Carbidopa/Levodopa Enteral Suspension (Duopa)

Outpatient Use in the USA

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I. INTRODUCTION
Carbidopa/levodopa enteral suspension (CLES; Duopa) is a suspension or gel formulation of carbidopa/levodopa that is approved for the treatment of advanced Parkinson’s disease (PD) patients with motor fluctuations. CLES is delivered at a constant rate continuously throughout the day into the jejunum through an infusion pump via a PEG-J tube implanted surgically. This delivery method avoids the stomach and therefore the issues of slowed or inconsistent gastric emptying, which can negatively impact the efficacy of carbidopa/levodopa. CLES is packaged in a single use 100mL cassette that contains carbidopa (4.63mg/mL) and levodopa (20mg/mL) for a total of 2000mg of levodopa that is typically delivered over a 16 hour period.

CLES efficacy was established in the USA based on a randomized, double-blind, double-dummy, active controlled, parallel group, 12-week study. (1) In this study, mean OFF time in the oral immediate release carbidopa/levodopa group was reduced by 2.1 hours and in the CLES group mean OFF time was reduced by 4.0 hours. This represents an additional reduction of 1.9 hours of daily OFF time in the CLES group compared to oral immediate release carbidopa/levodopa. There was also an increase of 1.9 hours of on time without troublesome dyskinesia in the CLES group compared to oral carbidopa/levodopa.

Similar to oral carbidopa/levodopa, it is critical to determine the most effective dose for each individual. Therefore, it is critical to understand the appropriate conversion of the current carbidopa/levodopa daily dosages to the CLES dosage and how to program the pump and titrate CLES to achieve the most effective dose. For the best results, the assembly of a consistent team of healthcare professionals is recommended. The team would consist of the neurologist for patient selection, dose conversion and titration, a proceduralist to implant the tube and address any post-surgical issues, and a nurse to assist with patient education and pump programming.

Patient Selection
This therapy is indicated in PD patients who are responsive to levodopa and have motor fluctuations despite optimal treatment with oral anti-PD medications. Patients should currently be taking oral carbidopa/levodopa therapy and should have at least tried at least one other class of PD medication like dopamine agonists, COMT inhibitors or MAO-B inhibitors. Since this therapy requires the surgical implantation of the jejunal tube, this therapy is contraindicated in patients who have gastric and intestinal disorders like intestinal obstruction, ascites, inflammatory and infiltrative diseases of the gastric and abdominal walls.

Figure 1. Cassette (black) and pump

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disorders like sepsis, peritonitis and coagulation disorders should be treated before considering this therapy.

**Therapy Hardware**

1. Cassette - CLES consists of a 100 mL cassette containing carbidopa/levodopa suspension at 4.63 mg/20 mg per mL. This cassette is designed for single use and majority of the patients use one cassette per day although rarely some patients taking more than 2000 mg of levodopa daily may require two cassettes daily. Although this therapy is approved for up to 16 hours per day, occasionally patients use it for more than 16 hours, particularly patients with nighttime OFF periods affecting sleep. The cassettes should be refrigerated but not frozen and should be at room temperature for 20 minutes prior to use.

2. Pump - The therapy is delivered by CADD-Legacy® 1400 infusion pump. The cassette is attached to the pump and the pump delivers CLES through the day.

3. Tubing - The system is composed of a jejunal tube, which is implanted via percutaneous endoscopic gastrostomy into the jejunum and exits through the stomach where it is connected to a PEG tube that is connected to the pump. The AbbVie J intestinal tube is 9 FR and the PEG is available in 2 sizes 15 and 20 FR. They have 2 ports; one in the stomach and the other one is in the jejunum (green color). If the stomach portion of the tube is also used for long-term enteral feeding, it is recommended that the 20 FR tube be used.

II. **SURGICAL PROCEDURE**

A percutaneous endoscopic gastrostomy procedure, using a jejunal tube (PEG-J) is performed by an experienced gastroenterologist, surgeon or interventional radiologist under local or general anesthesia. The majority of patients undergo the procedure under local anesthesia in an outpatient setting.

**Patient Instructions after jejunal tube placement:**

Patients should call their physicians immediately if they see drainage, redness, swelling, pain or warmth around the stoma which might indicate an infection. They should also call if they experience abdominal pain, constipation, nausea or vomiting, fever, blood in the stool or dark, tarry stools. Patients should be instructed to change the dressing regularly. The triangular fixation plate that is placed tightly against the skin by the surgeon should be left in place under moderate tension for 24-48 hours after which it should be loosened. The tube should not be moved in/out for the first 72 hours after the procedure and it should not be rotated. Long term management of the stoma should include checking the skin around the stoma for signs or infection or irritation. The stoma site should be cleaned with mild soap and water and the skin around the stoma should be kept dry.

The tube should be flushed every day with approximately 20 mL of room temperature drinking water. Both the tube connectors should be flushed. If flushing is difficult it may indicate blockage of the tube. It is better to avoid showering for 48 hours after the procedure. The pump should be disconnected before taking a shower, swimming or bathing. The stoma should be dried thoroughly after showering, swimming or bathing.

As part of the therapy care team, a specialized home nurse visits the patient prior to placement of the tube, following tube placement prior to titration, and following titration in order to assess for any issues and assist the patient in stoma care. There is no cost to the patient, this is provided by AbbVie as part of patient routine care as well as a 24/7 phone assistance program if needed.

**Surgical complications**

CLES is administered via a PEG-J that is implanted surgically and therefore, there is a risk of surgical complications and other gastrointestinal complications. In the CLES clinical trial, most adverse effects related to the surgical procedure or the
Device were mild to moderate in severity, occurred within the first week and resolved. (1) In the CLES clinical trial, the most common surgical complications included abdominal pain, incision site erythema, post-surgical discharge, wound infection and device complications which can involve breakage, insertion, dislocation, occlusion or leakage of the intestinal tube, percutaneous gastrojejunostomy, pump or stoma. In the case of discontinuing this therapy, the qualified provider should withdraw the tube and let the stoma heal.

**Dose Selection**

The initial dose can be programmed by the pharmacy when the pump is delivered. The initial dosage calculation is based on the total daily dosage of immediate release levodopa used prior to the procedure. If the patient is taking other forms of levodopa like sustained release carbidopa/levodopa, carbidopa/levodopa/entacapone, or carbidopa/levodopa extended release capsules the daily dosages should be converted to immediate release dosages before calculating the CLES dose. There are various conversion factors used but it is recommended that the sustained release carbidopa/levodopa dose be reduced by 25% (i.e., if taking 200mg/day this would be converted to 150mg/day), the carbidopa/levodopa/entacapone dose would be increased by 25% (i.e., 400mg/day would be equivalent to 450 mg/day) carbidopa/levodopa extended release capsules should be reduced by 50% (i.e., 435mg/day would be converted to approximately 218 mg/day). The patient can actually be converted to the immediate release dosage or the above formulas can be used to immediately convert the patient from current dosages and formulations to the CLES dose. Once the total daily immediate release dose is calculated, it is necessary to calculate the morning dose, continuous dose and extra dose if necessary. CLES is usually administered over a 16-hour infusion period, so calculations are initially based on 16 hours of use.

**Morning dose:**

The morning dose is calculated by determining the total amount of levodopa in the first dose of the day and multiplying by 0.8 and then dividing by 20 to convert the dose from mg to mL. This is based on the fact that the cassette contains 100mL of medication with one mL being equivalent to 20mg of levodopa. Once the morning dose is calculated, 3 mL should be added to account for the medication in the tube. For example if the patient’s first dose of the morning is two tablets of carbidopa/levodopa 25/100, the morning dose of CLES would be 200 x 0.8 or 160 mg which is then divided by 20 equaling 8mL. An additional 3mL would be added as a prime to fill the tube, for a total of 11mL for the morning dose. The morning dose is administered over 10 to 30 minutes. The system only allows the morning dose to be dispensed once every 20-24 hours. The usual morning dose is between 5 and 10mL and normally does not exceed 15mL.

**Continuous dose:**

The continuous dose is calculated by determining the amount of levodopa the patient is taking after the morning dose and before the bedtime time dose if any. That will be the total amount of continuous dose during the day. For example if the patient is receiving carbidopa/levodopa 25/100 2 tablets five times a day along with a sustained release carbidopa/levodopa 50/200 at bedtime, the morning dose and nighttime dose are removed for a total of 800 mg during the day. To convert the 800mg daily dose to mL, the daily dose would be divided by 20, equaling 40mL. It should be noted that for the continuous dose, the conversion does not include the 0.8 multiplier used to calculate the morning dose. Assuming that the continuous delivery will occur over 16 hours, this would result in 2.5mL per hour. The majority of patients receive the continuous dose over 16 hours; however, some patients may continue the delivery up to 24 hours, largely based on the presence of nighttime OFF time and resultant disruption of sleep. In the case of 24 hour delivery, the dose calculated for the 16 hour continuous delivery is not changed, only extended, as this was
determined to be the optimal hourly dose. The usual continuous dose is 2 to 6mL/hr and sometimes can be as low as 1mL/hr or as high as 10mL/hr.

**Extra dose:**
The system also has the capacity to provide an extra dose of medication for patients experiencing unpredictable OFF times. The patient initiated extra doses are pre-programmed by the physician to control the maximum amount and frequency that the patient is able to administer. We typically initially program the pump to allow 1mL bolus every hour as an extra dose, until the optimal continuous dosage is determined.

Should a patient feel that they do not have optimal control of symptoms, they can push the extra dose button to administer the pre-set bolus. It should be noted that if a patient is using multiple extra doses each day, the daily continuous dose should be adjusted. Typically, the extra doses are 0.5 to 2mL.

**Night time dose:**
If the patient typically takes a nighttime dose of carbidopa/levodopa. The usual oral dosage should be taken at bedtime or throughout the night, if the CLES delivery has been discontinued for the day.

**Other PD Medications:**
In general, one does not need to reduce or discontinue other anti-parkinsonian medications like dopamine agonists, MAO-B inhibitors or amantadine. However, as motor fluctuations decrease it might be worth trying to reduce the adjunctive medications to help reduce the pill burden on the patients and the risk of dyskinesia. It is important to remind the patients to keep a supply of oral carbidopa/levodopa tablets in case they are unable to administer the infusion or have a blockage or other complication with the system.

**III. INITIATION OF THERAPY**
The patient generally returns to clinic to initiate therapy within one week of the tube implant. At our Center, patients are instructed to arrive after having taken their usual dosages of oral levodopa; therefore, they are typically in the ON state. In this case, the morning CLES dose would not be administered and initiation would begin with the continuous dose. Should the patient arrive in the OFF state then initiation would begin with the morning dose followed by the continuous dose. The pump and cassettes are delivered to the patient. They will be pre-programmed for the morning dose, continuous dose and extra doses per the prescribing physician instructions. Once the continuous dose is started, the patient is asked to wait 30 to 60 minutes after which the physician assesses the patient for any adverse events.

The patient generally returns in one week to determine if any dose adjustments are necessary. For example, the dose would be increased if the patient is not experiencing a good ON or decreased if the patient is experiencing dyskinesia. The physician will determine the magnitude of the change. At our Center, changes are generally made by 0.1 to 0.3 mL/hr increments. Should they experience any problems they should contact the physician immediately.

The patient should be instructed on how to connect and use the pump as well as how to take care of the stoma and given flushing/cleaning instructions. The patient will be given detailed instructions regarding the care and use of the system. The specialized home nurse will also review these instructions during their home visits and the patients can call the Duo Connect support line at any time.

**Some key points:**
- For home use, the cassette is removed from the refrigerator and kept at room temperature for 20 minutes.
- The cassette is attached to the pump, the red cap at the end of tube is removed and is not used during the medication delivery. The tube is connected to the green end of the PEG-J tube.
- It is important that the cassette is attached properly to the pump or the delivery may not be accurate. The locking button can be turned with a coin to lock before use and to unlock after use.
- The pump and cassette are placed in a holster that is usually placed around the neck or waist.
- There are two lock levels regarding the administration of medication
  - The system is completely locked and only the physician programmed morning, continuous and extra doses can be used
  - The pump can be programmed to allow the patient to adjust the dosages within a range specified and programmed by the physician
  - At the end of the day, the cassette should be disconnected from the pump. The cassette tube is twisted to disconnect from the green colored connector. The stomach tube should not be twisted.
  - A syringe filled with 20mL of room temperature drinking water is used to flush internal and external tubes. Hot water should not be used. The system should be flushed through both the green connector and the smaller white connector.
  - It is important to note that when the jejunal tube is flushed, the medication in the tube (3mL or 60 mg of levodopa) is dispensed.
Medication Side Effects

Medication adverse effects are similar to those seen with oral carbidopa/levodopa. The adverse events that occurred in at least 7% of patients while receiving CLES and with a higher incidence than oral carbidopa/levodopa in the USA clinical trial included nausea, depression, pedal edema, hypertension, upper respiratory tract infection and oropharyngeal pain.

IV. SUMMARY

CLES is approved for the treatment of levodopa-responsive PD patients experiencing OFF time, typically at least 3 hours, not controlled by other medications. The system provides continuous delivery of carbidopa/levodopa into the jejunum, with the goal of providing stable control of symptoms throughout the day. CLES is delivered through a calculated morning dose, continuous dose and extra doses as needed, which are determined and programmed by the physician/nurse for each individual. Patient selection, medication initiation
and system use are summarized in flow diagrams and case studies below. CLES has been shown to be effective in reducing OFF time and therefore allowing more consistent control of symptoms throughout the day.

**Case 1**
A 63 year old male with a history of PD since 1994. His symptoms have been progressive with good improvement in his symptoms with carbidopa/levodopa. He has tried entacapone, pramipexole, and rasagiline, but due to continued motor complications, he presented for consideration of CLES. He recently had reduced his dose of carbidopa/levodopa due to dyskinesia, so it was decided to use 2 mL/hr as the continuous dose with 1 mL as needed per hour as an extra dose. The patient returned one week later and complained of OFF time in the morning and during the day. His morning dose was increased to 8 mL and the continuous dose was increased to 2.2 mL/hour. The following week he felt his morning dose was kicking in but he did not feel his ON state during the day was optimal. We increased his continuous dose to 2.4 mL/hr. He returned the following week and his OFF time was reduced to 1 hour/day with less than one hour dyskinesia and he did not want to make any further medication changes.

**Case 2**
A 73 year old male diagnosed with PD in 2001. He was started on carbidopa/levodopa with good improvement in symptoms. Over the years ropinirole was added, but due to continued OFF time he presented for consideration of CLES therapy. He complains of 6 hour s of OFF time daily with 2 hours of dyskinesia. His current medications include carbidopa/levodopa 25/250 1.5 tab five times a day at 7a,10a,1p,4p,7p; ropinirole 3 mg three times a day; trazodone 50 mg at bedtime; and bupropion XL 150 mg daily. On examination he was alert oriented with MOCA score of 18/30. He had mild resting tremor on both sides with mild bradykinesia and rigidity. His gait was slow and shuffling but he was independent.

The patient’s CLES morning dose is carbidopa/levodopa 25/250 1.5 tab which is 375mg. Therefore, 375 x 0.8 is 300 which is divided by 20 for a conversion to 15mL. The continuous dose would be based on 4 doses of 1.5 tablets of carbidopa/levodopa 25/250, equaling 1500mg. The continuous dose is determined by dividing 1500 by 20 for a total daily dose of 75mL or 4.7mL/hr. An extra dose was programmed for 1.5 mL as needed up to once per hour. The patient returned after one week and felt that neither the morning or continuous dose was giving him his best ON state and hence the morning dose was increased of the 3 mL to prime the tube, the morning dose is 7mL. During the day he is taking 7 tab of carbidopa/levodopa 25/100, therefore, 700 is divided by 20 is 35 total mL or approximately 2.2mL/hour (35 divided by 16). The patient had recently reduced his oral levodopa due to dyskinesia, so it was decided to use 2 mL/hr as the continuous dose with 1 mL as needed per hour as an extra dose.
increased to 20 mL and the continuous dose was increased to 4.9 mL/hr. The patient returned after a week and had good improvement in symptoms with only 1-2 hours of OFF time during the day and no dyskinesia. He did not want to make any additional changes.

V. Reference

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