Considerations For Initiation and Maintenance of Foslevodopa/ Foscarbidopa For Advanced Parkinson's Disease[1]

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INTRODUCTION

Foslevodopa/foscarbidopa (LDp/CDp) delivered as a continuous 24-h/day subcutaneous infusion, offers continuous levodopa delivery and stable plasma levodopa levels that reduce motor fluctuations.

This narrative review provides practical guidance for clinicians on the real-world use of LDp/CDp, including information on patient selection, treatment initiation, dose adjustments, and long-term management.

CLINICAL OUTCOMES

- **Reductions** in **"Off" time.**
- **Increases** in **"On"** time without **troublesome dyskinesia.**
- **Improvements in sleep associated with positive changes in QoL.**
- **A safety profile consistent with previous studies.**

Approved in US, Canada, Europe, Japan and Middle East

Patient Identification for LDp/CDp

Ideal Candidates:

- Patients who meet the 5–2-1 criteria (≥5 LD doses daily; or at least 2 h of "Off" time, or ≥1 h of troublesome dyskinesia during the waking hours)
- ≥400 mg LD equivalents/day.
- Younger patients (aged ≤65 years), more active, and experiencing motor fluctuations and dyskinesias despite medication adjustments.*

Other patients that may benefit:

- Patients with ongoing nighttime sleep disturbances or painful dystonia in the morning.
- Patients with difficulty swallowing oral medications, or who experience sudden, severe "Off" time.

Caution should be used if initiating LDp/CDp in patients with a previous history of hallucinations, PD psychosis that is controlled, or mild-to-moderate cognitive impairment.

Because LDp/CDp is reversible and does not require surgical placement, it can be offered to patients as a first-line option once oral therapies have been tried without achieving sufficient motor symptom control.

Treatment Expectation Setting

- Motor symptom improvement may be experienced as early as the first day after treatment initiation. However, patients should be advised that even with continuous LDp/CDp delivery, "Off" time symptoms may still occur.
- Monotherapy with LDp/CDp can simplify patients' therapeutic regimens and possibly reduce AEs by minimizing the need for additional medications. However, while monotherapy is acceptable and sometimes ideal, reducing or stopping oral therapies should not be rushed to avoid any unwanted conditions (such as dopamine agonist withdrawal syndrome [DAWS]).
- It is important to set patient expectations for gradual symptom improvement over the first weeks. An initial 10-week commitment treatment period is recommended.

Education for both patients and care partners, should cover preparation for improvement with therapy, risks, LDp-CDp initiation, dose adjustments, ongoing therapy maintenance, and strategies for troubleshooting potential issues.

Guidance should also be provided on infusion site care, including good skincare practices, regular hygiene, monitoring skin tolerability, and recognizing potential dopaminergic side effects.

Best Practices in LDp/CDp Dosing Conversion and Initiation

Determining the initial continuous dosage of LDp/CDp

- LDp/CDp is intended to replace all oral LD medications and COMT inhibitors; however, some patients may benefit from occasional oral LD dosing or continuation of COMT inhibitor therapy.
- Clinicians should assess their patients' existing treatment regimen to ensure they are receiving optimized oral therapy prior to conversion.
- Initial dose calculation should be based on total daily LD equivalents and COMT inhibitor use (conversion rate: ×1.33 or ×1.5 for opicapone).
- Approved maximum doses vary by region (≈2500 mg LD in the US; ≈4260 mg in Europe).

Online conversion calculator available

- Patients should present to the clinic in the "On" state and start LDp/CDp 30–60 min before their next scheduled dose.
- It takes approximately 2–3 h to reach steady state.

Adjusting the hourly infusion rate

- The goal of LDp/CDp dose adjustment is to maximize "On" time, minimize troublesome dyskinesias, and reduce periods of "Off" time.
- The dose may be fine-tuned by increasing or decreasing the rate by 0.01 mL/hour (approximately 1.7 mg/hour of LD), with changes of 0.03–0.05 mL/hour generally recommended.

Setting and utilizing the optional loading dose

- A loading dose may be required for patients starting LDp/CDp therapy in an "Off" state or if the pump has been off for >3 h.
- This dose, typically between 0.1 and 3.0 mL, can be adjusted in increments of 0.1 mL.

Setting alternate rates and extra doses

- The infusion pump can be programmed with two alternative infusion rates and offers an extra dose option.

Low Rate

- May be helpful during nighttime hours, particularly among patients with nocturnal dyskinesias or a history of hallucinations.

10–30% Lower than the prescribed infusion rate.

High Rate

- May benefit patients who experience predictable periods of feeling underdosed, such as in the afternoon or during intensive physical activity

5–10% Above the base infusion rate

Extra Dose

- Patients can activate the "extra dose" function on the pump to manage acute "Off" symptoms that may occur, despite continuous therapy.
- This dose has a longer response time (60-90 min) and if patients regularly require extra doses, consider increasing the base flow rate.

Co-medication considerations

- Although clinicians should not aim for monotreatment when starting LDp/CDp, 20–40% of patients may be able to be treated with LDp/CDp monotherapy after initial optimization.
- Dose optimization may be achieved more efficiently if the patient's concomitant non– LD-containing medications are kept stable on initiation of LDp/CDp.
- These medications can gradually be tapered down/discontinued if any AEs occur and/or to simplify the treatment.
- Tapering down recommended oder: MAO-B inhibitors, amantadine, and then dopamine agonists to avoid withdrawal (including DAWS).
- Tapering should occur over several weeks or months, following recent guidelines, and patients should be closely monitored for withdrawal symptoms.

Best Practices in Treatment Initiation and Optimization

- Initiation of LDp/CDp can occur in the outpatient or inpatient setting. In many cases, the setting for initiation is driven by geographic or institutional factors.

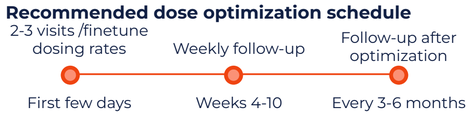
Outpatient initiation

- Standard in the US, suitable for most patients.
- Includes educational materials, practical demonstration of the delivery system and patients should be offered any available surport (e.g. home nurses) as appropriate.

Inpatient initiation

- Takes 3–10 days, depending on hospital and/or local health protocols, the patient's mobility, the patient's frailty, and the level of caregiver support.
- Training usually provided by Parkinson's nurses.

Recommended dose optimization schedule



Mitigation, Assessment, and Management

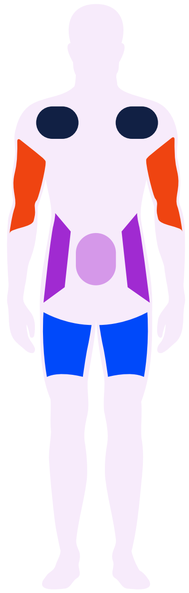
- Comparable or lower rates of infusion site events with LDp/CDp vs other subcutaneous infusion therapies.[2,3]
- The most common reasons for discontinuation were AEs, withdrawn consent, and lack of efficacy. Most discontinuations due to AEs occurred within the first 4–6 weeks of therapy.
- The **abdomen** is the preferred site, though other areas can be used: **hip, thigh, upper arm, scapula,** and **lateral abdomen.**
- Patients should try these alternative sites to determine what works best for them and to establish a good rotation to avoid infusion site events.

Preventive measures:

- Careful infusion site selection, good aseptic injection technique, and regular infusion site rotation are critical to prevent infusion site events.
- Rotate every 2-3 days. increase to daily or every other day if reactions or infections occur.
- Avoid areas with scarred tissue, stretch marks, or skin atrophy.

Cannula choice:

- 9 mm cannula is used more often. Preferred for patients with thick subcutaneous tissue around the infusion site or frequent physicial activity levels.
- 6 mm cannulas may be adequate for lean individuals with low body mass index and minimal subcutaneous tissue.
- Highly mobile sites may require additional adhesive support, regardless of cannula length.



Category	Key issues	Management/Recommendations
Drug Pooling	May appear as swelling (seldomly accompanied by redness) and can lead to reduced drug absorption.	✓Use a 9 mm cannula. ✓Ensure insertion device is pressed firmly and perpendicularly against taut skin during cannula placement. ✓Select new infusion site with sufficient subcutaneous fat without bony prominences or scarring. ✓Leave the used cannula in place for approximately 1 h after switching sites. ✓Use semi-permeable (or similar) dressings to reduce motion and support drug absorption. ✓Patients who experience recurrent pooling should consider site rotation every 24–48 h.
Nodules	Firm areas that may develop at or near the infusion site.	✓Change infusion site immediately. ✓Perform regular skin massage. ✓Apply firm, circular pressure for at least 10 min daily, or twice daily where persistent nodules exist. ✓In the case of a fibrotic nodule, corticosteroid injections may be considered after consultation with a dermatologist.
Skin Reactions	**Erythema, edema, dermatitis** Inflammatory infusion sites events typically present with signs of erythema, desquamation and pruritus.	✓Rotate infusion sites. ✓Some clinicians recommend topical corticosteroids for erythema. ✓Patch testing for allergic contact dermatitis may be considered if the local skin reaction persists despite infusion site rotation. ✓In mild cases of dermatitis, emollient use or application of low-potency topical corticosteroids may be considered.
Skin Infections	**Cellulitis** Signs of cellulitis may include pain, spreading erythema, edema, localized warmth, pus, and systemic signs such as fever. **Abscess** Signs of abscess ma include fluctuance, pain/tenderness, and fever.	✓If cellulitis is suspected, prompt intervention within 24h is essential. ✓Culture or empiric treatment with oral antibiotics should be initiated. ✓Patients should continue their infusion at a different site while cellulitis is being addressed. ✓Treatment of serious abscesses often requires incision and drainage in addition to appropriate systemic antibiotics.
Hallucinations	**Visual or auditory hallucinations** May be associated with: advancing PD, comorbid conditions and the use of certain medications (e.g DA).	✓Taper down or discontinue concomitant medications. ✓Reduce infusion rate overnight. ✓Consider antipsychotics (e.g., pimavanserin, quetiapine, clozapine), acetylcholinesterase inhibitors (donepezil, rivastigmine).

Conclusions

Successful initiation of LDp/CDp relies on thorough training and support. Healthcare providers and patients will experience a period of adjustment, but challenges in the first few weeks can be managed with education, hands-on guidance, and continued support.

Over time, this collaborative approach can lead to significant improvements in motor and nonmotor symptoms, sleep, and overall QoL for patients living with aPD, improving clinician and patient experiences.

*Patients in all age groups studied (aged <65 and ≥65 years) may benefit from treatment with LDp/CDp.

Abbreviations: AEs: Adverse Events; **aPD:** Advanced Parkinson's Disease; **COMT:** Catechol-O-methyl transferase; **DA:** Dopamine agonists; **DAWs:** Dopamine agonists to avoid withdrawal; **LD:** Levodopa; **LDp/CDp:** Foslevodopa/Foscarbidopa; **MAO-B:** Monoamine oxidase B inhibitors; **PD:** Parkinson's Disease; **QoL:** Quality of Life.

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