SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Credanil 25/250 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Carbidopa 25 mg BP (as Monohydrate) and Levodopa BP 250 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Antiparkinsonian agent.

For treatment of Parkinson's disease and syndrome.

4.2. Posology and method of administration

Posology

The optimum daily dosage of Credanil must be determined by careful titration in each patient. Credanil Tablets are available in a ratio of 1:4 or 1:10 of Carbidopa to Levodopa to provide facility for fine dosage titration for each patient.

General Considerations
Studies show that the peripheral dopa-decarboxylase is fully inhibited (saturated) by Carbidopa at doses between 70 and 100 mg a day. Patients receiving less than this amount of Carbidopa are more likely to experience nausea and vomiting.
Standard antiparkinsonian drugs, other than Levodopa alone, may be continued while Credanil is being administered, although their dosage may have to be adjusted.
Because both therapeutic and adverse effects are seen more rapidly with Credanil than with Levodopa, patients should be carefully monitored during the dosage adjustment period. Involuntary movements, particularly blepharospasm, are a useful early sign of excess dosage in some patients.

Patients not receiving Levodopa
Dosage may be best initiated with one tablet of Credanil-Plus three times a day. This dosage schedule provides 75 mg of Carbidopa per day. Dosage may be increased by one tablet of

Credanil-62.5 or Credanil-Plus every day or every other day, as necessary, until a dosage equivalent of eight tablets of Credanil-Plus a day is reached.
If Credanil-110 or Credanil-62.5 is used, dosage may be initiated with one tablet three or four times a day. Titration upward may be required in some patients to achieve optimum dosage of Carbidopa. The dosage may be increased by one tablet every day or every other day until a total of eight tablets (two tablets q.d.s.) is reached.
For patients starting with Credanil-275, the initial dose is one-half tablet taken once or twice daily. However, this may not provide the optimal amount of Carbidopa needed by many patients. If necessary, add one-half tablet every day or every other day until optimal response is reached.
Response has been observed in one day, and sometimes after one dose. Fully effective doses usually are reached within seven days as compared to weeks or months with Levodopa alone.
Credanil-62.5 or Credanil-110 may be used to facilitate dosage titration according to the needs of the individual patient.

Patients receiving Levodopa
Discontinue Levodopa at least 12 hours (24 hours for slow-release preparations) before starting therapy with Credanil. The easiest way to do this is to give Credanil as the first morning dose after a night without any Levodopa. The dose of Credanil should be approximately 20% of the previous daily dosage of Levodopa.
Patients taking less than 1,500 mg Levodopa a day should be started on one tablet of Credanil-Plus three or four times a day dependent on patient need. The suggested starting dose for most patients taking more than 1,500 mg Levodopa a day is one tablet of Credanil-275 three or four times a day.

Maintenance
Therapy with Credanil should be individualised and adjusted gradually according to response. When a greater proportion of Carbidopa is required, each tablet of Credanil-110 may be replaced with a tablet of Credanil-Plus or Credanil-62.5.
When more Levodopa is required, Credanil-275 should be substituted at a dosage of one tablet three or four times a day. If necessary, the dosage of Credanil-275 may be increased by half to one tablet every other day to a maximum of eight tablets a day. Experience with a total daily dosage greater than 200 mg Carbidopa is limited.

Patients receiving Levodopa with another decarboxylase inhibitor
When transferring a patient to Credanil from Levodopa combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours before Credanil is started. Begin with a dosage of Credanil that will provide the same amount of Levodopa as contained in the other Levodopa/decarboxylase inhibitor combination.

Patients receiving other antiparkinsonian agents
Current evidence indicates that other antiparkinsonian agents may be continued when Credanil is introduced, although dosage may have to be adjusted in line with manufacturers recommendations.

Use in children
The safety of Credanil in patients under 18 years of age has not been established.

Use in the elderly

There is wide experience in the use of this product in elderly patients. The recommendations set out above reflect the clinical data derived from this experience.

Method of administration
To be taken orally.

4.3. Contraindications

MAO inhibitors (except low doses of selective MAO-B inhibitors) and Credanil should not be given concomitantly, (these must be discontinued at least two weeks before starting Credanil); narrow-angle glaucoma; known hypersensitivity to any component of this medication. Because Levodopa may activate a malignant melanoma, it should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma. (See also 4.6 Pregnancy and Lactation).
Use in patients with severe psychoses.

4.4. Special warnings and precautions for use

Credanil is not recommended for the treatment of drug-induced extrapyramidal reactions.
Credanil should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease (because of the possibility of upper gastro-intestinal haemorrhage).

Care should be exercised when Credanil is administered to patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustment.

All patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with current psychoses should be treated with caution.

Dyskinesias may occur in patients previously treated with Levodopa alone because Carbidopa permits more Levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.

As with Levodopa, Credanil may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with Levodopa alone should be observed carefully when Credanil is substituted. These reactions are thought to be due to increased brain dopamine following administration of Levodopa, and use of Credanil may cause a recurrence. A syndrome resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Therefore, any abrupt dosage reduction or withdrawal of Credanil should be carefully observed, particularly in patients who are also receiving neuroleptics.

Concomitant administration of psycho-active drugs such as phenothiazines or butyrophenones should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect. Patients with a history of convulsions should be treated with caution.

As with Levodopa, periodic evaluation of hepatic, haematopoetic, cardiovascular and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with Credanil, provided the intra-ocular pressure is well controlled and the patient monitored carefully for changes in intra-ocular pressure during therapy.

If general anaesthesia is required, therapy with Credanil may be continued for as long as the patient is permitted to take fluids and medication by mouth. If therapy has to be stopped temporarily, Credanil may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Laboratory Tests
Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Credanil than with Levodopa. Transient abnormalities include elevated levels of blood urea, AST (SGOT) ALT (SGPT), LDH, bilirubin, and alkaline phosphatase.
Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported.
Positive Coombs' tests have been reported, both with Credanil and Levodopa alone, but haemolytic anaemia is extremely rare.
Credanil may cause a false positive result when a dipstick is used to test for urinary ketone; and this reaction is not altered by boiling the urine. The use of glucose oxidase methods may give false negative results for glycosuria.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Credanil 25/250 Tablets. Review of treatment is recommended if such symptoms develop.

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

Caution should be exercised when the following drugs are administered concomitantly with Credanil.

Antihypertensive agents
Postural hypotension can occur when Credanil is added to the treatment of patients already receiving antihypertensive drugs. Dosage adjustment of the antihypertensive agent may be required.

Antidepressants

Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants. (See 4.3 Contraindications for patients receiving MAOIs).

Other drugs
To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian drugs.
Phenothiazines, butyrophenones, Phenytoin and Papaverine may reduce the therapeutic effect of Levodopa. Patients taking these drugs with Credanil should be carefully observed for loss of therapeutic response.
Since Levodopa competes with certain amino acids, the absorption of Credanil may be impaired in some patients on a high protein diet.
Credanil may be given to patients with Parkinson's disease and syndrome who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

4.6. Fertility, pregnancy and lactation

Pregnancy
Although the effects of Credanil on human pregnancy are unknown, both Levodopa and combinations of Carbidopa and Levodopa have caused visceral and skeletal malformations in rabbits. Therefore, the use of Credanil in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Lactation
It is not known whether Carbidopa or Levodopa is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue breast-feeding or discontinue the use of Credanil, taking into account the importance of the drug to the mother.

4.7. Effects on ability to drive and use machines

No data are known about the effect on the ability to drive. If side effects such as dizziness or somnolence occur, they may affect the ability to drive and to operate machinery.

4.8. Undersirable effects

Side effects that occur frequently with Credanil are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by dosage reduction. The most common are dyskinesias including choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.

Other serious side effects are mental changes, including paranoid ideation and psychotic episodes; depression, with or without development of suicidal tendencies; and dementia. A common but less serious side effect is nausea.

Less frequent side effects are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence.

Gastro-intestinal bleeding, development of duodenal ulcer, hypertension, phlebitis, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, chest pain, dyspnoea and paraesthesia have occurred rarely.
Rarely convulsions have occurred; however, a causal relationship with Credanil has not been established.

Other side effects that have been reported with Levodopa and may be potential side effects with Credanil include:
Neurological
Ataxia, numbness, increased hand tremor, muscle twitching, muscle cramp, trismus, activation of latent Horner's syndrome.
Psychiatric
Confusion, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria.
Gastro-intestinal
Dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhoea, flatulence, burning sensation of the tongue.
Metabolic
Weight gain or loss, oedema.
Integumentary
Flushing, increased sweating, dark sweat, rash, hair loss.
Genito-urinary
Urinary retention, urinary incontinence, dark urine, priapism.
Special senses
Diplopia, blurred vision, dilated pupils, oculogyric crises.
Miscellaneous
Weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome, malignant melanoma (see 4.3 Contra-indications).
Other side effects that have been reported with Credanil CR and may be potential side effects with Credanil include:
Neurological
Falling, gait abnormalities

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Credanil 25/250 Tablets. (see section 4.4. “Special warnings and precautions for use”).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Management of acute overdosage with Credanil is basically the same as management of acute overdosage with Levodopa; however pyridoxine is not effective in reversing the actions of

Credanil. ECG monitoring should be instituted, and the patient carefully observed for the possible development of arrhythmias; if required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as Credanil should be taken into consideration. To date, no experience has been reported with dialysis, and hence its value in the treatment of overdosage is not known.
The terminal half-life of Levodopa is about two hours in the presence of Carbidopa.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Levodopa is a precursor of dopamine, and is given as replacement therapy in Parkinson's disease.
Carbidopa is a peripheral dopa decarboxylase inhibitor. It prevents metabolism of Levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine acts. A lower dose of Levodopa can be used, reducing the incidence and severity of side effects.
Credanil is useful in relieving many of the symptoms of parkinsonism, particularly rigidity and bradykinesia. It is frequently helpful in the management of tremor, dysphagia, sialorrhoea, and postural instability associated with Parkinson's disease and syndrome.
When response to Levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not controlled evenly throughout the day, substitution of Credanil usually reduces fluctuations in response. By reducing some of the adverse reactions produced by Levodopa alone, Credanil permits more patients to obtain adequate relief from the symptoms of Parkinson's disease.

5.2. Pharmacokinetic properties

Following oral dosing Levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastrointestinal tract. It has a plasma half life of about 1 hour and is mainly converted by decarboxylation to dopamine, a proportion of which is converted to Noradrenaline. Up to 30 % is converted to 3-O-methyldopa which has a half life of 9 to 22 hours. About 80 % of Levodopa is excreted in the urine within 24 hours mainly as homovanillic acid and dihydroxyphenylactic acid. Less than 1 % is excreted unchanged.
Once in the circulation it competes with other neutral amino acids for transport across the blood brain barrier. Once it has entered the striatal neurones it is decarboxylated to dopamine, stored and released from presynaptic neurones. Because Levodopa is so rapidly decarboxylated in the gastrointestinal tract and the liver very little unchanged drug is available for transport into the brain. The peripheral decarboxylation reduces the therapeutic effectiveness of Levodopa but is responsible for many of its side effects. For this reason Levodopa is usually administered together with a peripheral decarboxylase inhibitor such as Carbidopa so that lower doses may be given to achieve the same therapeutic effect.
Carbidopa in the absence of Levodopa, is rapidly but incompletely absorbed from the gastrointestinal tract following oral dosing. Following an oral dose approximately 50% is recorded in the urine with about 30 % of this as unchanged drug. It does not cross the blood brain barrier but crosses the placenta and is excreted in breast milk. Turnover of the drug is rapid and virtually all unchanged drug appears in the urine within 7 hours.

Carbidopa inhibits the peripheral decarboxylation of Levodopa to dopamine but as it does not cross the blood brain barrier, effective brain levels of dopamine get produced with lower levels of Levodopa therapy reducing the peripheral side effects noticeably nausea and vomiting and cardiac arrhythmias.

5.3. Preclinical safety data

Credanil is well established in medical use. Preclinical data is broadly consistent with clinical experience. (For reproductive toxicity, see section 4.6 Pregnancy and Lactation).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Povidone, Microcrystalline Cellulose, Sodium Starch Glycollate, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Talc, Brilliant Blue, Sunset Yellow E.110, Disodium Edetate, Glycerol.

6.2. Incompatibilities

Not Applicable.

6.3. Shelf life

5 Years.

6.4. Special precautions for storage

Store in a dry place below 25°C, protected from light.

6.5. Nature and contents of container

Retail packs containing 20 and 50 tablets in blister packs. Hospital packs containing 100, 500 and 1000 tablets in PP/PE Containers or in blister packs.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Not Applicable.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

06278/07972/REN/2021

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of latest renewal: Jul 25, 2021

10. DATE OF REVISION OF THE TEXT

11/07/2023