The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

SUMMARY INFORMATION ON REFERRAL OPINION FOLLOWING ARBITRATION

PURSUANT TO ARTICLE 30 OF COUNCIL DIRECTIVE 2001/83/EC FOR

Leponex and associated names

International NonProprietary Name (INN): clozapine

BACKGROUND INFORMATION

Clozapine is an antipsychotic drug with a broad range of antipsychotic activity. The low affinity for D_2 receptor deserves clozapine a unique profile, as its use is not associated with extrapyramidal side effects. However, due to a risk of agranulocytosis, the therapeutic indication has been restricted to schizophrenic patients resistant or intolerant to other antipsychotics. Furthermore, periodic white cell counting has been required throughout treatment, being more frequent during the first 18 weeks of treatment where 88% of the cases of agranulocytosis appear.

From the registrations in Member States, different Summaries of Product Characteristics have been issued, based on national, divergent decisions. On 31 October 2000, France presented to the EMEA a referral under Article 30 of Directive 2001/83/EC[1].

The referral procedure started on 26 April 2001 in order to harmonise the Summaries of Product Characteristics (SPC) within the Member States and Norway and Iceland. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, scientific discussion within the Committee and comments from the Marketing Authorisation Holders, was of the opinion that the benefit/risk ratio of clozapine is considered to be favourable for the agreed indications. The CPMP issued a positive opinion, on 2 August 2002, recommending the harmonisation of the SPC for Leponex and associated names. The grounds for referral are appended to this report.

An overall summary of the scientific evaluation is provided together with the amended summary of product characteristics.

A Decision was issued by the European Commission on 12 November 2002.

[1] Corresponding to Article 11 of Directive 75/319/EEC, for referrals presented before 18 December 2001

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SCIENTIFIC CONCLUSIONS

Overall Summary of the Scientific Evaluation of Leponex and Associated names

- Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (sections 6).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic Indications.
For all of the European Union Member States, the approved indication for Leponex is for the treatment of schizophrenia, however there was a disharmony in the labelling relating to;

- The indication "Psychotic disorders in Parkinson's disease (PD) in case of failure of the usual therapeutic strategy". Leponex is approved for use in this second indication in France and Italy and the MAH has submitted this indication to the Health Authority in Spain.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Leponex, the following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications
Leponex is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

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

Section 4.2. Posology and method of administration
The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to therapeutic daily dose range.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Leponex the following was considered to be the most suitable harmonised Section 4.2 Posology text:

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 $\geq 3500/mm^3$ ($3.5x10^9/L$) and an ANC $\geq 2000/mm^3$ ($2.0x10^9/L$) within standardised normal limits.

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

The following dosages are recommended:

Treatment-resistant schizophrenic patients

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 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 to 100 mg at half-weekly or, preferably, weekly intervals.

Use in the elderly
Initiation of treatment is recommended 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
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 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion 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 leukopenia), 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 special precautions for use), but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out 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 other antipsychotic should first be discontinued by tapering the dosage downwards.

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

The starting dose must not exceed 12.5 mg/day (half a 25 mg tablet), taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

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).

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.

- Safety issues

Section 4.3. Contra-indications

The MAH was requested to propose and scientifically justify a common EU wide approach as the contraindications text was considered to differ to a large extent between Member States especially relating to:

- Alcoholic and toxic psychosis/comatose conditions
- Circulatory collapse
- CNS depression
- Paralytic ileus
- Risk of narrow angle glaucoma
- Risk of urinary retention

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Leponex, the most suitable harmonised Section 4.3 Contraindications text was approved (See Annex). The text approved in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Leponex, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex). The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Leponex is favourable for use relating to treatment-resistant schizophrenic patients and psychotic disorders occurring during the course of Parkinson's disease in cases where standard treatment has failed.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion. The major divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision concerning this referral for arbitration; the text was valid at that time. It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<Leponex and associated names – see Annex I> <strength> tablets.

(To be implemented nationally)

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

- **with schizophrenia who are non-responsive to or intolerant of antipsychotic drug treatment, or with psychosis in Parkinson's disease when other treatment strategies have failed (see point 4.1)**
- **who have initially normal leukocyte findings (white blood cell count ≥ 3500/mm3($3.5x10^9$/L), and ANC ≥ 2000/mm3 ($2.0x10^9$/L)), and**
- **in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) 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.

<u>Myocarditis</u>

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, tachypnoea) 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.

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg, 50 mg or 100 mg clozapine.

For excipients, see section 6.1 List of excipients

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

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

4.2 Posology and method of administration

The dosage must be adjusted individually. For each patient the lowest effective dose should be used.

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

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Use in the elderly
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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 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion 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 leukopenia), 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 special precautions for use), but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out 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 other antipsychotic should first be discontinued by tapering the dosage downwards.

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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).

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

- Hypersensitivity to the active substance or to any of the excipients.
- 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 special precautions for use

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 $\geq 3500/mm^3$ ($3.5x10^9/L$) and ANC $\geq 2000/mm^3$ ($2.0x10^9/L$), 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 clozapine 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 $3000/mm^3$ ($3.0x10^9/L$) or the ANC is less than $1500/mm^3$ ($1.5x10^9/L$) 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 initiating Leponex treatment to ensure that only patients with normal WBC counts and ANC (WBC count ≥ 3500/mm^3 ($3.5x10^9$/L) and ANC ≥ 2000/mm^3 ($2.0x10^9$/L)) will receive the drug. After the start of Leponex treatment the WBC count and ANC must be monitored weekly for the first 18 weeks, and at least at four-week intervals thereafter.

Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Leponex or until haematological recovery has occurred (see below Low WBC count/ANC). 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/ANC

If, during Leponex therapy, either the WBC count falls to between 3500/mm^3 ($3.5x10^9$/L) and 3000/mm^3 ($3.0x10^9$/L) or the ANC falls to between 2000/mm^3 ($2.0x10^9$/L) and 1500/mm^3 ($1.5x10^9$/L), haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3000-3500/mm^3 (3.0-$3.5x10^9$/L) and 1500-2000/mm^3 (1.5-$2.0x10^9$/L), respectively, or higher.

Immediate discontinuation of Leponex treatment is mandatory if either the WBC count is less than 3000/mm^3 ($3.0x10^9$/L) or the ANC is less than 1500/mm^3 ($1.5x10^9$/L) during Leponex treatment. 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.

Blood cell count		Action required
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
≥ 3500 (≥$3.5x10^9$)	≥ 2000 (≥$2.0x10^9$)	Continue Leponex treatment
3000-3500 ($3.0x10^9$-$3.5x10^9$)	1500-2000 ($1.5x10^9$-$2.0x10^9$)	Continue Leponex treatment, sample blood twice weekly until counts stabilise or increase
<3000 (<$3.0x10^9$)	<1500 (<$1.5x10^9$)	Immediately stop Leponex treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

If Leponex has been withdrawn and either a further drop in the WBC count below 2000/mm^3 ($2.0x10^9$/L) occurs or the ANC falls below 1000/mm^3 ($1.0x10^9$/L), the management of this condition must be guided by an experienced haematologist.

Discontinuation of therapy for haematological reasons
Patients in whom Leponex has been discontinued as a result of either WBC 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 and the dose should be re-titrated (see section 4.2 Posology and method of administration).

Other precautions
In the event of **eosinophilia**, discontinuation of Leponex is recommended if the eosinophil count rises above 3000/mm^3 ($3.0x10^9$/L); therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 ($1.0x10^9$/L).

In the event of **thrombocytopenia**, discontinuation of Leponex therapy is recommended if the platelet count falls below 50 000/mm^3 ($50x10^9$/L).

Orthostatic hypotension, with or without syncope, can occur during Leponex treatment. Rarely, 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 may occur even after the first dose. Therefore, patients commencing Leponex treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

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 two months of treatment, and/or 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. 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.

Patients with stable pre-existing liver disorders may receive Leponex, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible **liver dysfunction**, such as nausea, vomiting and/or anorexia, develop during Leponex therapy. 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 "Re-starting therapy" under section 4.2) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of the drug.

Leponex exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**. Probably on account of its anticholinergic properties, Leponex has been associated with varying degrees of **impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction**, **faecal impaction** and **paralytic ileus** (see section 4.8 Undesirable effects). On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotic*s*, 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 reoccurrence. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.

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

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).

Orthostatic hypotension can occur with Leponex treatment and there have been reports of tachycardia, which may be sustained. Elderly patients, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

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

4.5 Interaction with other medicinal products and other forms of interaction

Contraindication of concomitant use
Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Leponex (see section 4.3. Contraindications).

Long-acting depot antipsychotics (which have myelosuppressive potential) should not be used concurrently with Leponex because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia (see section 4.3 Contraindications).

Alcohol should not be used concomitantly with Leponex due to possible potentiation of sedation.

Precautions including dose adjustment
Leponex may enhance the central effects of CNS depressants such as narcotics, antihistamines, and benzodiazepines. Particular caution is advised when Leponex therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic drug. 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. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment.

Because of the possibility of additive effects, caution is essential in the concomitant administration of drugs possessing anticholinergic, hypotensive, or respiratory depressant effects.

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

Concomitant administration of drugs known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of clozapine, and the dose of clozapine may need to be reduced to prevent undesirable effects. This is more important for CYP 1A2 inhibitors such as caffeine (see below) and the selective serotonin reuptake inhibitors fluvoxamine and (more controversial) paroxetine. Some of the other serotonin reuptake inhibitors such as fluoxetine and sertraline are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less likely. Similarly, pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin, and protease inhibitors are unlikely, although some have been reported. Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrese the plasma levels of clozapine, leading to reduced efficacy. Drugs known to induce the activity of cytochrome P450 enzymes and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppresive potential), phenytoin and rifampicin.

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

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.

Caution is called for in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines and type I_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

An outline of drug interactions believed to be most important with Leponex is given in Table 1 below (this is not an exhaustive list).

Table 1: Reference to the most common drug interactions with Leponex

Drug	**Interactions**	**Comments**
Bone marrow suppressants (e.g. carbamazapine, chloramphenicol, sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicilamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression	Leponex **should not be used** concomitantly with other agents having a well known potential to suppress bone marrow function (see Section 4.3 Contraindications)
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest	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.
Anticholinergics	Leponex potentiates the action of these drugs through additive anticholinergic activity	Observe patients for anticholinergic side –effects, e.g. constipation, especially when using to help control hypersalivation
Antihypertensives	Leponex can potentiate the hypotensive effects of these drugs due to its sympathomimetic antagonistic effects	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
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these drugs	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
Highly protein bound drugs (e.g. warfarin and digoxin)	Leponex may cause an increase in plasma concentration of these	Patients should be monitored for the occurrence of side effects associated with these drugs, and

	drugs due to displacement from plasma proteins	doses of the protein bound drug adjusted, if necessary
Phenytoin	Addition of phenytoin to Leponex drug regimen may cause a decrease in the clozapine plasma concentrations	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS)	Observe for signs and symptoms of NMS

4.6 Pregnancy and lactation

Pregnancy
For Leponex, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see 5.3). Caution should be exercised when prescribing to pregnant women.

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 child-bearing potential
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 2 below summarises the estimated incidence of agranulocytosis for each Leponex treatment period.

Table 2:Estimated incidence of agranulocytosis[1]

Treatment period	Incidence of agranulocytosis per 100,000 person-weeks[2] of observation
Weeks 0-18	32.0
Weeks 19-52	2.3
Weeks 53 and higher	1.8

[1] From the UK Clozaril Patient Monitoring Service lifetime registry experience between 1989 and 2001.

[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 Clozaril 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.

The table below (Table 3) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

Table 3: Treatment-Emergent Adverse Experience Frequency Estimate from Spontaneous and Clinical Trial Reports

Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <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
Uncommon	Agranulocytosis
Very rare	Thrombocytopenia
Metabolism and nutrition disorders	
Common	Weight gain
Rare	Impaired glucose tolerance, diabetes mellitus
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridaemia
Psychiatric disorders	
Rare	Restlessness, agitation
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks
Rare	Confusion, delirium
Very rare	Tardive dyskinesia
Cardiac disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, arrhythmias, myocarditis, pericarditis/pericardial effusion
Very rare	Cardiomyopathy, cardiac arrest
Vascular disorders	
Common	Hypertension, postural hypotension, syncope
Rare	Thromboembolism
Respiratory disorders	
Rare	Aspiration of ingested food
Very rare	Respiratory depression/arrest
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, anorexia, dry mouth
Rare	Dysphagia
Very rare	Parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction
Hepatobiliary disorders	
Common	Elevated liver enzymes
Rare	Hepatitis, cholestatic jaundice, pancreatitis
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
Reproductive system disorders	
Very rare	Priapism
General disorders	
Common	Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation
Uncommon	Neuroleptic malignant syndrome
Very rare	Sudden unexplained death
Investigations	
Rare	Increased CPK

4. 9 Overdose

In cases of acute intentional or accidental Leponex overdosage for which information on the outcome is available, mortality to date 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 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, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment
Gastric lavage and/or 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 D_1, D_2, D_3 and D_5 receptors, 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.

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 mainly 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 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.

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.

A potentially serious adverse reaction caused by Leponex therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7%, respectively. In view of this risk,

the use of Leponex should be limited to patients who are treatment-resistant or patients with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1 Therapeutic indications) and in whom regular haematological examinations can be performed (see sections 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

5.2 Pharmacokinetic properties

The absorption of orally administered Leponex is 90 to 95%; neither the rate nor the extent of absorption is influenced by food.

Leponex 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. Leponex 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.

Leponex is almost completely metabolised before excretion. Of the main metabolites only the demethyl 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Silica, colloidal anhydrous
Polyvinylpyrrolidone
Talc
Maize starch
Lactose

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

25 mg tablets: glass bottles 5 years, blister packs 4 years
50 mg tablets: blister packs 3 years
100 mg tablets: glass bottles 5 years; blister packs 4 years

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 contents of container

(See Annex I - to be implemented nationally)

Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

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

7. MARKETING AUTHORISATION HOLDER

(See Annex I - to be implemented nationally)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT