SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF MEDICINAL PRODUCT

Trade Name: TIDOMET FORTE

Generic Name: CO CARELDOPA TABLETS BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Carbidopa BP equivalent to
Carbidopa Anhydrous .....25 mg
Levodopa BP..... 250 mg
Excipients..... q.s.

3. PHARMACEUTICAL FORM

White to off white, round flat uncoated tablets with break line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antiparkinsonian agent.
For treatment of Parkinson's disease and syndrome.

4.2 Posology and method of administration

To be taken orally.
The optimum daily dosage of 'Tidomet Forte' must be determined by careful titration in each patient.
'Tidomet Forte' 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 and100 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 'Tidomet Forte' is being administered, although their dosage may have to be adjusted.
Because both therapeutic and adverse effects are seen more rapidly with 'Tidomet Forte' 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 'Tidomet Forte 25 mg/100 mg' three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet of 'Tidomet Forte 12.5 mg/50 mg' or 'Tidomet Forte 25 mg/100 mg' every day or every other day, as necessary, until a dosage equivalent of eight tablets of 'Tidomet Forte 25 mg/100 mg' a day is reached.

If 'Tidomet Forte 10 mg/100 mg Tablets' or 'Tidomet Forte 12.5 mg/50 mg Tablets' are 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.
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.
'Tidomet Forte 12.5 mg/50 mg Tablets' or 'Tidomet Forte 10 mg/100 mg Tablets' 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 'Tidomet Forte'.
The easiest way to do this is to give 'Tidomet Forte' as the first morning dose after a night without any levodopa. The dose of 'Tidomet Forte' 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 'Tidomet Forte 25 mg/100 mg' 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 'Tidomet Forte 25 mg/250 mg' three or four times a day.

Maintenance
Therapy with 'Tidomet Forte' should be individualised and adjusted gradually according to response. When a greater proportion of carbidopa is required, each tablet of 'Tidomet Forte 10 mg/100 mg' may be replaced with a tablet of 'Tidomet Forte 25 mg/100 mg' or 'Tidomet Forte 12.5 mg/50 mg'.
When more levodopa is required, 'Tidomet Forte 25 mg/250 mg Tablets' should be substituted at a dosage of one tablet three or four times a day. If necessary, the dosage of 'Tidomet Forte 25 mg/250 mg Tablets' may be increased by one tablet every day or 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 'Tidomet Forte' from levodopa combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours before 'Tidomet Forte' is started. Begin with a dosage of 'Tidomet Forte' 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 'Tidomet Forte' is introduced, although dosage may have to be adjusted in line with manufacturers recommendations.

Use in children
The safety of 'Tidomet Forte' in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

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.

4.3 ***Contraindications***

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with 'Tidomet Forte'. These inhibitors must be discontinued at least two weeks before starting 'Tidomet Forte'. 'Tidomet Forte' may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. selegiline hydrochloride).

'Tidomet Forte' is contraindicated in patients with narrow-angle glaucoma and in patients with known hypersensitivity to any component of this medication.

Since levodopa may activate a malignant melanoma, it should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

Use in patients with severe psychoses.

4.4 Special warnings and precautions for Use

'Tidomet Forte' is not recommended for the treatment of drug-induced extrapyramidal reactions.

'Tidomet Forte' 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 gastrointestinal haemorrhage).

Care should be exercised when 'Tidomet Forte' 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.

Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa.

Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

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, 'Tidomet Forte' 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 'Tidomet Forte' is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of 'Tidomet Forte' 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 'Tidomet Forte' 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 convulsionsshould 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 'Tidomet Forte', 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 'Tidomet Forte' 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, 'Tidomet Forte' may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 2-6 fold higher). It is unclear whether the increased risk observed was due to Parkinson's disease, or other factors such as drugs used to treat Parkinson's disease. Therefore patients and providers are advised to monitor for melanomas on a regular basis when using 'Tidomet Forte' for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

4.5 Interactions with other medicinal products and other forms of interaction

Caution should be exercised when the following drugs are administered concomitantly with 'Tidomet Forte'.

Antihypertensive agents

Postural hypotension can occur when 'Tidomet Forte' 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 first paragraph of 4.3 'Contraindications' for patients receiving MAOIs).

Anticholinergics

Anticholinergics may affect the absorption and thus the patient's response.

Iron

Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulphate or ferrous gluconate.

Other drugs

To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian drugs.

Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones, and risperidone) and isoniazid, may reduce the therapeutic effects of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with 'Tidomet Forte' should be carefully observed for loss

of therapeutic response.

Use of 'Tidomet Forte' with dopamine-depleting agents (e.g., tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone.
Since levodopa competes with certain amino acids, the absorption of 'Tidomet Forte' may be impaired in some patients on a high protein diet.
The effect of simultaneous administration of antacids with 'Tidomet Forte' on the bioavailability of levodopa has not been studied.
'Tidomet Forte' 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 'Tidomet Forte' 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 'Tidomet Forte' in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Breast-feeding mothers

It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human breast milk was reported. 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 'Tidomet Forte', taking into account the importance of the drug to the mother.

4.7 Effects on Ability to Drive and use Machines

Individual responses to medication may vary and certain side effects that have been reported with 'Tidomet Forte' may affect some patients' ability to drive or operate machinery. Patients treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines), until such recurrent episodes and somnolence have resolved.

4.8 Undesirable Effects

Side effects that occur frequently with 'Tidomet Forte' 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 and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.
Other side effects reported in clinical trials or in post-marketing experience include:
Body as a whole: syncope, chest pain, anorexia.
Cardiovascular: cardiac irregularities and/or palpitations, orthostatic effects including hypotensive episodes, hypertension, phlebitis.
Gastro-intestinal: vomiting, gastro-intestinal bleeding, development of duodenal ulcer, diarrhoea, dark saliva.
Haemotologic: leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.
Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura.

Nervous System/Psychiatric: neuroleptic malignant syndrome, bradykinetic episodes (the "on-off" phenomenon), dizziness, paraesthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, depression with or without development of suicidal tendencies, dementia, dream abnormalities, agitation, confusion, increased libido. Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.
Respiratory: dyspnoea.
Skin: alopecia, rash, dark sweat.
Urogenital: dark urine.
Rarely convulsions have occurred; however, a causal relationship with 'Tidomet Forte' has not been established.
Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side effects with 'Tidomet Forte' include:
Gastro-intestinal: dyspepsia, dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, flatulence, burning sensation of the tongue.
Metabolic: weight gain or loss, oedema.
Nervous System/Psychiatric: asthenia, decreased mental acuity, disorientation, ataxia, numbness, increased hand tremor, muscle cramp, trismus, activation of latent Horner's syndrome, insomnia, anxiety, euphoria, falling, gait abnormalities and Dopamine Dysregulation Syndrome.
Description of selected adverse reactions
Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias.
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 Tidomet Forte.
Skin: flushing, increased sweating.
Special senses: diplopia, blurred vision, dilated pupils, oculogyric crises.
Urogenital: urinary retention, urinary incontinence, priapism.
Miscellaneous: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, malignant melanoma.

4.9 Overdose

Treatment
Management of acute overdosage with 'Tidomet Forte' is basically the same as management of acute overdosage with levodopa; however pyridoxine is not effective in reversing the actions of 'Tidomet Forte'. 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 'Tidomet Forte' 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

Pharmacotherapeutic group: Antiparkinsonian agent.
ATC code: N04BA02

Mechanism of Action

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.

'Tidomet Forte' 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 'Tidomet Forte' usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, 'Tidomet Forte' 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 gastro-intestinal tract. t 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 gastro-intestinal 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 3% 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

'Tidomet Forte' is well established in medical use. Preclinical data is broadly consistent with clinical experience.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Polyvinyl Pyrrolidone (K-30)
Isopropyl Alcohol
Talc
Magnesium Stearate
Starch (Dried)
Colloidal Silicon Dioxide
Microcrystalline Cellulose (PH 102)

6.2 Incompatibilities

Not Applicable

6.3 Shelf-life

48 months from the date of manufacturing

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture

6.5 Nature and Contents of Container

Co-Careldopa Tablets are packed in Strip pack of 10 Tablets.

6.6 Special Precautions for Disposal and other Handling

Not applicable

7. MARKETING AUTHORIZATION HOLDER

Torrent Pharmaceuticals Ltd.,
"Torrent House",
Off Ashram Road,
Ahmedabad – 380 009
INDIA.
Tel. No.: 91-79-6583060 / 6585090
Fax. No.: 91-79-6582100

8. MARKETING AUTHORIZATION NUMBER

TOR/IND/022
06644/07959/REN/2021

9. DATE OF AUTHORIZATION OR OF THE LAST RENEWAL OF THE AUTHORIZATION

Last renewal date : Oct 19, 2021

10. DATE OF REVISION OF TEXT

30-01-2021