat did not indicate any development of tumours relevant to the clinical use of sertindole.

Genotoxicity

Sertindole was not toxic in a battery of *in vitro* and *in vivo* genotoxicity studies.

ADVERSE EFFECTS

Treatment-emergent Adverse Events with an incidence of $\geq 1\%$ in any group in the placebo-controlled trials are included in the Table below. Figures marked with * in the below table indicate adverse reactions (incidence in the sertindole group which is statistically significantly different from the incidence in the placebo group ($P < 0.05$)).

System Organ Class and Preferred Term	Placebo n (%)	Sertindole n (%)
Patients Treated	290	704
Patients with Treatment Emergent Adverse Event	251 (86.6%)	630 (89.5%)
BODY AS A WHOLE		
Abdominal pain	20 (6.9%)	43 (6.1%)
Accidental injury	22 (7.6%)	45 (6.4%)
Asthenia	26 (9.0%)	61 (8.7%)
Back pain	12 (4.1%)	42 (6.0%)
Chest pain	8 (2.8%)	30 (4.3%)
Fever	5 (1.7%)	16 (2.3%)
Headache	116 (40.0%)	265 (37.6%)
Infection	20 (6.9%)	60 (8.5%)
Malaise	4 (1.4%)	2 (0.3%)
Neck pain	6 (2.1%)	11 (1.6%)
Pain	14 (4.8%)	31 (4.4%)
Pelvic pain	2 (0.7%)	7 (1.0%)
CARDIOVASCULAR SYSTEM		
Electrocardiogram abnormal	4 (1.4%)	13 (1.8%)
Hypertension	4 (1.4%)	3 (0.4%)
Hypotension	4 (1.4%)	4 (0.6%)
Palpitation	4 (1.4%)	6 (0.9%)
Postural hypotension (See PRECAUTIONS)	4 (1.4%)	34 (4.8%)*
QT interval prolonged (See PRECAUTIONS)	0 (0.0%)	11 (1.6%)*
Tachycardia	2 (0.7%)	14 (2.0%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM		
Abnormal dreams	3 (1.0%)	10 (1.4%)
Abnormal gait	3 (1.0%)	11 (1.6%)
Agitation	3 (1.0%)	7 (1.0%)
Akathisia	17 (5.9%)	28 (4.0%)
Cogwheel rigidity	8 (2.8%)	14 (2.0%)
Depression	4 (1.0%)	3 (0.4%)
Dizziness	22 (7.6%)	85 (12.1%)*
Dyskinesia	4 (1.4%)	3 (0.4%)
Dystonia	8 (2.8%)	8 (1.1%)
Extrapyramidal syndrome	1 (0.3%)	9 (1.3%)
Hypertonia	15 (5.2%)	57 (8.1%)
Insomnia	96 (33.1%)	221 (31.4%)
Movement disorder	9 (3.1%)	15 (2.1%)

* = Statistically significant difference sertindole vs placebo (P < 0.05)

System Organ Class and Preferred Term	PLACEBO n (%)	Sertindole n (%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM (continued)		
Nervousness	5 (1.7%)	11 (1.6%)
Oculogyric crisis	3 (1.0%)	2 (0.3%)
Paraesthesia	1 (0.3%)	19 (2.7%)*
Somnolence	32 (11.0%)	103 (14.6%)
Speech disorder	1 (0.3%)	7 (1.0%)
Tardive dyskinesia	3 (1.0%)	4 (0.6%)
Tremor	22 (7.6%)	32 (4.5%)
GASTROINTESTINAL SYSTEM		
Anorexia	6 (2.1%)	4 (0.6%)
Constipation	31 (10.7%)	101 (14.3%)
Diarrhoea	9 (3.1%)	15 (2.1%)
Dry mouth	13 (4.5%)	67 (9.5%)*
Dyspepsia	47 (16.2%)	111 (15.8%)
Dysphagia	3 (1.0%)	8 (1.1%)
Faecal incontinence	3 (1.0%)	3 (0.4%)
Flatulence	7 (2.4%)	17 (2.4%)
Increased salivation	5 (1.7%)	11 (1.6%)
Liver function tests abnormal	0 (0.0%)	7 (1.0%)
Nausea	24 (8.3%)	49 (7.0%)
Nausea and vomiting	6 (2.1%)	10 (1.4%)
Tooth disorder	29 (10.0%)	55 (7.8%)
Vomiting	31 (10.7%)	50 (7.1%)
METABOLIC AND NUTRITIONAL		
Peripheral oedema	1 (0.3%)	21 (3.0%)*
Weight gain	3 (1.0%)	25 (3.6%)*
MUSCULOSKELETAL SYSTEM		
Arthralgia	5 (1.7%)	30 (4.3%)
Joint disorder	2 (0.7%)	9 (1.3%)
Myalgia	29 (10.0%)	81 (11.5%)
RESPIRATORY SYSTEM		
Cough increased	15 (5.2%)	41 (5.8%)
Dyspnoea	2 (0.7%)	20 (2.8%)*
Epistaxis	3 (1.0%)	16 (2.3%)
Lung disorder	1 (0.3%)	9 (1.3%)
Pharyngitis	15 (5.2%)	43 (6.1%)

* = Statistically significant difference sertindole vs placebo (P < 0.05)

System Organ Class and Preferred Term	PLACEBO n (%)	Sertindole n (%)
RESPIRATORY SYSTEM (continued)		
Rhinitis	32 (11.0%)	188 (26.7%)*
Wheezing	5 (1.7%)	17 (2.4%)
SKIN AND APPENDAGES		
Acne	5 (1.7%)	8 (1.1%)
Dry skin	3 (1.0%)	15 (2.1%)
Pruritus	3 (1.0%)	17 (2.4%)
Rash	19 (6.6%)	39 (5.5%)
Skin disorder	13 (4.5%)	23 (3.3%)
Sweating	5 (1.7%)	5 (0.7%)
SPECIAL SENSES		
Amblyopia	8 (2.8%)	25 (3.6%)
Conjunctivitis	2 (0.7%)	13 (1.8%)
Ear disorder	3 (1.0%)	13 (1.8%)
Ear pain	5 (1.7%)	8 (1.1%)
Eye disorder	4 (1.4%)	2 (0.3%)
Eye pain	4 (1.4%)	8 (1.1%)
Otitis media	3 (1.0%)	2 (0.3%)
UROGENITAL SYSTEM		
Abnormal ejaculation (gs)	6 (2.5%)	75 (12.9%)*
Dysuria	3 (1.0%)	6 (0.9%)
Dysmenorrhoea (gs)	3 (6.4%)	10 (8.2%)
Impotence	1 (0.4%)	14 (2.4%)
Urinary frequency	5 (1.7%)	9 (1.3%)
Urinary incontinence	12 (4.1%)	31 (4.4%)
Urinary tract infection	5 (1.7%)	5 (0.7%)
Vaginitis (gs)	1 (2.1%)	9 (7.4%)

* = Statistically significant difference sertindole vs placebo (P < 0.05) gs = gender-specific

Extrapyramidal Symptoms (EPS)

The incidences of patients treated with sertindole reporting EPS-related adverse events were similar to those of patients treated with placebo. In addition, in placebo-controlled clinical trials, the percentage of sertindole-treated patients requiring anti-EPS medication was indistinguishable from that of placebo-treated patients.

Some of the adverse drug reactions will appear at the beginning of treatment and disappear with continuous treatment, e.g. postural hypotension.

Other events observed during the pre-marketing evaluation of Serdolect

Following is a list of WHO terms that reflect adverse events occurring at an incidence of < 1% and serious adverse events from ongoing trials. All reported events are included except those already listed in the above Table or elsewhere in the Adverse Effects section, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with sertindole, they were not necessarily caused by it.

Events are further categorised by body system and are listed below. Uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients and rare adverse events are those that occurred in less than 1/1,000 patients but more than 1/10,000 patients.

Body as a whole

Uncommon: Chest pain substernal, face oedema, flu syndrome, neck rigidity, overdose, suicide attempt.

Cardiovascular system

Uncommon: Pallor, peripheral vascular disorder, syncope, Torsades de Pointes (see PRECAUTIONS), QT prolongation, vasodilation.

Rare (class effects): Ventricular arrhythmias – VF, VT, cardiac arrest, and sudden unexplained death.

Central and peripheral nervous system

Uncommon: Amnesia, anxiety, ataxia, confusion, incoordination, libido decreased, libido increased, miosis, nystagmus, personality disorder, psychosis, reflexes decreased, reflexes increased, stupor, suicidal tendency, urinary retention, vertigo.

Rare: Cases reported as Neuroleptic Malignant Syndrome (NMS) have been reported in association with sertindole (see PRECAUTIONS).

Endocrine system

Uncommon: Diabetes mellitus.

Gastrointestinal system

Uncommon: Abnormal stools, gastritis, gingivitis, glossitis, increased appetite, mouth ulceration, rectal disorder, rectal haemorrhage, stomatitis, tongue disorder, ulcerative stomatitis.

Haemic and lymphatic system

Uncommon: Anaemia, ecchymosis, hypochromic anaemia, leukopenia.

Metabolic and nutritional disorders

Uncommon: Hyperglycaemia, hyperlipemia, oedema.

Musculoskeletal system

Uncommon: Bone pain, myasthenia, twitching.

Respiratory system

Uncommon: Bronchitis, hyperventilation, pneumonia, sinusitis.

Skin and appendages

Uncommon: Furunculosis, herpes simplex, nail disorder, psoriasis, pustular rash, skin discolouration, skin hypertrophy, skin ulcer.

Special senses

Uncommon: Abnormal vision, keratoconjunctivitis, lacrimation disorder, otitis externa, pupillary disorder, taste perversion.

Urogenital system

Uncommon: Anorgasmia, penis disorder (gs), urinary urgency.

INTERACTIONS

Increases in the QT interval related to sertindole treatment may be exacerbated by the co-administration of other drugs known to significantly increase the QT interval. Co-administration of such drugs is therefore contraindicated (see CONTRAINDICATIONS).

Quinidine - The above interaction may occur e.g. between quinidine and sertindole. In addition to the effects on QT interval prolongation (see CONTRAINDICATIONS), CYP2D6 is markedly inhibited by quinidine.

Sertindole is extensively metabolised by the CYP2D6 and CYP3A isozymes of the cytochrome P450 system. CYP2D6 is polymorphic in the population and both isozymes can be inhibited by a variety of psychotropic and other drugs (see PRECAUTIONS).

Neuroleptics – Avoid concomitant use of neuroleptics.

CYP2D6 - The plasma concentration of sertindole is increased by a factor of 2 - 3 in patients concurrently taking fluoxetine or paroxetine (potent CYP2D6 inhibitors), sertindole should therefore only be used concomitantly with these or other CYP2D6 inhibitors with extreme caution. A lower maintenance dose of sertindole may be needed and careful ECG monitoring should be undertaken before and after any dose adjustment of these drugs (see PRECAUTIONS).

CYP3A - Minor increases (< 25%) in sertindole plasma concentrations have been noted for macrolide antibiotics (e.g. erythromycin, a CYP3A inhibitor) and calcium channel antagonists (diltiazem, verapamil). However, the consequences could be greater in CYP2D6 poor metabolisers (since elimination of sertindole by both CYP2D6 and CYP3A would be affected). Since it is not possible to routinely identify patients who are poor metabolisers of CYP2D6 the concomitant administration of CYP3A inhibitors and sertindole is contraindicated, as this may lead to significant increases in sertindole levels (see CONTRAINDICATIONS).

Agents known to induce CYP isozymes - The metabolism of sertindole may be significantly enhanced by agents known to induce CYP isozymes, notably rifampicin, carbamazepine, phenytoin and phenobarbital, which can decrease the plasma concentrations of sertindole by a factor of 2 - 3. Reduced antipsychotic efficacy in

patients receiving these drugs or other inducing agents may require the dose of sertindole to be adjusted to the upper dosage range.

Agents causing electrolyte imbalance – avoid concomitant use

OVERDOSAGE

Experience with sertindole in acute overdose is limited. Fatal cases have occurred. However, patients taking estimated dosages up to 840 mg have recovered without sequelae.

Symptoms

Reported signs and symptoms of overdose were somnolence, slurred speech, tachycardia, hypotension, and transient prolongation of the QTc interval. Cases of Torsade de Pointes have been observed, often in combination with other drugs known to induce TdP.

Treatment

In case of acute overdose, establishment of an airway and maintenance of adequate oxygenation should be ensured.

Continuous monitoring of ECG and vital signs should commence immediately. If the QTc interval is prolonged, it is recommended that the patient be monitored until the QTc interval has normalised. A half-life of sertindole of 2 - 4 days should be taken into account.

Intravenous access should be established, and the administration of activated charcoal with laxative should be considered. Activated charcoal may reduce absorption of the drug if given within 1 or 2 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

The possibility of multiple drug involvement should be considered.

There is no specific antidote to sertindole and it is not dialysable, therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, adrenaline and dopamine should be used with caution, since β stimulation combined with α_1 antagonism associated with sertindole may worsen hypotension.

If antiarrhythmic therapy is administered, agents such as quinidine, disopyramide, and procainamide carry a theoretical hazard of QT interval-prolonging effects that might be additive to those of sertindole.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PHARMACEUTICAL PRECAUTIONS

Store below 25°C. Store in the original package. Protect from light.

Shelf Life

5 years

MEDICINE CLASSIFICATION

Prescription Medicine

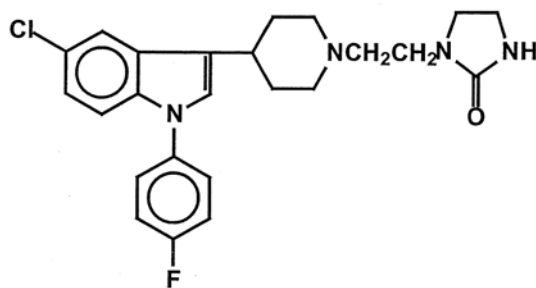
PACKAGE QUANTITIES

- Film-coated tablets containing 4 mg sertindole.
- Blister packs of 20, 28, 30, 50, 98 and 100 tablets.
- Film-coated tablets containing 12 mg sertindole.
- Blister packs of 20, 28, 30, 50, 98 and 100 tablets.
- Film-coated tablets containing 16 mg sertindole.
- Blister packs of 20, 28, 30, 50, 98 and 100 tablets.
- Film-coated tablets containing 20 mg sertindole.
- Blister packs of 20, 28, 30, 50, 98 and 100 tablets.

FURTHER INFORMATION

Serdolect (106516-24-9) is chemically described as 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone

Its structural formula is:



Sertindole is a white to off-white fine powder, practically insoluble in water. It is soluble in 0.1 N acetic acid, sparingly soluble in ethanol, and freely soluble in dichloromethane.

NAME AND ADDRESS

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“Serdolect” is the registered trademark of H. Lundbeck A/S.