NOVARTIS

Drug Regulatory Affairs

LEPONEX® / CLOZARIL® (clozapine)

25 mg or 100 mg tablets

Basic Prescribing Information

Notice

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on this BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to characterisation of risk and benefits.

Author(s):	Isabelle Lalande-Luesink, Karin Heidenreich, Fara Ramjane, Claire Souppart

GLC approval date:	05 March 2003, amended 21 November 2003, 26 March 2004, 05-Mar-2009 and 27-Oct-2009
Release date:	26-Nov-2009
Tracking number:	2009-PSB/GLC-0231-s
Document status:	Final
Number of pages:	18

1 Trade name of the medicinal product

LEPONEX® / CLOZARIL®

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/mm^3 (3.5 x 10^9/L) [41], 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 [117] 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.

2 Qualitative and quantitative composition

Tablets containing 25 mg and 100 mg clozapine.

For a full list of excipients, see section 6.1. List of excipients.

3 Pharmaceutical form

Tablets.

4 Clinical particulars

4.1 Therapeutic indications [12,13]

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 [3,4].

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 [163,164]

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 [162].

Psychosis during the course of Parkinson's disease [165,166]

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

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 $\geq 3500/mm^3$ ($3.5 \times 10^9/L$) and an ANC $\geq 2000/mm^3$ ($2.0 \times 10^9/L$), and within standardised normal limits [163].

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin re-uptake inhibitors [118] (see section 4.5. Interaction with other medicinal products and other forms of interaction).

The following dosages are recommended for ***oral administration***:

Treatment-resistant schizophrenia

Starting therapy [41]

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 [47].

Use in children

The safety and efficacy of Leponex in children have not been established [41].

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 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 [41]) 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 [123-128].

Re-starting therapy [41]

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 [163]

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 [164]

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.

Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed [166]

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.

The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.

The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.

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 there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, Leponex dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above).

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 section 4.4 (Special warnings and precautions for use). In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

4.3 Contraindications

- Known hypersensitivity to *clozapine* or to any of the excipients of Leponex.
- Patients unable to undergo regular blood tests [163].
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy) [117].
- Impaired bone marrow function.
- Uncontrolled epilepsy [58].
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause [47].
- Severe renal or cardiac disorders (e.g. myocarditis) [14,123,129,130].
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure [119].
- Paralytic ileus [163].

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 [14].

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

WBC and differential blood counts must be performed within 10 days prior to starting Leponex treatment to ensure that only patients with normal leukocyte and absolute neutrophil counts (WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$) will receive Leponex. After the start of Leponex treatment, the WBC count and ANC must be monitored weekly for 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. A differential blood count 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/mm^3 and 3000/mm^3 and/or the ANC falls to between 2000/mm^3 and 1500/mm^3, haematological evaluations must be performed at least twice weekly.

After 18 weeks of Leponex therapy, haematological evaluations should be performed at least twice weekly if the WBC count falls to between 3000/mm^3 and 2500/mm^3 and/or the ANC falls to between 1500/mm^3 and 1000/mm^3 [117].

In addition, if, during Leponex therapy, the WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count 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/mm^3 or the ANC is less than 1500/mm^3 during the first 18 weeks of therapy, or if the WBC count is less than 2500/mm^3 or the ANC is less than 1000/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 [42]. Following discontinuation of Leponex, haematological evaluation is required until haematological recovery has occurred [117].

If Leponex has been withdrawn and WBC count falls further to below 2000/mm^3 and/or the ANC falls below 1000/mm^3, 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 [60]. It is recommended that the colony stimulating factor therapy be discontinued when the neutrophil count has returned to a level above 1000/mm^3.

Patients in whom Leponex has been discontinued as a result of white blood cell deficiencies (see above) must not be re-exposed to Leponex [14,47].

It is recommended that the haematological values be confirmed by performing two blood counts on two consecutive days; however, Leponex should be discontinued after the first blood count [117].

Table 1 Blood monitoring during the first 18 weeks of 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.
3000-3500 (3.0 x 10^9-3.5 x 10^9)	1500-2000 (1.5 x 10^9-2.0 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.

Table 2 Blood monitoring after 18 weeks of Leponex therapy

Blood cell count		Action required
WBC/mm³ (/L)	ANC/mm³ (/L)	
≥ 3000 (> 3.0 x 10^9)	≥ 1500 (> 1.5 x 10^9)	Continue Leponex treatment.
2500-3000 (2.5 x 10^9-3.0 x 10^9)	1000-1500 (1.0 x 10^9-1.5 x 10^9)	Continue Leponex treatment, sample blood twice weekly until counts stabilise or increase.
< 2500 (< 2.5 x 10^9)	< 1000 (< 1.0 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 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 [84].

Other precautions

In the event of **eosinophilia,** discontinuation of Leponex is recommended if the eosinophil count rises above 3000/mm^3. Therapy should be re-started only after the eosinophil count has fallen below 1000/mm^3 [120].

In the event of **thrombocytopenia,** discontinuation of Leponex is recommended if the platelet count falls below 50 000/mm^3.

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 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 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 [41,123,129,130]. If the diagnosis of myocarditis is confirmed, Leponex should be

discontinued [28,29,66,123,129,130]. 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 [161].

Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

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 [41].

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 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 [119].

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 [131].

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 [41].

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 a few cases. The effect of Leponex on glucose metabolism in patients with diabetes mellitus has not been studied. Impaired glucose tolerance, severe hyperglycaemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycaemia. Exacerbation 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 [123,132,133].

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 [163].

Since Leponex may cause sedation and weight gain, thereby increasing the risk of **thromboembolism**, immobilisation of patients should be avoided [85].

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 [171].

As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation [175].

As with other antipsychotics, caution should be exercised when Leponex is prescribed with medicines known to increase the QTc interval [175].

Use in the elderly

It is recommended that treatment be initiated at a particularly low dose (12.5 mg given once on the first day) and subsequent dose increments be restricted to 25 mg/day [47].

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 [134,160].

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 [172].

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 [14,15,37,38].

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 [14,37,38].

Because of the possibility of additive effects, caution is essential when substances possessing anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly [14,15,37,38].

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS) [45,46].

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 [135].

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 [90,94,123,136-141].

As with other antipsychotics, caution should be exercised when Leponex is prescribed with medicines known to increase the QTc interval, or causing electrolyte imbalance [175].

Pharmacokinetic-related interactions

Clozapine is a substrate for many CYP 450 isoenzymes, in particular 1A2 [86,87] 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 [86,88,122,123,142-144].

No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines or type 1_C 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 [72,73,88,123], phenytoin [44] and rifampicin [123,144-149].
- 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 [123,150,151,163,169].

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 [43], erythromycin (3A4) [121-123,144], fluvoxamine (1A2) [75,88,89] and ciprofloxacin (1A2) [169].
- 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 [123,145].
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period [123,152-156].
- 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) [75,88,89], sertraline [118], fluoxetine [90] or citalopram [167].

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 [41].

Lactation

Animal studies suggest that clozapine is excreted in breast milk; therefore, mothers receiving Leponex should not breast-feed [41].

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 [163].

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 [41].

4.8 Undesirable effects [73,74,163]

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 3 Treatment-Emergent Adverse Experience Frequency estimate from Spontaneous and Clinical Trial Reports [163]

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.

Blood and lymphatic system disorders	
Common	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis [16-21]
Uncommon	Agranulocytosis [11,16-21,48,62]
Rare	Anaemia [168]
Very rare	Thrombocytopenia [63], thrombocythaemia [163]
Metabolism and nutrition disorders	
Common	Weight gain [40,41]
Rare	Impaired glucose tolerance, new onset diabetes [174], diabetes aggravated [163]
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia [70,123,132,133], hypercholesterolaemia [168], hypertriglyceridaemia [168]
Psychiatric disorders	
Common	Dysarthria [176]
Uncommon	Dysphemia [176]
Rare	Restlessness, agitation [65]
Nervous system disorders	
Very common	Drowsiness/sedation [13], dizziness [14]
Common	Blurred vision, headache [14], tremor [22], rigidity [22], akathisia [22], extrapyramidal symptoms [22], seizures/convulsions/myoclonic jerks [14, 49,50,64,157,158]
Rare	Confusion, delirium [65]
Very rare	Tardive dyskinesia [18,95-97], obsessive compulsive symptoms [173]
Cardiac disorders [23-29]	
Very common	Tachycardia [14,37,38]
Common	ECG changes [14]
Rare	Circulatory collapse, arrhythmias, myocarditis [28,29,66,123,129,130], pericarditis [51]
Very rare	Cardiomyopathy [161]
Vascular system disorders [23-29]	
Common	Hypertension [38], postural hypotension [14,37,38], syncope [14,37,38]
Rare	Thromboembolism [85]
Respiratory disorders	
Rare	Aspiration of ingested food [68], pneumonia and lower respiratory tract infection which may be fatal [170]
Very rare	Respiratory depression/arrest [14,37,38,67]

Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, dry mouth
Rare	Dysphagia [68]
Very rare	Parotid gland enlargement [159], intestinal obstruction/ileus/faecal impaction [69]
Hepatobiliary disorders	
Common	Elevated liver enzymes [23,30-32]
Rare	Hepatitis, cholestatic jaundice [28,29,33,34,119], pancreatitis [98,99]
Very rare	Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Renal and urinary disorders	
Common	Urinary incontinence, urinary retention
Very rare	Interstitial nephritis [100]
Reproductive system disorders	
Very rare	Priapism [52]
General disorders	
Common	Fatigue [13], benign hyperthermia, disturbances in sweating/temperature regulation
Uncommon	Neuroleptic malignant syndrome [41,45,46]
Very rare	Sudden unexplained death [21,35,36]
Investigations	
Rare	Increased CPK [69]

Very rare events of ventricular tachycardia, cardiac arrest and QT prolongation which may be associated with Torsades De Pointes have been observed although there is no conclusive causal relationship to the use of this medicine [175].

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 [40]. 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 [71].

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 Leponex ingestion [47]. (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 [47] because of the possibility of delayed reactions.

5 Pharmacological properties [1-5]

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 D_1, D_2 [41], D_3 and D_5 receptors [53,54], but shows high potency for the D_4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties [135].

Clinically Leponex produces rapid and marked sedation, and exerts antipsychotic effects in patients with schizophrenia resistant to other antipsychotic agents. In such cases, Leponex has proven effective in relieving both positive and negative schizophrenic symptoms in short- and long-term trials. In a double-blind clinical trial performed in 319 treatment-resistant patients, clinically relevant improvement was observed within 6 weeks in about 30% of the Leponex-treated patients [23]. Two open-label trials in which patients were treated for 12 months, showed clinically relevant improvement in 37% of patients within the first 6 weeks of treatment [23] and in an additional 39%-44% of patients by the end of 12 months [39,163]. The improvement was defined as a reduction of more than 20% from baseline in Brief Psychiatric Rating Scale Score [163]. In addition, improvement in some aspects of cognitive dysfunction has been described [76-81].

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 [82,163]. 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 [162-164].

Leponex is unique in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia. Furthermore, parkinsonian-like side effects and akathisia are rare [23,163]. In contrast to classical antipsychotics, clozapine produces little or no prolactin elevation [41], 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 [55] (see section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties [6-9]

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 [42]. 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 [56]. 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 [57].

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) [101-116].

Acute toxicity

Acute toxicity studies in mice, rats and guinea pigs revealed oral LD_{50} values of 190 to 681 mg/kg body weight. In dogs, the oral LD_{50} was approximately 145 mg/kg; signs of overdosage consisted of muscular tremor, aggressive behaviour and vomiting [101,102].

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) [103-107].

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 [108-111].

Reproductive toxicity [112-116]

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 Shelf life

Leponex tablets: 3 to 5 years, depending on climate and container.

6.4 Special precautions for storage

No special precautions for storage.

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

6.5 Nature and content of container

Leponex tablets are available in bottles made of type III brown glass with a closure consisting of a stopper made of colourless low-density polyethylene, and 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.

This is a non-referenced document.