LEPONEX®
(clozapine)

Tablets
Prescribing Information

1. Trade name of the medicinal product
LEPONEX®

Leponex® can cause agranulocytosis. Its use should be limited to patients:

- with schizophrenia who are non-responsive to or intolerant of classical antipsychotic agents, or with schizophrenia or schizoaffective disorder who are at risk of recurrent suicidal behaviour (see section 4.1. Therapeutic indications),
- who have initially normal leukocyte findings (white blood cell count (WBC) ≥ 3500/mm³ (3.5 x 10⁹/L), and absolute neutrophil counts (ANC) ≥ 2000/mm³ (2.0 x 10⁹/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 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Leponex.

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.

Myocarditis

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely.

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachycardia) or symptoms that mimic myocardial infarction.

If myocarditis or cardiomyopathy are suspected, Leponex treatment should be promptly stopped and the patient immediately referred to a cardiologist.

Patient who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

Increase mortality in elderly patients with dementia related psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen
placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Leponex (clozapine) is not approved for the treatment of patients with dementia-related psychosis.

2. Qualitative and quantitative composition
Tablet containing 25 mg and 100 mg clozapine.
For excipients, see section 6.1. List of excipients.

3. Pharmaceutical form
Tablets.

4. Clinical particulars
4.1. Therapeutic indications
Treatment-resistant schizophrenia
Treatment of resistant schizophrenic patients who are non-responsive to, or intolerant of classic neuroleptics.

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.

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

Risk of recurrent suicidal behaviour
Leponex® is indicated for reducing the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder 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.

4.2. Posology and method of administration
The dosage must be adjusted individually. For each patient the lowest effective dose should be used.

Initiation of Leponex treatment must be restricted to those patients with a WBC count ≥ 3500/mm³ (3.5 x 10⁹/L) and a ANC ≥ 2000/mm³ (2.0 x 10⁹/L), and within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacodynamic and pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section 4.5. Interaction with other medicinal products and other forms of interaction).
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 that treatment is initiated at a particularly low dose (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

Use in children
The safety and efficacy of Leponex in children under the age of 16 have not been established. It should not be used in this group until further data become available.

Therapeutic dose range
In most patients, antipsychotic efficacy can be expected with 200-300 to 450 mg/day given in divided doses. Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion being taken at bedtime. For maintenance dose, see below.

Maximum dose
To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (i.e. not exceeding 100 mg) are permissible up to 900 mg/day. The possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

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. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.

Ending therapy
In the event of planned termination of Leponex therapy, a gradual reduction in dose over a 1- to 2-week period is recommended. 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 (half 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 section 4.4. Special warnings and precautions for use), 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

It is generally recommended that Leponex should not be used in combination with other antipsychotics. 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 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 4.2. Posology and 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.

4.3. Contraindications

- Known hypersensitivity to the active substance or to any of the excipients 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).
- History of Leponex-induced agranulocytosis
- Impaired bone marrow function.
- Uncontrolled epilepsy.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS 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.
- Leponex treatment must not be started concurrently with drugs known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.

4.4. Special warnings and precautions for use

Special precautionary measure

Because of the association of Leponex with agranulocytosis, the following precautionary measures are mandatory:

Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Leponex. In addition, the concomitant use of long-acting depot
antipsychotics should be avoided because of the impossibility of removing these medications, which may be potentially myelosuppressive, from the body rapidly 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.

Leponex can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of WBC counts and ANC monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations.

Because of the risks associated with Leponex, its use is limited to patients in whom therapy is indicated as set out in section 4.1 (Therapeutic indications) and:

- who have initially normal leukocyte findings (WBC count \( \geq 3500/\text{mm}^3 \) \( \times 10^9/\text{L} \) and ANC \( \geq 2000/\text{mm}^3 \) \( \times 10^9/\text{L} \)), and
- in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 4-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Leponex.

Before initiating Leponex therapy patients should have a blood test (see “agranulocytosis”) and a history and physical examination. Patients with history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks (see Section 4.3). The treating physician should consider performing a pre-treatment ECG.

Prescribing physicians should comply fully with the required safety measures. Prior to treatment initiation, physicians must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation. Prescriptions should not be issued for periods longer than the interval between two blood counts.

Immediate discontinuation of Leponex is mandatory if either the WBC count is less than 3000/\text{mm}^3 \( \times 10^9/\text{L} \) or the ANC is less than 1500/\text{mm}^3 \( \times 10^9/\text{L} \) at any time during Leponex treatment. Patients in whom Leponex has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Leponex.

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. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are encouraged to keep a record of all patients’ blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

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 with the agreement of a haematologist.
**WBC counts and ANC monitoring**

WBC and differential blood counts must be performed within 10 days prior to starting Leponex treatment to ensure that only patients with normal WBC (leukocyte) and ANC (absolute neutrophil counts) counts (WBC count \( \geq 3500/\text{mm}^3 \) \((3.5 \times 10^9/\text{L})\) and ANC \( \geq 2000/\text{mm}^3 \) \((2.0 \times 10^9/\text{L})\)) will receive Leponex. After the start of Leponex treatment, the WBC count and ANC must be monitored weekly for the first 18 weeks, and thereafter at least 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. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

**Low WBC count and/or ANC**

If during the first 18 weeks of Leponex therapy, the WBC count falls to between 3500/\text{mm}^3 \((3.5 \times 10^9/\text{L})\) and 3000/\text{mm}^3 \((3.0 \times 10^9/\text{L})\) or the ANC falls to between 2000/\text{mm}^3 \((2.0 \times 10^9/\text{L})\) and 1500/\text{mm}^3 \((1.5 \times 10^9/\text{L})\), haematological evaluations must be performed at least twice weekly.

until the patient’s WBC count and ANC stabilise within the range 3000-3500/\text{mm}^3 \((3.0-3.5 \times 10^9/\text{L})\) and 1500-2000 \text{mm}^3 \((1.5-2.0 \times 10^9/\text{L})\), respectively, or higher.

After 18 weeks of Leponex therapy, haematological evaluation should be performed at least weekly if the WBC count falls to be between 3000/\text{mm}^3 and 2500/\text{mm}^3 and/or the ANC is falls to between 1500/\text{mm}^3 and 1000/\text{mm}^3.

In addition, if, during Leponex therapy, the WBC counts is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood counts should be performed. 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 three weeks.

Immediate discontinuation of Leponex is mandatory if the WBC count is less than 3000/\text{mm}^3 or the ANC is less than 1500/\text{mm}^3 during the first 18 weeks of therapy, or if the WBC count is less than 2500/\text{mm}^3 or the ANC is less than 1000/\text{mm}^3 after the first 18 weeks of 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. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, Leponex should be discontinued after the first blood count.

Following discontinuation of Leponex, haematological evaluation is required until haematological recovery has occurred.

**Table 1: Blood monitoring during the first 18 weeks of Leponex therapy**

<table>
<thead>
<tr>
<th>Blood cell count</th>
<th>Action required</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEP API DEC09 CL V3c</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2: Blood monitoring after 18 weeks of Leponex therapy

<table>
<thead>
<tr>
<th>WBC/mm³ (/L)</th>
<th>ANC/mm³ (/L)</th>
<th>Action required</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3500 (&gt; 3.5 x 10⁹)</td>
<td>≥ 2000 (&gt; 2.0 x 10⁹)</td>
<td>Continue Leponex treatment.</td>
</tr>
<tr>
<td>3000-3500 (3.0 x 10⁹-3.5 x 10⁹)</td>
<td>1500-2000 (1.5 x 10⁹-2.0 x 10⁹)</td>
<td>Continue Leponex treatment, sample blood twice weekly until counts stabilise or increase.</td>
</tr>
<tr>
<td>&lt; 3000 (&lt; 3.0 x 10⁹)</td>
<td>&lt; 1500 (&lt; 1.5 x 10⁹)</td>
<td>Immediately stop Leponex treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.</td>
</tr>
</tbody>
</table>

If Leponex has been withdrawn and WBC count falls further to below 2000/mm³ (2.0 x 10⁹/L) and/or the ANC falls below 1000/mm³ (1.0 x 10⁹/L), the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated. It is recommended that the colony stimulating factor therapy be discontinued when the neutrophil count has returned to a level above 1000/mm³.

Discontinuation of therapy for haematological reasons

Patients in whom Leponex has been discontinued as a result of either WBC - white blood cell deficiencies or ANC deficiencies (see above) must not be re-exposed to Leponex.

Prescribers are encouraged to keep a record of all patients, blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.

Discontinuation of therapy for other reasons

Patients who have been on Leponex for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Leponex treatment has
been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment.

Other precautions

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

In the event of eosinophilia, discontinuation of Leponex is recommended if the eosinophil count rises above 3000/mm$^3$ (3.0 x 10$^9$/L). Therapy should be re-started only after the eosinophil count has fallen below 1000/mm$^3$ (1.0 x 10$^9$/L).

In the event of thrombocytopenia, discontinuation of Leponex therapy is recommended if the platelet count falls below 50 000/mm$^3$ (50 x 10$^9$/L).

Orthostatic hypotension, with or without syncope, can occur during Leponex treatment. Rarely (about one case per 3000 Leponex-treated patients), collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of benzodiazepine or any other psychotropic agent (see section 4.5 Interaction with other medicinal products and other forms of interaction) and during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson’s disease.

Therefore, patients commencing Leponex treatment requires close medical supervision. Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of treatment and very rarely thereafter. 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, the treatment should be stopped unless the benefit clearly outweighs the risk to the patient.

Analysis of safety databases suggests that the use of Leponex is associated with an increased risk of myocarditis especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal. Pericarditis/ pericardial effusion and cardiomyopathy have also been reported in association with Leponex use; these reports also include fatalities. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first twomonths of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure. (e.g. unexplained fatigue, dyspnoea, tachycardia), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy are suspected, Leponex treatment should be promptly stopped and the patient immediately referred to a cardiologist.

Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Leponex.

Patients with a history of epilepsy should be closely observed during Leponex therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced (see section 4.2 Posology and method of administration) and, if necessary, an anti-convulsant treatment should be initiated.

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

Patients with stable pre-existing liver disorders may receive Leponex, but must undergo regular liver function tests. Such tests should be performed immediately in patients who develop symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia during Leponex treatment. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with Leponex must be discontinued. It may be resumed (see section 4.2. Posology and method of administration - Re-starting therapy) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Leponex.

Clozapine 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 section 4.8. Undesirable effects). On rare occasions these cases have proved fatal.

Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.

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.

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal. When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its occurrence. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed. There is a risk of altering the metabolic balance resulting in slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Since Leponex may be associated with thromboembolism, immobilisation of patients should be avoided.

An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Leponex should be used with caution in patients with risk factors for stroke.

Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal is recommended. If abrupt discontinuation is necessary (i.e. 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.

Use in the elderly

Initiation of treatment in the elderly is recommended at a lower dose (see section 4.2 Posology and method of administration). (12.5 mg given once on the first day) and subsequent dose increments be restricted 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.

Orthostatic hypotension can occur with Leponex treatment and there have been rare reports of tachycardia, which may be sustained, 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 clozapine, such as urinary retention and constipation.

Elderly patients with Dementia-related Psychosis

In elderly patients with dementia-related psychosis, the efficacy and safety of clozapine has not been studied. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In the published literature, risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include sedation, the presence of cardiac conditions (e.g. cardiac arrhythmias) or pulmonary conditions (e.g. pneumonia, with or without aspiration). Leponex should be used with caution in elderly patients with dementia.

4.5. Interactions with other medicinal products and other forms of interaction

Pharmacodynamic-related interactions

Medicinal products known to have a substantial potential to depress bone marrow function should not be used concurrently with Leponex (see section 4.4 Special warnings and precautions for use)

Clozapine may enhance the central effects of alcohol, MAO inhibitors and CNS depressants such as narcotics, antihistamines, and benzodiazepines.

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 anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly.

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

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

Rare but 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**

Clozapine is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimised. Nevertheless, caution is called for in patients receiving concomitant treatment with other substances that are either inhibitors or inducers of these enzymes.

No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines or type 1C anti-arrhythmics, which are known to bind to cytochrome P450 2D6.

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.

- Substances known to induce the activity of 3A4 and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppressive potential), phenytoin and rifampicin.

- Known inducers of 1A2 include, for instance, omeprazole and tobacco smoke. In cases of sudden cessation of tobacco smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.

- Substances known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4), fluvoxamine (1A2) and ciprofloxacin (1A2).

- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also 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 substances in combination with selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine (1A2), sertraline, fluoxetine or citalopram.

**Others**

Caution is called for in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of the cytochrome P450 isozymes. An outline of drug interactions believed to be most important with Leponex is given in Table 3 below (this is not an exhaustive list).

Table 3: Reference to the most common drug interactions with Leponex

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow suppressants (e.g. carbamazepine, chloramphenicol, sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g.</td>
<td>Interact to increase the risk and/or severity of bone marrow suppression</td>
<td>Leponex <strong>should not be used</strong> concomitantly with other agents having a well known potential to suppress bone marrow function (see Section</td>
</tr>
<tr>
<td>phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics</td>
<td>4.3 Contraindications</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest</td>
<td>Whilst the occurrence is rare, caution is advised when using these drugs together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when Leponex is added to an established benzodiazepine regimen.</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Leponex potentiates the action of these drugs through additive anticholinergic activity</td>
<td>Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Leponex can potentiate the hypotensive effects of these drugs due to its sympathomimetic antagonistic effects</td>
<td>Caution is advised if Leponex is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.</td>
</tr>
<tr>
<td>Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines</td>
<td>Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these drugs</td>
<td>Caution is advised if Leponex is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.</td>
</tr>
<tr>
<td>Highly protein bound drugs (e.g. warfarin and digoxin)</td>
<td>Leponex may cause an increase in plasma concentration of these drugs due to displacement from plasma proteins</td>
<td>Patients should be monitored for the occurrence of side effects associated with these drugs, and doses of the protein bound drug adjusted, if necessary.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Addition of phenytoin to Leponex drug regimen may cause a decrease in the clozapine plasma concentrations</td>
<td>If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.</td>
</tr>
</tbody>
</table>
Lithium

<table>
<thead>
<tr>
<th>Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS)</th>
<th>Observe for signs and symptoms of NMS</th>
</tr>
</thead>
</table>

4.6. Use during 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 and has an effect in the nursing infant; 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.

4.7. 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.

4.8. Undesirable effects

For the most part, the adverse event profile of clozapine is predictable from its pharmacological properties. An important exception is its propensity to cause agranulocytosis (see section 4.4 Special warnings and special precautions for use). Because of this risk, its use is restricted to treatment-resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed. While blood monitoring is an essential part of the care of patients receiving clozapine, the physician should be aware of other rare but serious adverse events, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to Leponex treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of the drug is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory (see section 4.4 Special warnings and special precautions for use). Table 4 below summarises the estimated incidence of agranulocytosis for each Leponex treatment period.

Table 4: Estimated incidence of agranulocytosis1

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</table>

LEP API DEC09 CL V3c 13 REF BPI 120509
### Treatment period

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Incidence of agranulocytosis per 100,000 person-weeks² of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 0-18</td>
<td>32.0</td>
</tr>
<tr>
<td>Weeks 19-52</td>
<td>2.3</td>
</tr>
<tr>
<td>Weeks 53 and higher</td>
<td>1.8</td>
</tr>
</tbody>
</table>


² Person-time is the sum of individual units of time that the patients in the registry have been exposed to Leponex before experiencing agranulocytosis. For example, 100,000 person-weeks could be observed in 1,000 patients who were in the registry for 100 weeks (100*1000=100,000), or in 200 patients who were in the registry for 500 weeks (200*500=100,000) before experiencing agranulocytosis.

The cumulative incidence of agranulocytosis in the UK Leponex Patient Monitoring Service lifetime registry experience (0 - 11.6 years between 1989 and 2001) is 0.78%. The majority of cases (approximately 70%) occur within the first 18 weeks of treatment.

### Metabolic and Nutritional Disorders

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported in patients on Leponex treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of Leponex and in a few cases hyperglycaemia recurred when treatment was reinitiated. Although most patients had risk factors for non-insulin-dependent diabetes mellitus, hyperglycaemia has also been documented in patients with no known risk factors(see section 4.4. Special warnings and special precautions for use).

### Nervous System Disorders

The very common adverse events observed include drowsiness/sedation, and dizziness.

Leponex can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsant drugs the possibility of a pharmacokinetic interaction should be considered. In rare cases, patients treated with Leponex may experience delirium.

Very rarely, tardive dyskinesia has been reported in patients on Leponex who had been treated with other antipsychotic agents. Patients in whom tardive dyskinesia developed with other antipsychotics have improved on Leponex.

### Cardiac Disorders

Tachycardia and postural hypotension with or without syncope may occur, especially in the initial weeks of treatment. The prevalence and severity of hypotension is influenced by the rate and magnitude of dose titration. Circulatory collapse as a result of profound hypotension,
in particular related to aggressive titration of the drug, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with Leponex.

A minority of Leponex-treated patients experience ECG changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of Leponex. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis have been reported, some of which have been fatal. The majority of the cases of myocarditis occurred within the first 2 months of initiation of therapy with Leponex. Cardiomyopathy generally occurred later in the treatment.

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

Signs and symptoms of myocarditis or cardiomyopathy include persistent tachycardia at rest, palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms.

Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving Leponex.

**Vascular Disorders**

Rare cases of thromboembolism have been reported.

**Respiratory System**

Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse (see sections 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).

**Gastrointestinal System**

Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur (see section 4.4 Special warnings and special precautions for use). Rarely Leponex treatment may be associated with dysphagia. Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

**Hepatobiliary Disorders**

Transient, asymptomatic elevations of liver enzymes and rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, Leponex should be discontinued (see section 4.4. Special warnings and special precautions for use). In rare cases, acute pancreatitis has been reported.

**Renal Disorders**

Isolated cases of acute interstitial nephritis have been reported in association with Leponex therapy.
**Reproductive and Breast Disorders**

Very rare reports of priapism have been received.

**General Disorders**

Cases of neuroleptic malignant syndrome (NMS) have been reported in patients receiving Leponex either alone or in combination with lithium or other CNS-active agents.

Acute withdrawal reactions have been reported (see section 4.4 Special warnings and special precautions for use).

The table below (Table 5) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

The adverse effects of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (see section 4.4 Special warnings and precautions for use).

**Table 5: 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 (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Thrombocytopenia, thrombocythaemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Rare</td>
<td>Impaired glucose tolerance, new onset diabetes, diabetes aggravated</td>
</tr>
<tr>
<td>Very rare</td>
<td>Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridaemia, hypercholesterolaeemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Restlessness, agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Restlessness, agitation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Drowsiness/sedation, dizziness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Drowsiness/sedation, dizziness</td>
</tr>
<tr>
<td>Common</td>
<td>Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>seizures/convulsions/myoclonic jerks</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Very rare</td>
<td>Confusion, delirium</td>
</tr>
<tr>
<td>Tardive dyskinesia, obsessive compulsive symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Rare</td>
<td>ECG changes</td>
</tr>
<tr>
<td>Circulatory collapse, arrhythmias, myocarditis, pericarditis</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Cardiomyopathy,</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Hypertension, postural hypotension, syncope</td>
</tr>
<tr>
<td>Rare</td>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Respiratory depression/arrest</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Constipation, hypersalivation</td>
</tr>
<tr>
<td>Common</td>
<td>Nausea, vomiting, anorexia, dry mouth</td>
</tr>
<tr>
<td>Rare</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>Rare</td>
<td>Hepatitis, cholestatic jaundice, pancreatitis</td>
</tr>
<tr>
<td>Very rare</td>
<td>Fulminant hepatic necrosis</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Skin reactions</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Urinary incontinence, urinary retention</td>
</tr>
<tr>
<td>Very rare</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Reproductive system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Priapism</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Very rare</td>
<td>Sudden unexplained death</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Increased CPK</td>
</tr>
</tbody>
</table>

4.9. **Overdose**

In cases of acute intentional or accidental Leponex overdosage, for which information on the outcome is available, to date the mortality is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg. There have been reports of patients recovering from an overdose in excess of 10 000 mg. However, in a few adult individuals, primarily those not previously exposed to Leponex, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 mg to 200 mg resulted in strong sedation or coma without being lethal.

**Signs and symptoms**

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyper-reflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, 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 a ‘reverse epinephrine’ effect.

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

5. **Pharmacological properties**

5.1. **Pharmacodynamic properties**

Pharmacotherapeutic group: Antipsychotic agent (ATC code NO5A H02)
Leponex has been shown to be an antipsychotic agent that is different from classic antipsychotics.

In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine receptor-blocking activity at D1, D2, D3 and D5 receptors, but shows high potency for the D4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotonergic properties.

Clinically Leponex produces rapid and marked sedation, and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatment. In such cases, Leponex has proven effective in relieving both positive and negative schizophrenic symptoms in short-term trials. In an open clinical trial performed in 319 treatment-resistant patients treated for 12 months, a clinically relevant improvement was observed in about 37% of patients within the first week of treatment and in an additional 44% by the end of 12 months. The improvement was defined as about 20% reduction from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

Epidemiological studies showed an approximately sevenfold decrease in suicide attempts and a four to six fold decrease in mortality from suicide in clozapine-treated patients with schizophrenia or schizoaffective disorder compared to non-treated patients. In a randomised, multicentre clinical trial performed in 980 patients, Leponex reduced the risk for suicidal behaviour (as measured by suicide attempts and hospitalisations to prevent suicide) by 26% over a 2-year period compared to olanzapine. This significant effect relative to olanzapine was achieved despite the fact that olanzapine-treated patients received significantly more concomitant antipsychotics, antidepressants anxiolytics, sedatives and mood stabilisers than the Leponex-treated patients.

Compared to classic antipsychotics, Leponex produces fewer major extrapyramidal reactions such as acute dystonia, parkinsonian-like side effects and akathisia. In contrast to classic antipsychotics, Leponex produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia,amenorrhoea, galactorrhoea, and impotence.

Potentially serious adverse reactions caused by Leponex therapy are granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7% respectively. (see section 4.4 Special warnings and precautions for use).

5.2. Pharmacokinetic properties

The absorption of orally administered clozapine is 90% to 95%; neither the rate nor the extent of absorption is 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 2.1 hours (range: 0.4 to 4.2 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: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days. Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.
Clozapine is almost completely metabolised before excretion. Of the main metabolites only the desmethyl metabolite was found to be active. Its pharmacological actions resemble 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 being excreted as metabolites in the urine and 30% in the faeces.

5.3. Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential (for reproductive toxicity, see section 4.6. Use during pregnancy and lactation).

Acute toxicity
Acute toxicity studies in mice, rats and guinea pigs revealed oral LD50 values of 190 to 681 mg/kg body weight. In dogs, the oral LD50 was approximately 145 mg/kg; signs of overdosage consisted of muscular tremor, aggressive behaviour and vomiting.

Mutagenicity
Clozapine and/or its metabolites were devoid of genotoxic potential when investigated for induction of gene mutations, chromosome aberrations and primary DNA-damage in a spectrum of in vitro mutagenicity tests. No clastogenic activity was observed in vivo (bone marrow micronucleus test in mice).

Carcinogenicity
In Sprague-Dawley (CD) rats treated in the diet for 24 months, maximum tolerated doses of 35 mg/kg per day revealed no carcinogenic potential of clozapine. Likewise, no evidence of tumorigenic effects was obtained in two 78-week feeding studies in Charles River (CD) mice. In the first study, oral dose levels of up to 64 mg/kg were administered to males, and of up to 75 mg/kg to females respectively. In the second study, the drug intake achieved for both sexes was 61 mg/kg per day.

Reproductive toxicity
No embryotoxic or teratogenic potential of clozapine was revealed in rats or rabbits. In male rats treated for 70 days prior to mating, fertility was unaffected.

In female rats, fertility as well as pre- and postnatal development of the offspring was not adversely affected by oral clozapine treatment prior to mating. When rats were treated during the later part of pregnancy and during lactation, survival rates of the youngs from lactating dams, treated at dose levels up to 40 mg/kg body weight, were lowered and the youngs were hyperactive. However, there was no lasting effect on pup development after weaning.

6. Pharmaceutical particulars

6.1. List of excipients
Leponex tablets: magnesium stearate; silica colloidal anhydrous; povidone; talc; maize starch; lactose monohydrate.

6.2. Incompatibilities
Not applicable.
6.3. **Special precautions for storage**

Store below 30°C

Leponex must be kept out of the reach and sight of children.

6.4. **Nature and content of container**

Leponex tablets are available in PVC or PVC/PVDC blister packs.

6.6. **Instructions to use and handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

**Manufacturer:**

Novartis Pharmaceuticals Ltd., UK.

for: Novartis Pharma AG, Basel, Switzerland.

**License Holder:**

Novartis Pharma Services AG,
36 Shacham st., Petach-Tikva.