For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

LOZAPIN

1. **Generic Name:**

   Clozapine Tablets I.P

2. **Qualitative and quantitative composition:**

   LOZAPIN-25
   Each uncoated tablet contains:
   Clozapine I.P.....25mg

   LOZAPIN-50
   Each uncoated tablet contains:
   Clozapine I.P.....50 mg

   LOZAPIN-100
   Each uncoated tablet contains:
   Clozapine I.P.....100 mg

   Excipients for 25, 50,100mg : lactose, starch, magnesium stearate, talc, polyvinyl pyrrolidone (k-30) ip, colloidal silicon dioxide (aerosil)ip, starch dried

3. **Dosage form and strength**

   Dosage form: Uncoated tablets
   Strength: Torasemide 25mg, 50mg and 100mg.

4. **Clinical particulars**

4.1 Therapeutic indication:

Indicated in the management of Schizophrenic patients

4.2 Posology and method of administration

Posology

The dosage must be adjusted individually. For each patient the lowest effective dose should be used. For doses not realisable/practicable with one strength, other strengths of this medicinal product are available. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.

Initiation of LOZAPIN treatment must be restricted to those patients with a WBC count ≥ 3500/mm3 (3.5x109/l) and an ANC ≥ 2000/mm3 (2.0x109/l) within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacodynamic and pharmacokinetic interactions with LOZAPIN, such as benzodiazepines or selective serotonin re-uptake inhibitors

Switching from a previous antipsychotic therapy to LOZAPIN

It is generally recommended that LOZAPIN should not be used in combination with other antipsychotics. When LOZAPIN 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.

The following dosages are recommended:

Treatment-resistant schizophrenic patients

Starting therapy

12.5 mg once or twice on the first day, followed by 25 mg once or twice 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.

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.

Maximum dose

To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day. However, 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 LOZAPIN therapy, a gradual reduction in dose over a 1 to 2-week period is recommended. If abrupt discontinuation is necessary, the patient should be carefully observed for the occurrence of withdrawal reactions.

Re-starting therapy

In patients in whom the interval since the last dose of LOZAPIN exceeds 2 days, treatment should be re-initiated with 12.5 mg 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, but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.

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

Starting therapy

The starting dose must not exceed 12.5 mg/day, 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.

Therapeutic dose range

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.

Maximum dose

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.

Maintenance dose

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, LOZAPIN 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. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Special populations

Hepatic impairment

Patients with hepatic impairment should receive LOZAPIN with caution along with regular monitoring of liver function tests.

Paediatric population

No paediatric studies have been performed. The safety and efficacy of LOZAPIN in children and adolescents under the age of 16 years have not yet been established. It should not be used in this group until further data become available.

Patients 60 years of age and older

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.

Method of administration

LOZAPIN is administered orally.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in.
- 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 LOZAPIN-induced agranulocytosis.

• LOZAPIN treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged

• 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.

4.4 Special warnings and precautions for use

Agranulocytosis

LOZAPIN can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of white blood cell (WBC) counts and absolute neutrophil count (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 LOZAPIN, its use is limited to patients in whom therapy is indicated.

• who have initially normal leukocyte findings (WBC count ≥ 3500/mm3 (3.5x109/l) and ANC ≥ 2000/mm3 (2.0x109/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 LOZAPIN.

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. The treating physician should consider performing a pre-treatment ECG.

Prescribing physicians must 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 LOZAPIN 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 LOZAPIN treatment. Patients in whom LOZAPIN has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to LOZAPIN.
At each consultation, a patient receiving LOZAPIN must 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 LOZAPIN.
Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may only be started on LOZAPIN with the agreement of a haematologist.

White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring

WBC and differential blood counts must be performed within 10 days prior to initiating LOZAPIN treatment to ensure that only patients with normal WBC counts and ANC (WBC count ≥ 3500/mm3 (3.5x109/l) and ANC ≥ 2000/mm3 (2.0x109/l)) will receive LOZAPIN. After the start of LOZAPIN treatment regular WBC count and ANC must be performed and 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 LOZAPIN or until haematological recovery has occurred (see "Low WBC count/ANC" below). At each consultation, the patient must 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 LOZAPIN therapy, either the WBC count falls to between 3500/mm3 (3.5x109/l) and 3000/mm3 (3.0x109/l) or the ANC falls to between 2000/mm3 (2.0x109/l) and 1500/mm3 (1.5x109/l), haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3000-3500/mm3 (3.0-3.5x109/l) and 1500-2000/mm3 (1.5-2.0x109/l), respectively, or higher.

Immediate discontinuation of LOZAPIN treatment is mandatory if either the WBC count is less than 3000/mm3 (3.0x109/l) or the ANC is less than 1500/mm3 (1.5x109/l) during LOZAPIN 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, LOZAPIN should be discontinued after the first blood count.

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

Table 1

Blood cell count		Action required
WBC/mm^3 (/l)	ANC/mm^3 (/l)	
≥ 3500 (≥ $3.5x10^9$)	≥ 2000 (≥ $2.0x10^9$)	Continue LOZAPIN treatment
Between ≥ 3000 and < 3500 (≥ $3.0x10^9$ and < $3.5x10^9$)	Between ≥ 1500 and < 2000 (≥ $1.5x10^9$ and < $2.0x10^9$)	Continue LOZAPIN treatment, sample blood twice weekly until counts stabilise or increase
< 3000 (< $3.0x10^9$)	< 1500 (< $1.5x10^9$)	Immediately stop LOZAPIN treatment,

		sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

If LOZAPIN has been withdrawn and either a further drop in the WBC count below 2000/mm3 (2.0x109/l) occurs or the ANC falls below 1000/mm3 (1.0x109/l), the management of this condition must be guided by an experienced haematologist.

Discontinuation of therapy for haematological reasons

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

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 LOZAPIN 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 LOZAPIN 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.

Other precautions

This medicinal product contains lactose monohydrate.

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

Eosinophilia

In the event of **eosinophilia**, discontinuation of LOZAPIN 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).

Thrombocytopenia

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

Cardiovascular disorders

Orthostatic hypotension, with or without syncope, can occur during LOZAPIN 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 a benzodiazepine or any other psychotropic agent and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients starting LOZAPIN 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 LOZAPIN 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 LOZAPIN 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 is suspected, LOZAPIN treatment should be promptly stopped and the patient immediately referred to a cardiologist.

In patients who are diagnosed with cardiomyopathy while on LOZAPIN treatment, there is potential to develop mitral valve incompetence. Mitral valve incompetence has been reported in cases of cardiomyopathy related to LOZAPIN treatment. These cases of mitral valve incompetence reported either mild or moderate mitral regurgitation on two-dimensional echocardiography (2DEcho).

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

Myocardial infarction

There have been post marketing reports of **myocardial infarction** including fatal cases. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

QT interval prolongation

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

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval.

Cerebrovascular adverse events

An approximately 3-fold increased risk of **cerebrovascular adverse events** has been seen in randomised placebo controlled clinical trials 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. Clozapine should be used with caution in patients with risk factors for stroke.

Risk of thromboembolism

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

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with LOZAPIN and preventive measures undertaken.

Seizures

Patients with a history of epilepsy should be closely observed during LOZAPIN therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced and, if necessary, an anti-convulsant treatment should be initiated.

Anticholinergic effects

LOZAPIN 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, LOZAPIN has been

associated with varying degrees of **impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction**, **faecal impaction, paralytic ileus, megacolon and intestinal infarction ischaemia**. 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 antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.

Fever

During LOZAPIN 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. If the diagnosis of NMS is confirmed, LOZAPIN should be discontinued immediately and appropriate medical measures should be administered.

Falls

LOZAPIN may cause seizures, somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Metabolic changes

Atypical antipsychotic drugs, including LOZAPIN, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.

Hyperglycaemia

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. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including LOZAPIN. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight gain

Weight gain has been observed with atypical antipsychotic use, including LOZAPIN. Clinical monitoring of weight is recommended.

Rebound, withdrawal effects

Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal 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.

Special populations

Hepatic impairment

Patients with stable pre-existing liver disorders may receive LOZAPIN, 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 LOZAPIN therapy. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with LOZAPIN must be discontinued. It may be resumed only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of LOZAPIN.

Patients aged 60 years and older

Initiation of treatment in patients aged 60 years and older is recommended at a lower dose.

Orthostatic hypotension can occur with LOZAPIN treatment and there have been reports of tachycardia, which may be sustained. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of LOZAPIN, such as urinary retention and constipation.

Increased mortality in elderly people with dementia:

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

LOZAPIN is not approved for the treatment of dementia-related behavioural disturbances.

4.5 Drug-Interaction

Contraindication of concomitant use

Substances known to have a substantial potential to depress bone marrow function must not be used concurrently with LOZAPIN.

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

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

Precautions including dose adjustment

LOZAPIN may enhance the central effects of CNS depressants such as narcotics, antihistamines and benzodiazepines. Particular caution is advised when LOZAPIN therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic agent. 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 substances possessing anticholinergic, hypotensive, or respiratory depressant effects.

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

Concomitant administration of substances 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), perazine and the selective serotonin reuptake inhibitor fluvoxamine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine, and, to a lesser degree, 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. Hormonal contraceptives (including combinations of estrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore initiation or discontinuation of hormonal contraceptives, may require dose adjustment of clozapine according to the individual medical need. 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.

Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated.

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine, leading to reduced efficacy. Substances 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. Known inducers of CYP1A2, such as omeprazole, may lead to decreased clozapine levels. The potential for reduced efficacy of clozapine should be considered when it is used in combination with these substances.

Other

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 LOZAPIN 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 substances which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines and type 1_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval, or causing electrolyte imbalance.

An outline of drug interactions believed to be most important with LOZAPIN is given in Table 2 below. The list is not exhaustive.

Table 2: Reference to the most common drug interactions with LOZAPIN

Drug	**Interactions**	**Comments**
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	LOZAPIN **must not be used** concomitantly with other agents having a well known potential to suppress bone marrow function.
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 agents together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when LOZAPIN is added to an established benzodiazepine regimen.
Anticholinergics	LOZAPIN potentiates the action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensives	LOZAPIN can potentiate the hypotensive effects of these agents due to its sympathomimetic antagonistic effects.	Caution is advised if LOZAPIN 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 substances.	Caution is advised if LOZAPIN 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 substances (e.g. warfarin and digoxin)	LOZAPIN may cause an increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.
Phenytoin	Addition of phenytoin to LOZAPIN 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.
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances e.g. fluvoxamine, caffeine, ciprofloxacin, perazine or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there may be a decrease in clozapine levels. The effect of CYP2C19 inhibition may be minimal.

4.6 Fertility, pregnancy and lactation

Pregnancy

For clozapine, 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. Caution should be exercised when prescribing to pregnant women.

Neonates exposed to antipsychotics (including LOZAPIN) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia,

hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breastfeeding

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving LOZAPIN should not breast-feed.

Fertility

Limited data available on the effects of clozapine on human fertility are inconclusive. In male and female rats, clozapine did not affect fertility when administered up to 40 mg/kg, corresponding to a human equivalence dose of 6.4 mg/kg or approximately a third of the maximum permissible adult human dose.

Women of child-bearing potential

A return to normal menstruation may occur as a result of switching from other antipsychotics to LOZAPIN. 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 LOZAPIN 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

Summary of the safety profile

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. 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 reactions, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever. The most common side effects are drowsiness/sedation, dizziness, tachycardia, constipation, and hypersalivation.

Data from the clinical trials experience showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leukopenia, somnolence, dizziness (excluding vertigo) and psychotic disorder.

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to LOZAPIN treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory. Table 3 below summarises the estimated incidence of agranulocytosis for each LOZAPIN treatment period.

Table 3: Estimated incidence of agranulocytosis1

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 LOZAPIN 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 were exposed to LOZAPIN 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 LOZAPIN 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 LOZAPIN treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of LOZAPIN 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.

Nervous system disorders

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

LOZAPIN 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 the possibility of a pharmacokinetic interaction should be considered. In rare cases, patients treated with LOZAPIN may experience delirium.

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

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, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with LOZAPIN.

A minority of LOZAPIN-treated patients experience ECG changes similar to those seen with other antipsychotics, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of LOZAPIN. 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 LOZAPIN. 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 LOZAPIN.

Vascular disorders

Rare cases of thromboembolism have been reported.

Respiratory system

Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse.

Gastrointestinal system

Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur. Rarely LOZAPIN 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, LOZAPIN should be discontinued. In rare cases, acute pancreatitis has been reported.

Renal disorders

Isolated cases of acute interstitial nephritis have been reported in association with LOZAPIN 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 LOZAPIN either alone or in combination with lithium or other CNS-active agents.

Acute withdrawal reactions have been reported.

Tabulated list of adverse reactions:

The table below (Table 4) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

Table 4: 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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations	
Not known:	Sepsis*
Blood and lymphatic system disorders	
Common:	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon:	Agranulocytosis
Rare:	Anaemia
Very rare:	Thrombocytopenia, thrombocythaemia
Immune system disorders	
Not known:	Angioedema*, leukocytoclastic vasculitis*, Drug rash with eosinophilia and systemic symptoms (DRESS)*
Endocrine disorders	
Not known:	Pseudophaeochromocytoma*
Metabolism and nutrition disorders	
Common:	Weight gain
Rare:	Diabetes mellitus, impaired glucose tolerance, obesity*
Very rare:	Hyperosmolar coma, ketoacidosis, severe hyperglycaemia, hypercholesterolemia, hypertriglyceridemia
Psychiatric disorders	
Common:	Dysarthria
Uncommon:	Dysphemia
Rare:	Agitation, restlessness
Nervous system disorders	
Very common:	Drowsiness/sedation, dizziness
Common:	Seizures/convulsions/myoclonic jerks, extrapyramidal symptoms, akathisia, tremor, rigidity, headache
Uncommon:	Neuroleptic malignant syndrome
Rare:	Confusion, delirium
Very rare:	Tardive dyskinesia, obsessive compulsive symptoms
Not known:	Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*, restless leg syndrome*
Eye disorders	
Common:	Blurred vision

Cardiac disorders	
Very common:	Tachycardia
Common:	ECG changes
Rare:	Circulatory collapse, arrhythmias, myocarditis, pericarditis/ pericardial effusion
Very rare:	Cardiomyopathy, cardiac arrest
Not known:	Myocardial infarction*,**, myocarditis*,**, chest pain/angina pectoris*, atrial fibrillation*, palpitations*, mitral valve incompetence associated with clozapine related cardiomyopathy*
Vascular disorders	
Common:	Syncope, postural hypotension, hypertension
Rare:	Thromboembolism
Not known:	Hypotension*, Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
Rare:	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal, sleep apnoea syndrome*
Very rare:	Respiratory depression/arrest
Not known:	Pleural effusion*, nasal congestion*
Gastrointestinal disorders	
Very common:	Constipation, hypersalivation
Common:	Nausea, vomiting, anorexia, dry mouth
Rare:	Dysphagia
Very rare:	Intestinal obstruction/paralytic ileus/faecal impaction, parotid gland enlargement
Not known:	Megacolon*,**, intestinal infarction/ischaemia*,**, intestinal necrosis*,**, intestinal ulceration*,** and intestinal perforation*,**, diarrhoea*, abdominal discomfort/heartburn/dyspepsia*, colitis*
Hepatobiliary disorders	
Common:	Elevated liver enzymes
Rare:	Pancreatitis, hepatitis, cholestatic jaundice
Very rare:	Fulminant hepatic necrosis
Not known:	Hepatic steatosis*, hepatic necrosis*, hepatotoxicity*, hepatic fibrosis*, hepatic cirrhosis*, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant*.
Skin and subcutaneous tissue disorders	
Very rare:	Skin reactions
Not known	Pigmentation disorder*
Musculoskeletal and connective tissue disorders	
Not known:	Rhabdomyolysis*, muscle weakness*, muscle spasms*, muscle pain*, systemic lupus erythematosus*

Renal and urinary disorders	
Common:	Urinary retention, urinary incontinence
Very rare:	Tubulointerstitial nephritis
Not known:	Renal failure*, Nocturnal enuresis*
Pregnancy, puerperium and perinatal conditions	
Not known	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	
Very rare:	Priapism
Not known	Retrograde ejaculation*
General disorders and administration site conditions	
Common:	Benign hyperthermia, disturbances in sweating/temperature regulation, fever, fatigue
Very rare:	Sudden unexplained death
Not known:	Polyserositis*
Investigations	
Rare:	Increased CPK
Injury, poisoning and procedural complications	
Uncommon:	Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)*

* Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases.

** These adverse drug reactions were sometimes fatal.

Very rare events of ventricular tachycardia 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.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

In cases of acute intentional or accidental LOZAPIN overdose 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 LOZAPIN, 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

There are no specific antidotes for LOZAPIN.

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

Mechanism of action

LOZAPIN has been shown to be an antipsychotic agent that is different from classic antipsychotics.

In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine-receptor-blocking activity at D1, D2, D3 and D5 receptors, but shows high potency for the D4 receptor.

Pharmacodynamic effects

LOZAPIN has potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinical efficacy and safety

Clinically LOZAPIN produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatment. In such cases, LOZAPIN 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, LOZAPIN produces fewer major extrapyramidal reactions such as acute dystonia, parkinsonian-like side effects and akathisia. In contrast to classic antipsychotics, LOZAPIN produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea and impotence.

A potentially serious adverse reaction caused by LOZAPIN therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7%, respectively. In view of this risk, the use of LOZAPIN should be limited to patients who are treatment-resistant or patients

with psychosis in Parkinson's disease when other treatment strategies have failed and in whom regular haematological examinations can be performed.

5.2 Pharmacokinetic properties

Absorption

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

LOZAPIN is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60%.

Distribution

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. LOZAPIN is approximately 95% bound to plasma proteins.

Biotransformation/metabolism

LOZAPIN is almost completely metabolised before excretion by CYP1A2 and CYP3A4, and to some extent by CYP2C19 and CYP2D6. 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.

Elimination

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.

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.

Linearity/non-linearity

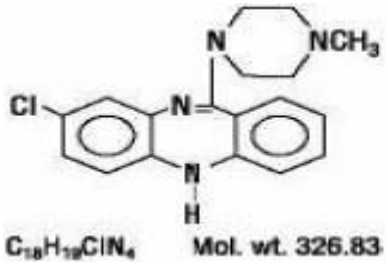
Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.

6. Pharmaceutical particulars

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential

7. Description

Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics. Clozapine 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. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors. It is designated chemically as 8-chloro-11(4 Methyl piperazin 1-y1)5H,Dibenzo [b,e,] [1,4] diazepine and has a molecular eight of 326.8. Its empirical formula is C18H19ClN4 and its structural formula is:



Excipients FOR 25,50,100mg : Lactose, starch, magnesium stearate, talc, POLYVINYL PYRROLIDONE (K-30) IP, COLLOIDAL SILICON DIOXIDE (AEROSIL)IP, STARCH DRIED

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

LOZAPIN is available in Blister of 10 Tablets

8.4 Storage and handing instructions:

Sore at a temperature not exceeding 30°c, protected from light and moisture.

Keep out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

LOZAPIN

Clozapine Tablets I.P

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What LOZAPIN is and what it is used for

9.2 What you need to know before you take LOZAPIN

9.3 How to take LOZAPIN

9.4 Possible side effects

9.5 How to store LOZAPIN

9.6 Contents of the pack and other information

9.1. What LOZAPIN is and what it is used for

The active ingredient of LOZAPIN is clozapine which belongs to a group of medicines called antipsychotics (medicines that are used to treat specific mental disorders such as psychosis).

LOZAPIN is used to treat people with schizophrenia in whom other medicines have not worked. Schizophrenia is a mental illness which affects how you think, feel and behave. You should only use this medicine if you have already tried at least two other antipsychotic medicines, including one of the newer atypical antipsychotics, to treat schizophrenia, and these medicines did not work, or caused severe side effects that cannot be treated.

LOZAPIN is also used to treat severe disturbances in the thoughts, emotions and behaviour of people with Parkinson's disease in whom other medicines have not worked.

9.2. What you need to know before you take LOZAPIN Do not take LOZAPIN Tablets if:

Do not take LOZAPIN if you are

- -are allergic (hypersensitive) to clozapine or any of the other ingredients of LOZAPIN.
- – are not able to have regular blood tests.
- – have ever been told you have a low white blood cell count (e.g. leucopenia or agranulocytosis), especially if this was caused by medicines. This does not apply if you have had low white blood cell count caused by previous chemotherapy.
- – had to stop using LOZAPIN previously because of severe side effects (e.g. agranulocytosis or heart problems).
- – are being or have been treated with long-acting depot injections of antipsychotics.
- – suffer from bone marrow disease or have ever suffered from bone marrow disease.
- – suffer from uncontrolled epilepsy (seizures or fits).
- – have an acute mental illness caused by alcohol or drugs (e.g. narcotics).
- – suffer from reduced consciousness and severe drowsiness.
- – suffer from circulatory collapse which may occur as a result of severe shock.
- – suffer from any severe kidney disease.
- – suffer from myocarditis (an inflammation of the heart muscle).
- – suffer from any other severe heart disease.
- – have symptoms of active liver disease such as jaundice (yellow colouring of the skin and eyes,
- feeling sick and loss of appetite).
- – suffer from any other severe liver disease.
- – suffer from paralytic ileus (your bowel does not work properly and you have severe
- constipation).
- – use any medicine that stops your bone marrow from working properly.
- – use any medicine that reduces the number of white cells in your blood.
- If any of the above applies to you, tell your doctor and do not take LOZAPIN.
- LOZAPIN must not be given to anyone who is unconscious or in a coma.
- Warnings and Precautions

Warnings and precautions

The safety measures mentioned in this section are very important. You must comply with them to minimise the risk of serious life-threatening side effects.

Before you start treatment with LOZAPIN, tell your doctor if you have or ever had:

– blood clots or family history of blood clots, as medicines like these have been associated with formation of blood clots.

– glaucoma (increased pressure in the eye).

– diabetes. Elevated (sometimes considerably) blood sugar levels, has occurred in patients with or without diabetes mellitus in their medical history.

– prostate problems or difficulty in urinating.

– any heart, kidney or liver disease.

– chronic constipation or if you are taking medicines which cause constipation (such as anticholinergics).

– galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

– controlled epilepsy.

– large intestine diseases.

– abdominal surgery.

– a heart disease or family history of abnormal conduction in the heart called "prolongation of the QT interval".

– a risk for having a stroke, for example if you have high blood pressure, cardiovascular problems or blood vessel problems in the brain.

Tell your doctor immediately before taking the next LOZAPIN tablet if you:

– get signs of a cold, fever, flu-like symptoms, sore throat or any other infection. You will have to have an urgent blood test to check if your symptoms are related to your medicine.

– have a sudden rapid increase in body temperature, rigid muscles which may lead to unconsciousness (neuroleptic malignant syndrome) as you may be experiencing a serious side effect which requires immediate treatment.

– have fast and irregular heartbeat, even when you are at rest, palpitations, breathing problems, chest pain or unexplained tiredness. Your doctor will need to check your heart and if necessary refer you to a cardiologist immediately.

– experience nausea (feeling sick), vomiting (being sick) and/or loss of appetite. Your doctor will need to check your liver.

– experience constipation, abdominal pain, abdominal tenderness, fever, bloating and/or

bloody diarrhoea. Your doctor will need to examine you.

Medical check-ups and blood tests

Before you start taking LOZAPIN, your doctor will ask about your medical history and do a blood test to ensure that your white blood cells count is normal. It is important to find this out, as your body needs white blood cells to fight infections.

Make sure that you have regular blood tests before you start treatment, during treatment and after you stop treatment with LOZAPIN.

– Your doctor will tell you exactly when and where to have the tests. LOZAPIN may only be taken if

You have a normal blood count.

– LOZAPIN can cause a serious decrease in the number of white cells in your blood

(agranulocytosis). Only regular blood tests can tell the doctor if you are at risk of developing

agranulocytosis.

– During the first 18 weeks of treatment, tests are needed once a week. Afterwards, tests are

needed at least once a month.

– If there is a decrease in the number of white blood cells, you will have to stop LOZAPIN treatment immediately. Your white blood cells should then return to normal.

You will need to have blood tests for another 4 weeks after the end of LOZAPIN treatment.

Your doctor will also do a physical examination before starting treatment. Your doctor may do an electrocardiogram (ECG) to check your heart, but only if this is necessary for you, or if you have any special concerns.

If you have a liver disorder you will have regular liver function tests as long as you continue to take

LOZAPIN. If you suffer from high levels of sugar in the blood (diabetes) your doctor may regularly check your level of sugar in the blood.

LOZAPIN may cause alteration in blood lipids. LOZAPIN may cause weight gain. Your doctor may monitor your weight and blood lipid level.

If you already suffer from feeling or if LOZAPIN makes you feel light-headed, dizzy or faint, be careful when getting up from a sitting or lying position as these may increase the possibility of falling.

If you have to undergo surgery or if for some reason you are unable to walk around for a long time, discuss with your doctor the fact that you are taking LOZAPIN. You may be at risk of thrombosis (blood clotting within a vein).

Children and adolescents under 16 years

If you are under 16 years of age you should not use LOZAPIN as there is not enough information on its use in that age group.

Older people (aged 60 years and over)

Older people (aged 60 years and over) may be more likely to have the following side effects during treatment with LOZAPIN: faintness or light-headedness after changing position, dizziness, fast heartbeat, difficulty in passing urine, and constipation. Tell your doctor or pharmacist if you suffer from a condition called dementia.

Other medicines and LOZAPIN

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other

Medicines. This includes medicines obtained without a prescription or herbal therapies. You might need to take different amounts of your medicines or to take different medicines.

Do not take LOZAPIN together with medicines that stop the bone marrow from working properly and/or decrease the number of blood cells produced by the body, such as:

– carbamazepine, a medicine used in epilepsy.

– certain antibiotics: chloramphenicol, sulphonamides such as co-trimoxazole.

– certain painkillers: pyrazolone analgesics such as phenylbutazone.

– penicillamine, a medicine used to treat rheumatic joint inflammation.

– cytotoxic agents, medicines used in chemotherapy.

– long-acting depot injections of antipsychotic medicines.

These medicines increase your risk of developing agranulocytosis (lack of white blood cells).

Taking LOZAPIN at the same time as another medicine may affect how well LOZAPIN and/or the other medicine works. Tell your doctor if you plan to take, if you are taking (even if the course of treatment is about to end) or if you have recently had to stop taking any of the following medicines:

– medicines used to treat depression such as lithium, fluvoxamine, tricyclic antidepressants, MAO

inhibitors, citalopram, paroxetine, fluoxetine, and sertraline.

– other antipsychotic medicines used to treat mental illnesses such as perazine.

– benzodiazepines and other medicines used to treat anxiety or sleep disturbances.

– narcotics and other medicines which can affect your breathing.

– medicines used to control epilepsy such as phenytoin and valproic acid.

– medicines used to treat high or low blood pressure such as adrenaline and noradrenaline.

– warfarin, a medicine used to prevent blood clots.

– antihistamines, medicines used for colds or allergies such as hay fever.

– anticholinergic medicines, which are used to relieve stomach cramps, spasms and travel

sickness.

– medicines used to treat Parkinson’s disease.

– digoxin, a medicine used to treat heart problems.

– medicines used to treat a fast or irregular heartbeat.

– some medicines used to treat stomach ulcers, such as omeprazole or cimetidine.

– some antibiotic medicines, such as erythromycin and rifampicin.

– some medicines used to treat fungal infections (such as ketoconazole) or viral infections (such as protease inhibitors, used to treat HIV infections).

– atropine, a medicine which may be used in some eye drops or cough and cold preparations.

– adrenaline, a medicine used in emergency situations.

– hormonal contraceptives (birth-control tablets).

This list is not complete. Your doctor and pharmacist have more information on medicines to be careful with or to avoid while taking LOZAPIN. They will also know if the medicines you are taking belong to the listed groups. Speak to them.

Taking LOZAPIN with food and drink.

Do not drink alcohol during treatment with LOZAPIN.

Tell your doctor if you smoke and how often you have drinks containing caffeine (coffee, tea, cola). Sudden changes in your smoking habits or caffeine drinking habits can also change the effects of LOZAPIN.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the benefits and possible risks of using this medicine during pregnancy. Tell your doctor immediately if you become pregnant during treatment with LOZAPIN.

The following symptoms may occur in newborn babies, of mothers that have used LOZAPIN in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor. Some women taking some medicines to treat mental illnesses have irregular or no periods. If you have been affected in this way, your periods might return when your medicine is changed to LOZAPIN. This means you should use effective contraception.

Do not breast-feed during treatment with LOZAPIN. Clozapine, the active substance of LOZAPIN, may pass into your milk and affect your baby.

Driving and using machines

LOZAPIN might cause tiredness, drowsiness and seizures, especially at the beginning of treatment. You should not drive or operate machines while you have these symptoms.

LOZAPIN contains lactose.

If you have been told by your doctor that you have an intolerance to some sugars, discuss this with your doctor before taking LOZAPIN.

9.3. How to take LOZAPIN

In order to minimise the risk of low blood pressure, seizures and drowsiness it is necessary that your doctor increases your dose gradually. Always take LOZAPIN tablets exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
It is important that you do not change your dose or stop taking LOZAPIN without asking your doctor first. Continue taking the tablets for as long as your doctor tells you. If you are 60 years or older, your doctor may start you on a lower dose and increase it more gradually because you might be more likely to develop some unwanted side effects.
If the dose you are prescribed cannot be achieved with this strength tablet, other strengths of this medicinal product are available to achieve the dose.

Treatment of schizophrenia
The usual starting dose is 12.5 mg (one half of a 25 mg tablet) once or twice on the first day followed by 25 mg once or twice on the second day. Swallow the tablet with water. If tolerated well, your doctor will then gradually increase the dose in steps of 25-50 mg over the next 2-3 weeks until a dose up to 300 mg per day is reached. Thereafter, if necessary, the daily dose may be increased in steps of 50 to 100 mg half-weekly or, preferably, at weekly intervals. The effective daily dose is usually between 200 mg and 450 mg, divided into several single doses per day. Some people might need more. A daily dose of up to 900 mg is allowed.
Increased side effects (in particular seizures) are possible at daily doses over 450 mg. Always take the lowest effective dose for you. Most people take part of their dose in the morning and part in the evening. Your doctor will tell you exactly how to divide your daily dose. If your

daily dose is only 200 mg, then you can take this as a single dose in the evening. Once you have been taking LOZAPIN with successful results for some time, your doctor may try you on a lower dose. You will need to take LOZAPIN for at least 6 months.

Treatment of severe thought disturbances in patients with Parkinson's disease
The usual starting dose is 12.5 mg (one half of a 25 mg tablet) in the evening. Swallow the tablet with water. Your doctor will then gradually increase the dose in steps of 12.5 mg, not faster than two steps a week, up to a maximum dose of 50 mg by the end of the second week. Increases in the dosage should be stopped or postponed if you feel faint,
Light-headed or confused. In order to avoid such symptoms your blood pressure will be measured during the first weeks of treatment.
The effective daily dose is usually between 25 mg and 37.5 mg, taken as one dose in the evening. Doses of 50 mg per day should only be exceeded in exceptional cases. The maximum daily dose is 100 mg. always take the lowest effective dose for you.

If you take more LOZAPIN than you should
If you think that you may have taken too many tablets, or if anyone else takes any of your tablets, contact a doctor immediately or call for emergency medical help.
The symptoms of overdose are:
Drowsiness, tiredness, lack of energy, unconsciousness, coma, confusion, hallucinations, agitation, incoherent speech, stiff limbs, trembling hands, seizures (fits), increased production of saliva, widening of the black part of the eye, blurred vision, low blood pressure, collapse, fast or irregular heartbeat, shallow or difficult breathing.

If you forget to take LOZAPIN
If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, leave out the forgotten tablets and take the next dose at the right time. Do not take a double dose to make up for a forgotten dose. Contact your doctor as soon as possible if you have not taken any LOZAPIN for more than 48 hours.

If you stop taking LOZAPIN
Do not stop taking LOZAPIN without asking your doctor, because you might get withdrawal reactions. These reactions include sweating, headache, nausea (feeling sick), vomiting (being sick) and diarrhoea. **If you have any of the above signs, tell your doctor straight away. These signs may be followed by more serious side effects unless you are treated immediately.** Your original symptoms might come back. A gradual reduction in dose in steps of 12.5 mg over one to two weeks is recommended, if you have to stop treatment. Your doctor will advise you on how to reduce your daily dose. If you have to stop LOZAPIN treatment suddenly, you will have to be checked by your doctor.
If your doctor decides to re-start the treatment with LOZAPIN and your last dose of LOZAPIN was over two days ago, this will be with the starting dose of 12.5 mg.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Tell a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment.

Like all medicines, Clozaril can cause side effects, although not everybody gets them.
Some side effects can be serious and need immediate medical attention: Tell your doctor immediately before taking the next Clozaril tablet if you experience any of the following:

Very common *(affects more than 1 in 10 people):*
– **Severe constipation**. Your doctor will have to treat this in order to avoid further complications.
– Fast heart beat

Common *(affects up to 1 in 10 people):*
– Signs of a **cold, fever, flu-like symptoms, sore throat or any other infection**. You will have to have an urgent blood test to check if your symptoms are related to your medicine.
– Seizures.
– Sudden fainting or sudden loss of consciousness with muscle weakness (syncope).

Uncommon *(affects up to 1 in 100 people):*
– if you have a sudden rapid increase in body temperature, rigid muscles which may lead to unconsciousness (neuroleptic malignant syndrome) as you may be experiencing a serious side effect which requires immediate treatment.
– Light-headedness, dizziness or fainting, when getting up from a sitting or lying position as it may increase the possibility of falling.

Rare (affects up to 1 in 1,000 people):
– Signs of a respiratory tract infection or pneumonia such as fever, coughing, difficulty breathing, wheezing.
– Severe, burning, upper abdominal pain, extending to the back accompanied by nausea and vomiting due to inflammation of the pancreas.
– Fainting and muscle weakness due to a significant drop in blood pressure (Circulatory collapse).
– Difficulty in swallowing (which may cause inhalation of food).
– **Nausea (feeling sick), vomiting (being sick)** and/or **loss of appetite**. Your doctor will need to check your liver.
– Interruption in breathing with or without snoring during sleep
– Signs of becoming obese or increasing obesity

Rare *(affects up to 1 in 1,000 people)* or **very rare** *(affects up to 1 in 10,000 people):*
– **Fast and irregular heartbeat**, even when you are at rest, **palpitations, breathing problems, chest pain** or **unexplained tiredness**. Your doctor will need to check your heart and if necessary refer you to a cardiologist immediately.

Very rare *(affects up to 1 in 10,000 people):*
– Persistent painful erection of the penis, if you are a man. This is called priapism. If you have an erection which lasts more than 4 hours immediate medical treatment may be needed in order to avoid further complications.
– Spontaneous bleeding or bruising, which might be signs of a decrease in numbers of blood platelets.
– Symptoms due to uncontrolled blood sugar (such as nausea or vomiting, abdominal pain, excessive thirst, excessive urination, disorientation or confusion.
– Abdominal pain, cramping, swollen abdomen, vomiting, constipation and failure to pass gas which may be signs and symptoms of bowel obstruction.
– Loss of appetite, swollen abdomen, abdominal pain, yellowing of the skin, severe weakness and malaise. These symptoms may be signs that you are starting to develop a liver disorder that may advancement fulminant liver necrosis.

– Nausea, vomiting, fatigue, weight loss which may be symptoms of inflammation of the kidney.

Unknown *(frequency cannot be estimated from the available data)*
– crushing chest pain, sensation of chest tightness, pressure or squeezing (chest pain may radiate to the left arm, jaw, neck and upper abdomen), shortness of breath, sweating, weakness, light headedness, nausea, vomiting and palpitations (symptoms of heart attack) which may lead to death. You should seek emergency medical treatment immediately.
– Chest pressure, heaviness, tightness, squeezing, burning or choking sensation (signs of insufficient blood flow and oxygen to the heart muscle) which may lead to death. Your doctor will need to check your heart.
– Intermittent "thumping", "pounding" or "fluttering" sensation in the chest (palpitations).
– Rapid and irregular heartbeats (atrial fibrillation). There may be occasional heart palpitations, fainting, shortness of breath, or chest discomfort. Your doctor will need to check your heart.
– Symptoms of low blood pressure such as light-headedness, dizziness, fainting, blurred vision, unusual fatigue, cold and clammy skin or nausea.
– Signs of blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing.
– proven or strongly suspected infection along with fever or low body temperature, abnormally rapid breathing, rapid heart rate, change in responsiveness and awareness, drop in blood pressure (sepsis).
– Profuse sweating, headache, nausea, vomiting and diarrhoea (symptoms of cholinergic syndrome).
– Severely decreased urine output (sign of kidney failure).
– An allergic reaction (swelling mainly of the face, mouth and throat, as well as, the tongue, which may be itchy or painful).
– Loss of appetite, swollen abdomen, abdominal pain, yellowing of the skin, severe weakness and malaise. This may indicate possible liver disorders that involve replacement of normal liver tissue with scar tissue leading to loss of liver function, including those liver events leading to life threatening consequences such as liver failure (which may lead to death), liver injury (injury of liver cells, bile duct in the liver, or both) and liver transplant.
– burning upper abdominal pain, particularly between meals, early in the morning, or after drinking acidic drinks; tarry, black, or bloody stools; bloating, heartburn, nausea or vomiting, early feeling of fullness (intestinal ulceration of stomach and/or gut) -which may lead to death
– severe abdominal pain intensified by movement, nausea, vomiting including vomiting blood (or liquid with what looks like coffee grounds); abdomen becomes rigid with (rebound) tenderness spreading from point of perforation across the abdomen; fever and/or chills (intestinal perforation of stomach and/or gut or ruptured bowel) which may lead to death
– Constipation, abdominal pain, abdominal tenderness, fever, bloating, bloody diarrhoea. This may indicate possible megacolon (enlargement of the intestines) or intestinal infarction/ischaemia/necrosis which may lead to death. Your doctor will need to examine you.
– Sharp chest pain with shortness of breath and with or without coughing
– Increased or new muscle weakness, muscle spasms, muscle pain. This may indicate possible a muscle disorder (rhabdomyolysis). Your doctor will need to examine you.
– Sharp chest or abdominal pain with shortness of breath and with or without coughing or fever.
– Extremely intense and serious skin reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS syndrome), have been reported during use of X. The adverse

reaction of the skin may appear as rashes with or without blisters. Skin irritation, oedema and fever and flulike
Symptoms may occur. Symptoms of DRESS syndrome usually appear approximately 2–6 weeks (possibly up to 8 weeks) after treatment begins.

If any of the above apply to you, please tell your doctor immediately before taking the next Clozaril tablet.

Other side effects:

Very common *(affects more than 1 in 10 people):*
Drowsiness, dizziness, increased production of saliva.

Common *(affects up to 1 in 10 people):*
High level of white blood cells (leukocytosis), high level of a specific type of white blood cell (eosinophilia), weight gain, blurred vision, headache, trembling, stiffness, restlessness, convulsions, jerks, abnormal movements, inability to initiate movement, inability to remain motionless, changes in ECG heart machine, high blood pressure, faintness or light-headedness after changing position, nausea (feeling sick), vomiting (being sick), loss of appetite, dry mouth, minor abnormalities in liver function tests, loss of bladder control, difficulty in passing urine,
tiredness, fever, increased sweating, raised body temperature, speech disorders (e.g. slurred speech).

Uncommon *(affects up to 1 in 100 people):*
Lack of white blood cells (agranulocytosis), speech disorders (e.g. stuttering).

Rare (affects up to 1 in 1,000 people):
Low level of red blood cells (anaemia), restlessness, agitation, confusion, delirium, irregular heartbeat, inflammation of the heart muscle (myocarditis) or the membrane surrounding the heart muscle (pericarditis), fluid collection around the heart (pericardial effusion), high level of sugar in the blood, diabetes mellitus, blood clot in the lungs (thromboembolism), inflammation of the liver (hepatitis), liver disease causing yellowing of the skin/dark urine/itching, raised levels of an enzyme called creatinine phosphokinase in the blood.

Very rare *(affects up to 1 in 10,000 people):*
Increase in numbers of blood platelets with possible clotting in the blood vessels, uncontrollable movements of mouth/tongue and limbs, obsessive thoughts and compulsive repetitive behaviours (obsessive compulsive symptoms), skin reactions, swelling in front of the ear (enlargement of saliva glands), difficulty in breathing, very high levels of triglycerides or cholesterol in the blood, disorder of the heart muscle (cardiomyopathy), stopped heart beat (cardiac arrest), sudden unexplained death.

Unknown *(frequency cannot be estimated from the available data)*
Changes in brain waves machine (electroencephalogram/EEG), diarrhoea, stomach discomfort, heartburn, stomach discomfort after a meal, muscle weakness, muscle spasms, muscle pain, stuffy nose, nocturnal bedwetting, sudden, uncontrollable increase in blood pressure (pseudophaeochromocytoma), uncontrolled bending of the body to one side (pleurothotonus), ejaculatory disorder if you are a male, in which semen enters the bladder instead of ejaculating through the penis (dry orgasm or retrograde ejaculation), rash, purplish-red spots, fever or itching due to inflammation of blood vessel, inflammation of the colon resulting in diarrhoea, abdominal pain, fever, change in skin colour, “butterfly” facial rash, joint pain, muscle pain, fever and fatigue (lupus erythematous), restless legs syndrome (irresistible urge to move your legs or arms, usually accompanied by uncomfortable sensations during periods of rest, especially in the evening or at night and temporarily relieved by movement).

In elderly people with dementia, a small increase in the number of people dying has been reported for patients taking antipsychotics.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5. How to store LOZAPIN

- Keep this medicine out of the sight and reach of children.
- Do not take LOZAPIN Tablets after the expiry date, which is stated on the carton and blister pack after EXP. The expiry date refers to the last day of that month.
- Store in a cool and dry place. Keep the blister strip in the outer carton in order to protect from light and moisture.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6. Contents of the pack and other information

What LOZAPIN contains

The active substances is Clozapine. Each tablet contains 25mg, 50mg and 100mg Clozapine.

PRESENTATION

LOZAPIN is available in Blister of 10 Tablets

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok, Sikkim – 737135

OR

Manufactured in India by:

Windlas Biotech Limited (Plant-IV)

Plot No. 183 & 192,

Mohabewala Industrial Area,

Dehradun-248110, Uttarakhand

11. Details of permission or licence number

Mfg Lic No. M/563/2010 issued on 23.12.2016

Windlas Biotech Limited (Plant-IV)

Mfg. Lic No. 47/UA/2009

12. Date of revision

APR 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ LOZAPIN 25mg, 50mg, 100mg/APR-2022/03/PI