SCHEDULING STATUS S5

PROPRIETARY NAMES (AND DOSAGE FORM)
LEPONEX® 25 mg Tablet
LEPONEX® 100 mg Tablet

WARNING
Because of the significant risk that LEPONEX can cause agranulocytosis. Its use should be limited to patients:

- **with schizophrenia who is non-responsive to or intolerant of classical antipsychotic agents, or with schizophrenia or schizoaffective disorder who are at risk of recurrent suicidal behaviour.**
- **and who have initially normal leukocyte findings (white blood cell count (WBC) ≥ 3500/mm^3 (3,5 X 10^9/L), and absolute neutrophil counts (ANC) ≥ 2000/mm^3 (2,0 x 10^9/L).**
- **and in whom regular white blood cell counts and, absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 2 weeks thereafter up till 52 weeks and at least every 4 weeks throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of LEPONEX.**
- **Orthostatic hypotension, with or without syncope, can occur with LEPONEX treatment. Collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; but they may occur even after the first dose. Therefore, patients commencing LEPONEX treatment require close medical supervision.**

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving LEPONEX should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.
LEPONEX must be dispensed under strict medical supervision in accordance with official recommendations.

COMPOSITION
Tablet 25 mg: Each tablet contains 25 mg clozapine.
Tablet 100 mg: Each tablet contains 100 mg clozapine.

List of excipients:
Magnesium stearate; silica, colloidal anhydrous; povidone; talc; maize starch; lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION
A 2.6.5 Tranquillizer (miscellaneous structures).

PHARMACOLOGICAL ACTION
Clozapine is classified as an atypical antipsychotic agent.

In pharmacological experiments, it has weak dopamine receptor-blocking activity at D_1, D_2, D_3 and D_5 receptors, but shows higher potency for the D_4 receptor, in addition to anti-α-adrenergic, anticholinergic, antihistaminic, and arousal reaction- inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Pharmacokinetics:
The absorption of orally administered clozapine is 90 % to 95 %; the rate or extent of absorption is not influenced by food.

Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50 % to 60 %. In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2,5 hours (range: 1 to 6 hours), and the volume of distribution is 1,6 L/kg. Clozapine is approximately 95 % bound to plasma proteins. Its elimination is biphasic, with a mean terminal half-life of 12 hours (range 4 to 66 hours).

Clozapine is almost completely metabolised prior to excretion. Of the main metabolites only the desmethyl metabolite was found to be active. Its pharmacological activity resembles those of clozapine, but are considerably weaker and of short duration. Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50 % of the administered dose is excreted as metabolites in the urine and 30 % in the faeces.

INDICATIONS

Treatment-resistant schizophrenia:

LEPONEX is indicated in patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.

Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations and at adequate dosages.

Intolerance is defined as the impossibility of achieving adequate clinical benefit with standard antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side-effects or tardive dyskinesia).

Risk of recurrent suicidal behaviour:

LEPONEX is also indicated for reducing the risk of recurrent suicidal behaviour in patients with schizophrenia who are judged to be at chronic risk for re-experiencing suicidal behaviour, based on history and recent clinical state. Suicidal behaviour refers to actions by a patient that put him/herself at high risk for death.

Drug-induced Psychosis during the course of Parkinson's disease:

LEPONEX is indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

The failure of standard treatment is defined as the lack of control of the psychotic symptoms and/or the onset of functionally unacceptable motoric deterioration occurring after the following measures have been taken:

- Withdrawal of anti-cholinergic medication including tricyclic anti-depressants.
- Attempt to reduce the dose of antiparkinsonian medication with dopaminergic effect.

CONTRA-INDICATIONS

- Known hypersensitivity to *clozapine* or to any other components of LEPONEX.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- Concomitant therapy with other medication known to suppress bone marrow function.
- Impaired bone marrow function.
- Uncontrolled epilepsy.
- Concomitant use of LEPONEX and carbamazepine.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Glaucoma.
- Circulatory collapse and/or Central Nervous System depression of any cause.
- Severe renal or cardiac disorders (e.g. myocarditis) .
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure
- Paralytic ileus.
- Children under the age of 16 years as safety and efficacy have not been demonstrated.
- Patients at increased risk for venous thromboembolism.

WARNINGS

Orthostatic hypotension, with or without syncope, can occur with LEPONEX treatment. Collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; but they may occur even after the first dose. Therefore, patients commencing LEPONEX treatment require close medical supervision.

Seizure has been estimated to occur in association with LEPONEX use at a cumulative incidence at one year of approximately 5 %, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to LEPONEX during its clinical testing prior to domestic marketing (i.e. a crude rate of 3.5 %). Dose appears to be an important predictor of seizure, with a greater likelihood at the higher LEPONEX doses used. Caution should be used in administering LEPONEX to patients having a history of seizures or other predisposing factors.

Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g. the operation of complex machinery, driving a vehicle, swimming, climbing, etc.

Since LEPONEX may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilisation of the patient should be avoided.

INTERACTIONS

Pharmacodynamic-related interactions:

Medicines known to have a substantial potential to depress bone marrow function should not be used concurrently with LEPONEX (**see also *Contra-indications* and *Special Precautionary Measures***).

LEPONEX may enhance the central effects of alcohol, mono-amine oxidase inhibitors and central nervous system depressants such as narcotics, antihistamines and benzodiapines.

Particular caution is recommended when LEPONEX therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other psychotropic agent, as these patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest.

Because of the possibility of additive effects, caution is essential when substances possessing with anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly.

Concomitant use of LEPONEX and lithium or other central nervous system agents may increase the risk of development of neuroleptic malignant syndrome.

Owing to its anti-α-adrenergic properties, LEPONEX may reduce the blood pressure-increasing effect of norepinephrine or other predominantly α-adrenergic agents and reverse the pressor effect of adrenaline.

Serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where LEPONEX was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Pharmacokinetic-related interactions:

LEPONEX is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. Caution is called for in patients receiving concomitant treatment with other drugs, which are either inhibitors or inducers of these enzymes.

With tricyclic antidepressants, phenothiazines and type I_c anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

On theoretical grounds, however, it is possible that the plasma levels of such medicines are increased by LEPONEX, so it may be appropriate to use them at doses lower than usually prescribed.

Concomitant administration of medicines known to induce cytochrome P450 enzymes may reduce the plasma levels of LEPONEX and may be associated with the recurrence of psychotic symptoms:

- Substances known to induce the activity of 3A4 and with reported interactions with LEPONEX include, carbamazepine, phenytoin and rifampicin.
- Known inducers of 1A2 include, omeprazole and nicotine. In cases of sudden cessation of nicotine abuse, the plasma LEPONEX concentration may be increased, thus leading to an increase in adverse effects.

Concomitant administration of medicines known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of LEPONEX, possibly resulting in adverse effects.

- Medicines known to inhibit the activity of the major isozymes involved in the metabolism of LEPONEX and with reported interactions include cimetidine, erythromycin (3A4), fluvoxamine (1A2), sertraline, fluoxetine, citalopram and paroxetine.
- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, may increase clozapine plasma concentrations; no interactions have been reported to date, however.
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50 % following a 5-day caffeine-free period.
- Elevated clozapine plasma concentrations also have been reported in patients receiving the medicine in combination with selective serotonin re-uptake inhibitors such as paroxetine (1A2), sertraline, fluoxetine, citalopram or fluroxamine.

PREGNANCY AND LACTATION

Pregnancy:

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. However, the safe use of LEPONEX in pregnant women has not been established. Therefore, LEPONEX should be used in pregnancy only if the expected benefit clearly outweighs any potential risk.

Lactation:

Animal studies suggest that clozapine is excreted in breast milk; therefore, mothers receiving LEPONEX should not breast-feed.

Women of childbearing potential:

Some female patients treated with antipsychotics other than LEPONEX may become amenorrheic. A return to normal menstruation may occur as a result of switching from other antipsychotics to LEPONEX. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

DOSAGE AND DIRECTIONS FOR USE

The dosage must be adjusted individually and is different for the individual indications. For each patient the lowest effective dose should be used.

Initiation of LEPONEX treatment must be restricted to those patients with a WBC count $\geq 3500/mm^3$ ($3,5 \times 10^9/L$) and an absolute neutrophil count (ANC) $\geq 2000/mm^3$ ($2,0 \times 10^9/L$), and within standardised normal limits.

Dose adjustment is indicated in patients receiving medicines interacting with clozapine, such as benzodiazepines and medicine with selective serotonin re-uptake (**see *Interactions***).

The following dosages for oral administration are recommended:

Treatment-resistant schizophrenia:

Starting therapy: 12,5 mg (half a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals.

Use in the elderly:

It is recommended to initiate treatment at a particularly low dose (12,5 mg given once on the 1st day) and to restrict subsequent dose increments to 25 mg per day.

Therapeutic dose range:
In most patients, antipsychotic efficacy can be expected with 300 mg to 450 mg per day given in divided doses. Some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion at bedtime. For maintenance dose see below.

Maximum dose:
A few patients, however, may require larger doses to obtain maximum therapeutic benefit, in which case judicious increments (not to exceed 100 mg per increment) are permissible to a maximum dose of 900 mg per day. The possibility of increased adverse reactions (in particular seizures) occurring at doses of over 450 mg per day must be considered.

Maintenance dose:
After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. With daily doses not exceeding 200 mg, a single administration in the evening may be appropriate.

Ending therapy:
In the event of planned termination of LEPONEX therapy, a gradual reduction in dose is recommended over a 1 to 2 week period. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Re-starting therapy:
In patients in whom the interval since the last dose of LEPONEX exceeds 2 days, treatment should be re-initiated with 12,5 mg (one-half of a 25 mg tablet) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see *Other precautions*), but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Switching from a previous antipsychotic therapy to LEPONEX:
LEPONEX should not be used in combination with other antipsychotic.

When LEPONEX therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the dosage of other antipsychotics be reduced or discontinued by gradually tapering it downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to totally discontinue the other antipsychotic therapy before initiating treatment with LEPONEX.

Reducing the risk of suicidal behaviour in schizophrenia and schizoaffective disorder:
The dosage and administration recommendations described in the preceding section Method of administration regarding the use of LEPONEX in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behaviour.
A course of treatment with LEPONEX of at least two years is recommended in order to maintain the reduction of risk for suicidal behaviour. It is recommended that the patient’s risk of suicidal behaviour be reassessed after two years of treatment and that thereafter the decision to continue treatment with LEPONEX be re-visited at regular intervals, based on thorough assessments of patient’s risk for suicidal behaviour during treatment.

Drug-induced Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed:
The starting dose must not exceed 12,5 mg/day (half a 25 mg tablet), taken in the evening. Subsequent dose increases must be by 12,5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening. Higher doses are associated with significant adverse effects.
The mean effective dose is usually between 25 and 37,5 mg/day.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.
When ending therapy, a gradual reduction in dose by steps of 12,5 mg over a period of at least one week (preferably two) is recommended.
Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis as indicated in (See *Special precautions for use*). In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
The adverse effects of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (see *Special precautions for use*).

Table 3: Treatment-Emergent Adverse Experience Frequency estimate from Spontaneous and Clinical Trial Reports:
Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, < 1/1000), very rare (< 1/10000), including isolated reports.

Blood and lymphatic system disorders	
Common	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon	Agranulocytosis
Rare	Anaemia
Very rare	Thrombocytopenia , thrombocythaemia
Metabolism and nutrition disorders	
Common	Weight gain
Rare	Impaired glucose tolerance, diabetes aggravated
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia
Psychiatric disorders	
Rare	Restlessness, agitation
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks
Rare	Confusion, delirium
Very rare	Tardive dyskinesia
Cardiac disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, arrhythmias, myocarditis, pericarditis
Very rare	Cardiomyopathy
Vascular system disorders	
Common	Hypertension, postural hypotension, syncope
Rare	Thromboembolism
Respiratory disorders	
Rare	Aspiration of ingested food
Very rare	Respiratory depression/arrest
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, dry mouth
Rare	Dysphagia
Very rare	Parotid gland enlargement, intestinal obstruction/ileus/faecal impaction
Hepatobiliary disorders	

Common Rare Very rare	Elevated liver enzymes Hepatitis, cholestatic jaundice, pancreatitis Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Renal and urinary disorders	
Common Very rare	Urinary incontinence, urinary retention Interstitial nephritis
Reproductive system disorders	
Very rare	Priapism
General disorders	
Common Uncommon Very rare	Fatigue, benign hyperthermia, disturbances in sweating/temperature regulation Neuroleptic malignant syndrome Sudden unexplained death
Investigations	
Rare	Increased CPK

Special Precautionary Measures:
Because of the association of LEPONEX with agranulocytosis, the following precautionary measures are mandatory:
LEPONEX should not be used concurrently with medicines associated with a substantial potential to depress bone marrow function. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because of the inability of removing these medications, which may have the potential to be myelosuppressive, to be rapidly removed from the body in situations where this may be required, e.g. granulocytopenia.

Patients with a ***history of primary bone marrow disorders*** may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting LEPONEX.

Patients who have low WBC counts because of ***benign ethnic neutropenia*** should be given special consideration and may be started on LEPONEX after agreement of a haematologist.

WBC counts and ANC monitoring:
Before starting LEPONEX treatment, a White Blood Cell count and a differential blood count must be performed within 10 days prior to starting LEPONEX treatment to ensure that only patients with normal leukocyte count and normal absolute neutrophil count (ANC) (WBC count $\geq$ 3 500/mm^3 and ANC $\geq$ 2 000/mm^3) will receive the medicine. After the start of LEPONEX treatment the WBC count and, if possible, ANC must be monitored weekly for 18 weeks and thereafter at least every 2 weeks for one year and thereafter every four weeks throughout treatment, and for 4 weeks after complete discontinuation of LEPONEX.
At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. An immediate differential blood count must be performed if any symptoms or signs of an infection occur.

In case of low WBC count/ANC:
During LEPONEX therapy, if the WBC count falls to between 3500/mm^3 and 3000/mm^3 and/or the ANC falls to between 2000/mm^3 and 1500/mm^3, at least twice weekly haematological evaluations are necessary.

In addition, if, during LEPONEX therapy, the WBC count has dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be done. A substantial drop is defined as a single drop of 3000/mm^3 or more in the WBC count or a cumulative drop of 3000/mm^3 or more within 3 weeks.

Immediate *discontinuation* of LEPONEX treatment is mandatory if the WBC count is less than 3000/mm^3 or the ANC is less than 1500/mm^3 during LEPONEX therapy, WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like

symptoms or other symptoms suggestive of infection. Following discontinuation of LEPONEX, haematological evaluation is required until haematological recovery has occurred.

If LEPONEX has been withdrawn and a further fall of WBC count below 2000/mm^3 occurs and/or neutrophil granulocytes decrease below 1000/mm^3, the management of this condition must be guided by an experienced haematologist.

Patients in whom LEPONEX has been discontinued as a result of white blood cell deficiencies (see above), must never be re-exposed to LEPONEX.

Confirmation of the haematological values is recommended by performing two blood counts done on two consecutive days; however, LEPONEX should be discontinued after the first blood count.

Table 1: Blood monitoring during LEPONEX therapy:

Blood cell count		**Action required**
WBC/mm³ (/L)	**ANC/mm³ (/L)**	
≥ 3500 (> 3,5 x 10^9)	≥ 2000 (> 2,0 x 10^9)	Continue LEPONEX treatment.
3000 to 3500 (3,0 x 10^9 to 3,5 x 10^9)	1500 to 2000 (1,5 x 10^9 to 2,0 x 10^9)	Continue LEPONEX treatment, sample blood twice weekly until counts stabilise or increase.
< 3000 (< 3,0 x 10^9)	< 1500 (< 1,5 x 10^9)	Immediately stop LEPONEX treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

In the event of interruption of therapy for non-haematological reasons:
Patients who have been on LEPONEX for more than 18 weeks and have had the treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and, if possible, ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 2 weeks may be resumed. If LEPONEX treatment has been interrupted for 4 weeks or longer, weekly monitoring is required as for patients never exposed to LEPONEX.

Other precautions:
In the event of eosinophilia, it is recommended to discontinue LEPONEX if the eosinophil count rises above 3000/mm^3, and to re-start therapy only after the eosinophil count has fallen below 1000/mm^3.

In the event of thrombocytopenia, it is recommended to discontinue LEPONEX therapy if the platelet count falls below 50000/mm^3.

Orthostatic hypotension, can occur with LEPONEX treatment (**See *Warnings***). Rarely (about one case per 3000 LEPONEX treated patients), resulting in collapse and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing LEPONEX treatment require close medical supervision. Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may occur. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. If the diagnosis of myocarditis is confirmed, LEPONEX should be discontinued.

Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, LEPONEX should be stopped.

Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease as severe hypotension and orthostatic hypotension may occur.

Effects on ability to drive and use machines:

Owing to the ability of LEPONEX to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

In patients with a history of seizures, or suffering from cardiovascular or renal disorders (note: severe, renal or cardiovascular disorders are contra-indications) the initial dose should be 12,5 mg given once on the first day, and dosage increase should be slow and in small increments.

LEPONEX exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Probably on account of its anticholinergic properties, LEPONEX has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus (**see *Side-effects***). On rare occasions these cases have been fatal.

During LEPONEX therapy, patients may experience transient temperature elevations above 38 °C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered.

Patients with stable pre-existing liver disorders may receive LEPONEX, but need regular liver function tests. In patients in whom, during LEPONEX treatment, symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia develop, liver function tests should be performed immediately. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with LEPONEX must be discontinued.

LEPONEX treatment may be resumed (see re-starting therapy) only when the liver function tests have returned to normal values. In such cases, liver function should be closely monitored after the re-introduction of the medicine.

On rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma has been reported during LEPONEX treatment in patients with no prior history of hyperglycaemia. While a causal relationship to LEPONEX use has not been definitely established, glucose levels returned to normal in most patients after discontinuation of LEPONEX, and re-challenge produced a recurrence of hyperglycaemia in individual cases. The effect of LEPONEX on glucose metabolism in patients with diabetes mellitus has not been in impairment of glucose studied. Impaired glucose tolerance, severe hyperglycaemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycaemia. Exacerbation of diabetes should be considered in patients receiving LEPONEX who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia or weakness. In patients with significant treatment-emergent hyperglycaemia, discontinuation of LEPONEX should be considered.
There is a risk of altering the metabolic balance resulting in impairment of glucose homeostasis and an unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Since LEPONEX may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilisation of the patient should be avoided.

Use in elderly:
It is recommended to initiate treatment at a particularly low dose (12,5 mg given once on the first day) and to restrict subsequent dose increments to 25 mg/day.

Clinical studies with LEPONEX did not include sufficient numbers of subjects aged 65 years and over to determine whether or not they respond differently from younger subjects.

Hypotension:
Orthostatic hypotension can occur with LEPONEX treatment and there have been rare reports of tachycardia, which may be substained, in patients taking LEPONEX. Elderly patients, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Elderly patients may also be particularly susceptible to the anticholinergic effects of LEPONEX, such as urinary retention and constipation.

Use in pregnancy, lactation and children:
(Refer to *contra-indications*.)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Fatal overdosages have been reported with LEPONEX, mostly at doses above 2000 mg.

Signs and symptoms:
Drowsiness, lethargy, coma, areflexia; confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyper-reflexia; convulsions; hypersalivation, mydriasis, blurred vision; thermolability; tachycardia, hypotension, collapse, cardiac arrhythmias (in particular AV-block, extrasystoles), aspiration, pneumonia, dyspnea, heart block; respiratory depression or failure.

Treatment:
Gastric lavage and/or the administration of activated charcoal, within the first 6 hours after the ingestion of the drug. (Peritoneal dialysis and haemodialysis are unlikely to be effective). Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of "reverse epinephrine effect".
Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

IDENTIFICATIONS
LEPONEX® 25 mg Tablet:
A yellow, circular, flat, bevelled edged tablet with a facilitated parting line, marked “LO” on the one side and “SANDOZ” on the other side. Diameter: 6,3 mm.

LEPONEX® 100 mg Tablet:
A yellow, circular, flat, bevelled edged tablet with a facilitated parting line, marked “ZA” on the one side and “SANDOZ” on the other side. Diameter: 10 mm.

PRESENTATION
LEPONEX® 25 mg Tablet:

PVC/PVDC blister pack with heat sealable lacquered aluminium as the backing component. Pack size: 100 tablets per pack enclosed in a cardboard box with a package insert.

LEPONEX® 100 mg Tablet:

PVC/PVDC blister pack with heat sealable lacquered aluminium as the backing component. Pack size: 100 tablets per pack enclosed in a cardboard box with a package insert.

STORAGE INSTRUCTIONS
Store in a cool, dry place. Store at or below 30 °C.
KEEP LEPONEX TABLETS OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS
LEPONEX® 25 mg Tablet: F/2.6/70
LEPONEX® 100 mg Tablet: F/2.6/71

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

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