PROFESSIONAL INFORMATION

WARNINGS:

The use of CLOMENT should be limited to severely ill schizophrenic patients who are non-responsive to, or intolerant of classical neuroleptic drug treatment, due to significant risk that CLOMENT can cause fatal agranulocytosis.

Physicians who prescribe this medicine should comply fully with the required safety measures. Each patient who receives CLOMENT should be reminded at every consultation 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 any other evidence of infection, which may be indicative of neutropenia.

Patients who are being treated with CLOMENT must have initially normal leucocyte findings (baseline white blood cell count ≥ 3500/mm^3 and absolute neutrophil count ≥ 2000/mm^3) before initiation of treatment. Regular white blood cell (WBC) counts and, if possible, absolute neutrophil counts (ANC) should be performed weekly during the first 18 weeks and at least every two weeks thereafter up till 52 weeks and at least every 4 weeks throughout treatment and for one month after discontinuation of treatment.

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

Caution should be used in administering CLOMENT to patients having a history of seizures or other predisposing factors. The dose appears to be an important predictor of a seizure, with a greater likelihood at the higher CLOMENT doses used. Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g. the operation of complex machinery, driving a vehicle, swimming, climbing, etc.

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with CLOMENT.

Patients with an established diagnosis of diabetes mellitus who are started on CLOMENT 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 CLOMENT should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with CLOMENT should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when CLOMENT was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

There is an increased risk of cerebrovascular adverse events (including strokes and transient ischaemic attacks) and mortality associated with the use of atypical antipsychotics in elderly patients with dementia. Before prescribing, physicians are advised to carefully assess the risks and benefits of the use of atypical antipsychotics in elderly patients with dementia, taking into account risk predictions for stroke in the individual patient (e.g. hypertension, diabetes, current smoking, atrial fibrillation, and age > 80 years). Where the use of antipsychotics in the elderly is considered essential, the lowest effective dose should be used. CLOMENT is not indicated for use in elderly patients with dementia exhibiting behavioural disturbances.

SCHEDULING STATUS: **S5**

PROPRIETARY NAME AND DOSAGE FORM:

CLOMENT 25 tablet

CLOMENT 100 tablet

COMPOSITION:

Each tablet contains 25 mg or 100 mg clozapine.

Excipients: lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycollate.

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Tranquillisers (miscellaneous structures)

PHARMACOLOGICAL ACTION:

Clozapine is classified as an atypical antipsychotic agent.

It has weak dopamine receptor-blocking activity at D_1, D_2, D_3 and D_5 receptors, but shows higher potency for the D_4 receptor, in addition to potent noradrenolytic, anti-cholinergic, antihistaminic and arousal reaction inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Pharmacokinetic properties:

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

Clozapine undergoes a moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60 %.

In steady-state conditions, when given twice daily, peak blood level occurs on an average at 2,5 hours (range: 1 to 6 h), and the volume of distribution is 1,6 litre/kg.

Clozapine is approximately 95 % bound to plasma proteins. Its elimination is biphasic with a mean terminal half-life of 12 hours (between 4 to 66 h).

Clozapine is almost completely metabolised prior to excretion. One of the main metabolites, the des-methyl metabolite, was found to be active. The pharmacological activity of this metabolite resembles those of clozapine, but are considerably weaker and of short duration. Only trace amounts of unchanged medicine are detected in the urine and faeces.

Approximately 50 % of the administered dose is excreted in the urine and 30 % in the faeces as metabolites.

INDICATIONS:

Treatment-resistant schizophrenia: CLOMENT is indicated for the treatment of severely ill schizophrenic patients, failing to respond adequately to standard acceptable antipsychotic medication, either because of insufficient effectiveness or because of intolerable side effects caused by the medication.

Because of the significant risk of agranulocytosis and seizure associated with its use, **CLOMENT** should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard antipsychotic medicines, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those medicines (see **WARNINGS and SPECIAL PRECAUTIONS**).

It is strongly recommended that a patient be given at least 2 trials, each with a different standard antipsychotic product, at an adequate dose and for an adequate duration.

Because of the significant risk of agranulocytosis and seizure with **CLOMENT** it presents a continuing risk over time; the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.

In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should periodically be re-evaluated.

Risk of recurrent suicidal behaviour:

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

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

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

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

-Withdrawal of anti-cholinergic medication including tricyclic anti-depressants.

-Attempt to reduce the dose of antiparkinsonian medication with dopaminergic effect.

CONTRA-INDICATIONS:

- Hypersensitivity to any of the components in **CLOMENT**.
- Patients unable to undergo regular blood tests.

- Patients with a history of drug-induced, toxic or idiosyncratic granulocytopenia/agranulocytosis or neutropenia.
- Should not be given simultaneously with other agents, which have a well-known potential to suppress bone marrow function.
- Impaired bone marrow function, myeloproliferative disorders or any abnormalities of white blood cell count or differential blood count.
- Uncontrolled epilepsy.
- Concomitant use of **CLOMENT** and carbamazepine.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions and glaucoma.
- Circulatory collapse and/or central nervous system depression of any cause.
- Severe renal or cardiac disorders.
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease and hepatic failure.
- Paralytic ileus.
- Safety in children under the age of 16 years has not been established.
- Since **CLOMENT** may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilisation of the patient should be avoided.

WARNINGS and SPECIAL PRECAUTIONS:

Because of the association of **CLOMENT** with agranulocytosis the following precautionary measures are mandatory:

CLOMENT should not be used concurrently with medicines associated with a substantial potential to depress bone marrow function. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because of the inability of these medications, which may have the potential to be myelosuppressive, to be rapidly removed from the body in situations where this may be required, e.g. granulocytopenia.

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

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

WBC counts and ANC monitoring: Before starting **CLOMENT** treatment, a WBC count and a differential blood count must be performed within 10 days prior to **CLOMENT** treatment to ensure that only patients with normal leucocyte count and normal absolute neutrophil count (WBC count $\geq$ 3 500/mm^3 and ANC $\geq$ 2 000/mm^3) will receive the medicine. After the start of **CLOMENT** treatment the WBC count and, if possible, ANC must be monitored weekly for 18 weeks and thereafter at least every two weeks throughout treatment, and for one month after discontinuation of **CLOMENT**.

At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, or fever, sore throat or other flu-like symptoms develop. An immediate differential blood count must be performed if any symptoms or signs of an infection occur.

In case of low WBC count/ANC: During the first 18 weeks of **CLOMENT** therapy, if the WBC count falls to between 3 500/mm^3 and 3 000/mm^3 and/or the ANC falls to between 2 000/mm^3 and 2 500/mm^3 and/or the ANC falls to between 1 500/mm^3 and 1 000/mm^3, WBC and ANC counts should be done twice a week as well as in the event of where the WBC count has dropped by a substantial amount from baseline. A substantial drop is defined as a single drop of 3 000/mm^3 or more in the WBC count or a cumulative drop of 3 000/mm^3 within 3 weeks.

Immediate discontinuation of **CLOMENT** treatment is mandatory if the WBC count is less than 3 000/mm^3 or the ANC is less than 1 500/mm^3 during the first 18 weeks of **CLOMENT** therapy, and if the WBC count is less than 2500/mm^3 or the ANC count is less than 1 000/mm^3 after the first 18 weeks of **CLOMENT** therapy. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of **CLOMENT**, haematological evaluation is required until haematological recovery has occurred.

If **CLOMENT** has been withdrawn and a further fall of WBC count below 2 000/mm^3 occurs and/or neutrophil granulocytes decrease below 1 000/mm^3, the patient should be referred immediately to a specialised centre.

Patients in whom **CLOMENT** has been discontinued as a result of white blood cell deficiencies (see above), must not be re-exposed to **CLOMENT**.

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

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

Information for patients:

Physicians are advised to discuss the following issues with patients for whom they prescribe **CLOMENT**.

1. Patients who are to receive **CLOMENT** should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.
2. Patients should be informed of the significant risk of seizure during **CLOMENT** treatment and they should be advised to avoid driving and any other potentially hazardous activity while taking **CLOMENT**.
3. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose instructions.
4. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter medicines or alcohol.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Female patients should not breast feed whilst taking **CLOMENT**.
7. Patients should be informed that if they stop taking **CLOMENT** for more than 2 days, they should not start their medication at the same dosage, but should contact their physician for dosing instructions.
8. Patients should notify their physician if they have diabetes mellitus or if they have risk factors for diabetes mellitus.

Other precautions

In the event of eosinophilia, it is recommended to discontinue **CLOMENT** if the eosinophil count rises above 3000/mm^3 and to re-start therapy only after the eosinophil count has fallen below 1000/mm^3 (good medical practice as recommended by haematologists).

In the event of thrombocytopenia, it is recommended to discontinue **CLOMENT** therapy if the platelet count falls below 50 000/mm^3

Orthostatic hypotension can occur with **CLOMENT** treatment. Rarely (about one case per 3000 treated patients) resulting in collapse and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing **CLOMENT** treatment require close medical supervision. Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure may occur.

The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. If the diagnosis of myocarditis is confirmed, **CLOMENT** should be discontinued.

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

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

Effects on ability to drive and use machines: Owing to the ability of **CLOMENT** to cause sedation and lower the seizure threshold, activities of driving or operating machinery should be avoided, especially during the initial weeks of treatment.

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

CLOMENT exerts anticholinergic activity; therefore, careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Probably on account of its anticholinergic properties, **CLOMENT** has been associated with varying degrees of impairment of intestinal

peristalsis, ranging from constipation to intestinal obstruction, faecal impactions and paralytic ileus (see **SIDE-EFFECTS**).

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

Patients with stable pre-existing liver disorders may receive **CLOMENT**, but need regular liver function test monitoring. In patients whom, during **CLOMENT** treatment, symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia develop, liver function tests should be performed immediately. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with **CLOMENT** must be discontinued. It may be resumed (see Re-starting therapy) only when the liver function tests have returned to normal values. In such cases, liver function should be closely monitored after the re-introduction of the medicine.

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

Patients with an established diagnosis of diabetes mellitus or patients with risk factors for diabetes mellitus that are started on **CLOMENT** should be monitored for symptoms of hyperglycaemia.

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

Since orthostatic hypotension can occur with **CLOMENT** treatment and there have been reports of tachycardia, 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 **CLOMENT**, such as urinary retention and constipation.

Use in pregnancy, lactation and children: (See **CONTRA-INDICATIONS** and **PREGNANCY AND LACTATION**)

INTERACTIONS:

Medicines which are known to potentially depress bone marrow function significantly, such as carbamazepine, co-trimoxazole, chloramphenicol, penicillamine, sulphonamides, antineoplastics and azapropazone should not be used concomitantly with **CLOMENT** (see also **CONTRAINDICATIONS** and **WARNINGS and SPECIAL PRECAUTIONS**).

The possibility of a pharmacokinetic interaction should be considered with anticonvulsant medicines. Valproic acid did not increase **CLOMENT** blood levels significantly. However, serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where reported with the concomitant use of valproic acid. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

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

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

CLOMENT should immediately be discontinued in these patients when neuroleptic malignant syndrome develops.

Long acting depot antipsychotics should not be used with **CLOMENT** as they cannot be withdrawn rapidly should neutropenia occur.

Particular caution is advised when **CLOMENT** therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine, or any other psychotrophic agent, as these patients may have an increased risk of circulatory collapse, which less frequently can be profound and may lead to cardiac and/or respiratory arrest.

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

Since clozapine is highly bound to plasma proteins, the administration of **CLOMENT** to a patient taking another medicine, which is highly bound to protein (e.g. warfarin), may cause an increase in plasma concentrations of this medicine, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clozapine by other highly protein-bound medicines.

Concomitant administration of **CLOMENT** with cimetidine or erythromycin, (medicines known to inhibit the cytochrome P450 enzyme system), may increase the plasma levels of clozapine, possibly resulting in adverse effects.

Since the metabolism of clozapine is mainly mediated by cytochrome P450 1A2 and cytochrome P450 3A4 and, probably to a minor extent by cytochrome P450 2D6, the concomitant administration of medicines which possess affinity for these enzymes may result in an increase in the plasma levels of clozapine and/or the co-administered medicine. Therefore, caution is called for in patients receiving concomitant treatment with other medicines, which are either inhibitors or inducers of these enzymes. However, with tricyclic antidepressants, phenothiazines and type 1c anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far. On theoretical grounds, however, it is possible that the plasma levels of such medicines are increased by clozapine, so it may be appropriate to use them at doses lower than usually prescribed.

Elevated serum levels of clozapine (sometimes massive) have been reported in patients receiving the medicine in combination with fluvoxamine (up to tenfold), or other selective serotonin re-uptake inhibitors such as citalopram, paroxetine, sertraline or fluoxetine.

Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors may increase clozapine plasma concentrations.

The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50 % following a 5-day caffeine-free period.

Concomitant administration of phenytoin, and possibly other medicines known to induce the cytochrome P450 enzyme system, may reduce the plasma levels of clozapine and may be associated with the recurrence of psychotic symptoms.

Known inducers of 1A2 include omeprazole and nicotine. In cases of sudden cessation of nicotine abuse, the plasma clozapine concentration may be increased, leading to an increase in adverse effects.

Owing to its noradrenolytic action, **CLOMENT** may reduce the blood pressure-increasing effect of noradrenalin or the predominantly α–adrenergic agents and reverse the pressure effect of adrenaline.

PREGNANCY AND LACTATION:

Pregnancy: Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. However, the safe use of **CLOMENT** in pregnant women has not been established.

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

Lactation: Animal studies suggest that clozapine is excreted in breast milk, therefore mothers receiving **CLOMENT** should not breast-feed.

DOSAGE AND DIRECTIONS FOR USE:

The dosage must be adjusted individually for each patient, using the lowest possible effective dose. Initiation of **CLOMENT** treatment must be restricted to those patients with a white blood cell count $\geq$ 3500/mm^3 and an absolute neutrophil count $\geq$ 2000 mm^3. Dose adjustment is required in patients receiving medicines interacting with **CLOMENT** such as benzodiazepines and medicines with selective serotonin re-uptake (see **INTERACTIONS**).

In the elderly or underweight patients or those suffering from renal, hepatic or cardiovascular disorders, or suffering from cerebral vascular insufficiency or cerebral sclerosis, the initial dose should be low, and any dose titration should be slow.

The following dosages for oral administration are recommended:

Treatment-resistant schizophrenia:

Initial dose: 12,5 mg (one-half of 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 dosage may then be increased slowly in increments of 25 to 50 mg, in order to achieve a dose level of up to 300 mg per 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: It is recommended to initiate treatment at a particularly low dose (12,5 mg given once on the first day) and to restrict subsequent dose increments to 25 mg per day.

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

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

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

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

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

Switching from a classical neuroleptic to **CLOMENT**: It is generally recommended that **CLOMENT** should not be used in combination with classical neuroleptics. When **CLOMENT** therapy is to be initiated in a patient undergoing oral neuroleptic therapy, it is recommended that the classical neuroleptic should first be discontinued by tapering the dosage downwards over a period of approximately one week. Based on the clinical circumstances, the prescribing physician should judge whether or not to totally discontinue the other neuroleptic therapy before initiating treatment with **CLOMENT**.

Reducing the risk of suicidal behaviour in schizophrenia and schizoaffective disorder

The dosage and administration recommendations described in the preceding section regarding the use of **CLOMENT** in patients with treatment-resistant schizophrenia should be followed when treating patients with schizophrenia or schizoaffective disorder at risk of recurrent suicidal behaviour.

A course of treatment with **CLOMENT** of at least two years is recommended in order to maintain the reduction of risk of suicidal behaviour. It is recommended that the patient's risk of suicidal behaviour be reassessed after two years of treatment and that thereafter the decision to continue treatment with **CLOMENT** be re-visited at regular intervals, based on thorough assessments of the patient's risk for suicidal behaviour during treatment.

Drug-induced psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

The starting dose must not exceed 12,5 mg/day (one-half of 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 second week. The total daily amount should preferably be given as a single dose in the evening. Higher doses are associated with significant adverse effects.

The mean effective dose is usually between 25 and 37,5 mg/day.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

When ending therapy, a gradual reduction in dose by steps of 12,5 mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis as indicated under **WARNINGS and SPECIAL PRECAUTIONS**. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

SIDE-EFFECTS:

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: Leucopenia/decreased white blood cell count/neutropenia, eosinophilia, leukocytosis

Uncommon: Agranulocytosis

Rare: Anaemia

Very rare: Thrombocytopenia, thrombocythaemia

Granulocytopenia and agranulocytosis are risks inherent in **CLOMENT** treatment. Although generally reversible on withdrawal of the medicine, agranulocytosis may prove fatal. The majority of cases occur in the first 18 weeks of treatment. Because immediate withdrawal of the medicine is required to prevent the development of life-threatening agranulocytosis, monitoring of the white blood cell count (as described under **WARNINGS and SPECIAL PRECAUTIONS**) is mandatory.

Unexplained eosinophilia and/or leucocytosis may occur, especially in the initial weeks of treatment.

Metabolism and nutrition disorders:

Common: Weight gain

Rare: Impaired glucose tolerance, diabetes aggravated

Very rare: Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia

Psychiatric disorders:

Rare: Restlessness, agitation

Nervous system disorders:

Very common: Drowsiness/sedation, dizziness

Common: Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsion, myoclonic jerks.

Rare: Confusion, delirium

Very rare: Tardive dyskinesia

CLOMENT lowers the seizure threshold in a dose-dependent manner and may cause electro-encephalogram changes, including occurrence of spike and wave complexes. If seizures occur, the dose should be reduced and, if necessary, anticonvulsant treatment initiated. With anticonvulsant medicines the possibility of pharmacokinetic interactions should be considered.

Cardiac disorders:

Very common: Tachycardia

Common: ECG changes

Rare: Circulatory collapse, arrhythmias, myocarditis, pericarditis

Very rare: Cardiomyopathy

Vascular disorders:

Common: Hypertension, postural hypotension, syncope

Rare: Thromboembolism

Respiratory, thoracic and mediastinal disorders:

Rare: Aspiration of ingested food

Very rare: Respiratory depression/arrest

Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

Gastrointestinal disorders:

Very common: Constipation, hypersalivation

Common: Nausea, vomiting, dry mouth

Rare: Dysphagia

Very rare: Parotid gland enlargement, intestinal obstruction/ileus/faecal impaction

Hepato-biliary 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, benign hyperthermia, disturbances in sweating/temperature regulation

Uncommon: Neuroleptic malignant syndrome

Very rare: Sudden unexplained death

Investigations:

Rare: Increased CPK

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Fatal overdosages have been reported with **CLOMENT**, mostly at doses above 2000 mg.

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

Treatment: Gastric lavage followed by 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 adrenaline and its derivatives should be avoided in the treatment of hypotension because of the possibility of "reverse adrenaline effect". Close medical supervision is necessary for several days because of the possibility of delayed reactions.

IDENTIFICATION:

CLOMENT 25: A round, yellow flat bevel-edged tablet with ‘25’ over a pressure sensitive breakline on one side, and plain on the other side.

CLOMENT 100: A round, yellow flat bevel-edged tablet with ‘100’ over a pressure sensitive breakline on one side, and plain on the other side.

PRESENTATION:

CLOMENT 25: Clear transparent PVC/PVDC/PE/Aluminium blister packs of 100 tablets packed in an outer carton.

CLOMENT 100: Clear transparent PVC/ PVDC/PE/Aluminium blister packs of 100 tablets packed in an outer carton.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CLOMENT 25: 35/2.6.5/0373

CLOMENT 100: 35/2.6.5/0374

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Acino Pharma (Pty) Ltd

106 16th Road

MIDRAND

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Original date of registration and approved professional information: 8 August 2002