デュオドーパ配合経腸用液
に関する資料

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1.5 起原又は発見の経緯及び開発の経緯

略号及び用語の定義一覧

略号

略語又は用語	省略していない表現又は説明（英語）	省略していない表現又は説明（日本語）
PD	Parkinson's disease	パーキンソン病
COMT	Catechol-O-methyltransferase	カテコール-O-メチルトランスフェラーゼ
DBS	Deep Brain Stimulation	脳深部刺激療法
IV	Intravenous	静脈内
JP	Japanese Pharmacopeia	日本薬局方
ICH	International Conference on Harmonization	日米 EU 医薬品ハーモナイゼーション国際会議
PVC	polyvinyl chloride	ポリ塩化ビニル
AUC	Area under the plasma concentration-time curve	血漿中濃度-時間曲線下面積
DHPA	3,4-dihydroxyphenylacetone	3,4-ジヒドロキシフェニルアセトン
DHPPA	2-methyl-3-(3, 4-dihydroxyphenyl)propionic acid	2-メチル-3-（3,4-ジヒドロキシフェニル）プロピオン酸
LCIG	Levodopa-Carbidopa Intestinal Gel	レボドパ / カルビドパ水和物配合経腸用液
3-OMD	3-O-methyldopa	3-O-メチルドパ
PK	Pharmacokinetics	薬物動態
AE	Adverse Event	有害事象
UPDRS	Unified Parkinson's Disease Rating Scale	統一パーキンソン病評価尺度
PDQ-39	Parkinson's Disease Questionnaire-39	—

1.5.1 起原又は発見の経緯

パーキンソン病（PD）は，アルツハイマー病に次いで 2 番目に多い神経変性疾患である [1]。PD の罹患率は，65 歳から 69 歳までででは約 0.5%から 1%であり，80 歳以上では 1%から 3%に上昇する [2]。厚生労働省が平成 23 年に実施した患者調査（宮城県の石巻医療圏，気仙沼医療圏及び福島県を除く）では，日本における PD 患者の総数は 14.1 万人（男性：5.7 万人，女性：8.4 万人）と推定されており，年齢では 65 歳以上が 12.1 万人と全体のほとんどを占めている。これらのことから，高年齢化が進む日本では，今後，PD 患者数が増加していくものと推察される。また，PD 患者のうち，特定疾患の認定基準（H&Y 重症度 III 以上で，かつ生活機能障害度 2～3 度）を満たす患者は，特定疾患患者として認定され，特定疾患医療受給者証が交付されている 。

この疾患の特徴は，ドパミン作動性黒質線条体路の進行性変性及びドパミン枯渇であり，その結果，動作緩慢，筋固縮，振戦，姿勢反射障害などの中核的な運動症状が発現する [3]。レボドパはドパミンのアミノ酸前駆体であり，枯渇した線条体ドパミンを補充する。レボドパは，末梢でレボドパからドパミンへの変換を阻害する脳外ドパ脱炭酸酵素の活性阻害剤であるカルビドパと併用される [4]。レボドパ－カルビドパ配合錠は，PD 治療における第一選択薬である [5,6]。

レボドパとカルビドパの配合剤は，PD 患者の運動症状を劇的に改善させる最も有効な治療法であるが [7-10]，長期間の使用により，運動合併症（運動症状の日内変動及びジスキネジア）を引き起こすようになる。この運動合併症は，レボドパを 5 年から 10 年服用してきた PD 患者の最大 90%に認められることが報告されている。レボドパに関連して発現する運動合併症はコントロールが非常に困難であり，進行期 PD 患者における重要な機能障害を代表するものとなっている。現在までの研究により，運動合併症が誘発される原因は，半減期の短い経口レボドパが線条体ドパミン受容体に断続的かつ強力に作用するためと考えられている。

レボドパの反応性が一定しなくなる現象を解消するためにいくつかの方法が行われている。レボドパの投与量，投与頻度は患者の状態に応じて調節されるが，多くの患者にとって頻回の投与は負担となっている。レボドパの経口剤はしばしば長期作用性のドパミンアゴニスト，モノアミン酸化酵素阻害剤，カテコール-O-メチル転位酵素（COMT）阻害剤と併用される。しかしながら，これらの既存の薬剤のそれぞれの最適な使用方法にも関わらず，進行期 PD の運動障害は治療が困難な場合がある。いくつかのより侵襲的手法が研究されており，レボドパの静脈内投与 [11-14]，脳深部刺激療法（Deep Brain Stimulation：DBS）[15] 等が試みられている。脳深部刺激療法は進行期 PD の治療に使用されており，運動症状の日内変動に効果が認められているが，持続的な合併症が多くの患者で認められ，また，高価であり，すべての PD 患者が脳手術の対象とはならないことから，その使用には限界がある [16]。レボドパの静脈内持続投与は技術的な問題のために臨床的に実用的な方法ではない。しかしながら，レボドパの一定速度での静脈内投与方法は進行期 PD の運動障害に対して著明な効果が認められている [13,14]。そして，ドパミン受容体を断続的にではなく，持続的に刺激することにより，運動合併症の誘発が抑制され，安定した抗 PD 効果が得られると考えられている [7,13,14,17,18]。また，近位腸管へのレボドパの直接投与は，標準的な経口治療と比較して，運動症状の日内変動を軽減させることが明らかになっており，効果的な投与方法と考えられている。

LCIG は，レボドパ及びカルビドパを 4 対 1 の割合で含むゲル剤であり，[redacted]した薬物粒子を均一に分布させるのに適した粘性を有するカルボキシメチルセルロースナトリウム溶液に懸濁している。LCIG をコンピュータ制御式携行輸液ポンプ CADD Legacy® 1400 及び経皮的内視鏡的胃瘻造設術により挿入した空腸チューブ（PEG-J）を通して空腸へ直接投与することにより，レボドパはその部位で溶解し，空腸に局在する能動的担体輸送システムによって速やかに吸収される。LCIG の空腸への直接投与は，断続的な胃からの排泄の影響を回避し，レボドパの血中濃度を個々の患者の治療ウィンドウ内に保つことで，脳内のドパミン受容体を断続的ではなく持続的に刺激する。このことにより，運動症状の日内変動を軽減させるとともに，長年にわたり経口レボドパ治療を受けてきた進行期 PD 患者の ON 時間を増加させ，ジスキネジアの発症をも抑制する[8]。ABT-SLV187 投与により，経口投与により重篤化した PD の症状が著明に改善したことが報告されている[19]。

本剤は，2009 年 5 月 12 日に希少疾病用医薬品の指定を受けた［指定番号：（21 薬）第 224 号］。

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1.5.2 開発の経緯

1.5.2.1 品質に関する試験

(1)原薬

日本薬局方　医薬品各条のレボドパ（原薬等登録原簿）又はカルビドパ水和物（原薬等登録原簿）を[redacted]したものである。レボドパ（[redacted]）及びカルビドパ水和物（[redacted]）の規格は，日本薬局方　医薬品各条の規格に加え[redacted]を設定した。ICH ガイドラインに従ってレボドパ（[redacted]）及び日局カルビドパ水和物（[redacted]）の安定性試験（長期保存試験及び加速試験）を実施した。レボドパ（[redacted]）は，48 ヵ月間長期安定性試験のデータに基づき，リテスト期間を[redacted]ヵ月間に設定した。日局カルビドパ水和物（[redacted]）は，36 ヵ月長期安定性試験のデータに基づき，リテスト期間を[redacted]ヵ月間に設定した。これらの長期安定性試験は 60 ヵ月まで継続する。

(2)製剤
本品はレボドパとカルビドパ水和物を水溶性ゲル中に均一に懸濁した製剤であり，ポリ塩化ビニルバッグに充填され，医療用カセットに格納されている。製剤の規格はアッヴィ社にて ICH ガイドラインに従って設定した。ICH ガイドラインに従って製剤の安定性試験（長期保存試験，加速試験及び苛酷試験）に加えて段階的安定性試験を実施した。本剤をカセット容器に充填して実施した長期保存試験（-20℃，24 ヵ月間，5℃，15 週間）及び段階的安定性試験のデータに基づき，有効期間を解凍後 5℃ で 15 週間に設定した。

(3)新添加物
ゲル化剤として配合しているカルメロースナトリウムの含有量が使用前例量を超えていることが確認された。そのため，カルメロースナトリウムを新医薬品添加物として新医薬品添加物委員会に提出する。

1.5.2.2　非臨床試験

1.5.2.2.1　薬理試験

本申請に伴い新たな試験は実施していない。

1.5.2.2.2　薬物動態試験

レボドパ / カルビドパ水和物配合経腸用液（以下「LCIG」）には 4:1 の配合比でレボドパ及びカルビドパ水和物が含まれる。レボドパは LCIG の有効成分であり，芳香族アミノ酸脱炭酸酵素によるドパミンへの脱炭酸により主として代謝される。ドパミンはカテコールアミンの一種である神経伝達物質で，運動機能の制御において重要な役割を担っている。カルビドパは芳香族アミノ酸脱炭酸酵素の競合的阻害剤である。レボドパと併用投与すると，カルビドパは末梢でレボドパの脱炭酸を阻害する。ラットにおいてカルビドパと併用投与するとレボドパの薬物動態が改善すること（クリアランスの減少，半減期の増加，AUC の増加）が報告されている。非臨床動物種及びヒトにおけるカルビドパの分解物 / 代謝物として 3,4-ジヒドロキシフェニル

アセトン （以下「DHPA」），2-メチル-3-（3,4-ジヒドロキシフェニル）プロピオン酸（以下「DHPPA」）及びヒドラジンが含まれる。

単独投与及び併用投与時のレボドパ及びカルビドパの非臨床薬物動態プロファイルを公表文献に基づき評価し，本概要にまとめた。本概要に記載した新たな情報として，ラットにおける一連の試験により，カルビドパ，DHPA 及び DHPPA を静脈内及び経口投与したときの薬物動態を明らかにした。更に Swiss Webster マウス及び Wistar 系ラットによる一連の試験で，ヒドラジンを経口投与した後の薬物動態を明らかにした。

1.5.2.2.3 毒性

レボドパ単剤，カルビドパ単剤及びレボドパ/カルビドパの併用による新規の一般毒性試験は実施しなかった。LCIG の投与方法について毒性評価するあたり，ミニブタを用いて LCIG 投与後の消化管に対する刺激性を評価するための毒性試験を実施した。その他，規格値設定のために，カルビドパの代謝物/分解物である DHPA 及び DHPPA の *in vitro* 遺伝毒性試験毒性及び 4 週間反復投与毒性試験を実施した。主要な毒性試験は，医薬品の安全性に関する非臨床試験の実施の基準（以下「GLP」）に準拠して実施した。

1.5.2.3 臨床試験

1.5.2.3.1 国内における開発

1.5.2.3.1.1 治験相談

各臨床試験実施に先立ち，医薬品医療機器総合機構と以下の対面助言行った。

1.5.2.3.1.1.1 医薬品[redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

主な機構の見解

- [redacted]
- [redacted]
- [redacted]

以上の見解を踏まえ，[redacted]を検討することとした。

1.5.2.3.1.1.2 医薬品[redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

主な機構の見解

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

[redacted]

1.5.2.3.1.1.3 医薬品[redacted]相談[redacted]（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

主な機構の見解

- [redacted]
  - [redacted]
  - [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]について，20[redacted]年[redacted]月[redacted]日に医薬品[redacted]相談を行った。

1.5.2.3.1.2　国内での臨床試験

既存の治療で十分な効果が得られていない進行期 PD 患者を対象に，本邦における第 II 相臨床試験（M12-925 試験），アジア地域（日本，韓国及び台湾）における第 III 相臨床試験（M12-921 試験），及び M12-921 試験を完了した被験者並びに M12-925 試験に参加した被験者を対象とした第 III 相長期投与試験（M12-923 試験）を実施した。なお，M12-923 試験は試験継続中である。

M12-925 試験の主目的は，進行期 PD 患者を対象に，LCIG の安全性と忍容性を経口レボドパ - カルビドパ製剤と比較することであった。ベースラインから LCIG 治療終了までの OFF 時間の変化は FAS で平均-2.68 時間であった(P=0.002)。ビデオ評価は盲検下で行うことが可能となるメリットがあるものの，3 人の評価委員会メンバー間で一貫性のある評価結果が得られなかった。この結果より，第 III 相試験においては，患者日誌がより適切な評価結果を得られると結論付けられた。進行期 PD 患者の治療の質を改善するために，OFF 時間の減少には重要な意味がある。M12-921 試験と M12-923 試験においては，LCIG/PEG-J の治療を受けた患者では，ベースラインから 12 週あるいは 24 週での標準化された OFF 時間に著しい減少が認められた(それぞれ–4.64 時間と -4.55 時間, P<0.001)。

評価試験（M12-921 試験，M12-923 試験及び M12-925 試験）においては，薬剤に由来する有害事象が既存の経口レボドパ - カルビドパ製剤で見られるものと同等であった。このことから，他の PD 治療で適切に管理できないレボドパに反応を示す進行期の特発性 PD 患者の運動症状の日内変動の長期にわたる治療においては，LCIG システムは安全性及び忍容性に関して許容できるものである。また，試験中に見られた AE の大部分は軽度か中等度の重症度であった。

M12-921 試験を無事に完了することが出来た全ての患者は，LCIG の忍容性を確認し，システム全体を受け入れて M12-923 試験へ移行した。

1.5.2.3.2 海外における開発

1993 年に，スウェーデン ウプサラ大学の Bredberg 等はレボドパの頻回投与にもかかわらず重度の運動合併症を有する進行期 PD 患者 5 名に対し，レボドパ / カルビドパ配合剤を粉砕し，水性懸濁液中に分散させた薬液を経鼻空腸チューブによりポンプを用いて持続的に投与した結果，経口投与（徐放製剤）と比較して，十二指腸投与では血漿中レボドパ濃度の安定，ON 時間の増加，ジスキネジアの減少が認められたことを報告した。

この報告を基に，スウェーデンの NeoPharma AB 社（現，AbbVie Inc.）は，[redacted]と共同で LCIG の開発に着手し，19[redacted] 年に臨床試験を開始した。LCIG は，2001 年 5 月に欧州で希少疾病用医薬品に指定され，2004 年 1 月に「既存のパーキンソン病治療薬では十分な効果の得られない重度の運動症状の日内変動（motor fluctuations）及びジスキネジアを有するレボドパ反応性の進行期パーキンソン病」に対する治療薬として，スウェーデンで初めて承認を取得している。その後，EU 諸国のフランス（2004 年），ドイツ（2005 年）及びイギリス（2005 年）等の主要国で承認が取得され，上市されている。

また，米国では Solvay Pharmaceuticals 社（現，アッヴィ社）が 2000 年 1 月に希少疾病用医薬品の指定を受けて開発に着手し，2015 年 1 月に承認を取得した。

2016 年 2 月現在で，LCIG は 48 ヵ国で承認されており，大部分の国では Duodopa®という商品名（米国においては，Duopa®の商品名）で販売されている。

これまでに実施した臨床試験成績から，LCIG システムは，他の PD 治療薬では十分にコントロールができない進行期 PD 患者の運動症状の日内変動の治療において，統計的に有意であり臨床的にも有意義な利益が示されている。LCIG システムは，このような治療選択肢が限られている患者集団にとって重大な医学的アンメットニーズに対処できる可能性があると考えられる。LCIG システムは，PD の最も有効な治療薬で，その処方が世界的に 30 年以上市販されてきたレボドパ送達の代替手段となり得る。また，レボドパ-カルビドパは，PD 治療に関し十分に特徴づけられており，医療従事者，患者および規制当局にも十分に認識されている。LCIG システムの一部である医療機器も既存の技術に適応し，その部品も製剤と適合していることが示されている。また，本システムは，個々の患者毎に最適化した持続的薬物送達を可能にする。

これまでに実施した臨床試験データから，LCIG システムの有効性に関する強力なエビデンスが得られている。複数の解析において，この試験結果の堅牢性のほか，進行した PD の被験者にみる持続的な運動変動の改善において，LCIG システムが経口 LC 製剤を上回る効果が示されている。主要な有効性評価では OFF 時間の減少が示され，重要な副次有効性評価では日常生活に支障となるジスキネジアを伴わない ON 時間の改善が示されている。このような PD 症状における臨床的に意義のある治療効果は，PDQ-39，CGI-I および UPDRS Part II においても一致した改善をもたらしている。このような改善は運動症状だけでなく，LCIG システムが，被験者の全体的な健康状態のほか，生活の質を改善するような日常生活の活動に従事するための患者の運動能力に利益を及ぼすことを示した。

この第Ⅲ相臨床試験の安全性プロファイルでは，LCIG 治療が一般に安全で忍容性も良好であることが示されている。全体として，殆どの有害事象の重篤度は軽度～中等度であると評価されているが，注目すべき点は，試験群の早期中断率が低い(≤ 11%)ことであり，このことは被験者らが LCIG システムから得た利益が，有害事象が原因で患者らが経験したリスクを上回っていたことを示した。

しかし，LCIG システムでは，医療機器の留置のために内視鏡的手技が必要であり，どの侵襲的手技にも伴うような関連リスクを伴う。例えば，腹膜炎，腸閉塞，腸出血，腸穿孔，腸虚血，イレウス，留置部位の潰瘍などの重篤な消化器関連の有害事象を伴う可能性があり，まれではあるが，致死的な転帰が生じる可能性もある。

ラベル表示に従った適切な患者集団を対象とし，適切な RMP（リスクマネージメントプラン）が整っていれば，LCIG システムは，非常に重要な代替治療の選択肢を提供し，重大な医療的アンメットニーズを伴う患者らの生活を改善することが可能と考える。ここで報告した統計的に有意で臨床的にも意義のある有効性の結果は，US 臨床試験群で観察された全体的な安全性の所見と共に，進行した PD 患者における LCIG システムに関する肯定的な利益-リスク プロファイルを構成している。

1.5.3 本剤の特徴及び有用性

レボドパは，進行期 PD 患者における治療の標準治療薬である。しかし，疾患の進行と共に狭くなる治療ウィンドウのために，経口レボドパ - カルビドパ治療では持続的に十分に運動症状の日内変動をコントロールすることが出来ない。進行期 PD 患者にとっては，起床している時間の大部分が「オフ」状態かあるいは日常生活に支障のあるジスキネジアを伴う「オン」状態となる。これらの持続的な運動症状の日内変動は日常運動動作を制限し，生活の質を低下させる。米国における第 III 相ピボタル試験の結果から，LCIG は，投与経路の変更により進行期 PD 患者に対し標準治療薬とされる経口薬治療を超える症状の改善をもたらすことが示された。

LCIG システムにより，他の抗 PD 薬で十分にコントロールすることができない進行期 PD 患者の運動症状の日内変動の治療に対して，統計学的に有意で臨床的に意味のあるベネフィットをもたらすことが示された。現在，日常生活に支障のあるジスキネジアを伴う ON 時間を悪化させることなく OFF 時間を減少させることのできる治療薬はない。LCIG システムは，PD に最も有効で，30 年以上に亘り世界中で販売されている治療法であるレボドパを送達するための新たな方法である。レボドパ-カルビドパの組み合わせは，PD 治療に関わる医療提供者，患者及び規制当局によって広く認識されている。LCIG システムの一部である医療機器は，既存の技術を用いたものであり，製剤との適合性も確認されている。これらの機器の使用により，個々の患者に対し個別に調整した用量を連続して投与することが可能となる。

国内外の臨床試験で得られたデータにより，LCIG システムの効果が強く裏付けられている。進行期 PD 患者の運動症状の日内変動に対し，LCIG システムが経口 LC 製剤に勝ることが統計学的な解析により証明されている。有効性の主要評価項目とした OFF 時間の減少や，主要な副

次的評価項目とした日常生活に支障のあるジスキネジアのない ON 時間の改善が示されている。また，国内第 III 相試験においては，ベースラインからの PDQ-39 スコアの改善，臨床全般印象度（CGI-C）の改善及び患者全般印象度（PGI-C）の改善が，PD 症状における臨床的に意味のある治療効果として認められた。これらの運動症状の改善により，LCIG システムが，患者の全般的な健康状態及び生活の質を改善させる日常生活動作に改善をもたらすことが示された。

海外で実施された臨床第 III 相試験においては，PD 症状を治療するために個々の患者に最適に調整した用量を投与している。投与量の評価や比較は実施していないものの，経口レボドパに比して LCIG により血漿中濃度の変動を抑え安定した状態に保つことで，経口レボドパで必要となるよりも低用量のレボドパ投与で PD 症状をコントロールできる可能性のあることが示されている。加えて，経口レボドパの間歇的な刺激と血漿中濃度の大きな変動を避けることで，日常生活に支障のあるジスキネジアを伴う ON 時間の悪化がなく，そして OFF 時間の一層の減少が得られるように，必要に応じて，経口レボドパよりも高用量の LCIG を投与することもできる可能性がある。また，単剤治療による運動症状の日内変動を改善することで，複数の抗 PD 薬が投与されている患者は併用薬の使用を減らし，服薬に伴う苦しみや関連するリスクを減少させる機会が得られるようになる。

また，海外の第 III 相オープン試験では，LCIG の単剤治療により，54 週間もの間，効果の減少や耐薬性を生じることがなく 75%を超える患者が運動症状のコントロールを行うことが可能であった。

海外の第Ⅲ相試験（S187-3-001/S187-3-002 及び S187-3-004）の成績の概要について，以下の表に示す。

海外臨床試験の成績の概要

試験番号 フェーズ (実施国)	被験者数 対象	試験 デザイン	試験成績
S187-3-001/ S187-3-002 Phase III (米国，ドイツ，ニュージーランド)	71名 最適に調整された既存のPD治療薬では十分なコントロールが得られない運動症状の日内変動を有する進行期PD患者	無作為化 二重盲検 ダブルダミー 経口レボドパ/カルビドパ対照 並行群間試験	〈主な有効性の評価〉 主要評価項目は，標準化された1日あたりの平均OFF時間（時間）のベースラインから12週目（エンドポイント）までの変化量である。 LCIG投与群及び経口LC投与群との標準化されたOFF時間の変化量のLS Meanの差が–1.91時間であり，統計学的に有意（$P = 0.0015$）であった。12週間の治療後，標準化された1日あたりの平均OFF時間は，LCIG投与群で経口LC投与群よりも大きく減少（改善）し，臨床的に意義のある変化であった（LS Mean：–4.04時間 vs. –2.14時間）。統計学的に有意な標準化された平均OFF時間の減少（改善）は，LCIG治療の最初の4週間に顕著であり，主要有効性評価項目のMMRM解析で示されたように，12週間の試験期間を通じて維持された。
			〈主な有害事象の割合〉 被験者71名中12名（16.9%）に重篤な有害事象が少なくとも1件発現し，群別の内訳はLCIG投与群で37名中5名（13.5%），経口LC投与群で34名中7名（20.6%）であった。高度の有害事象を発現した被験者は，LCIG投与群で37名中8名（21.6%），経口LC投与群で34名中11名（32.4%）であり，LCIG投与群の方が少なかった。中止に至った有害事象を少なくとも1件発現した被験者は，71名中3名であった。ほとんどの被験者（71名中69名，97.2%）に有害事象が発現した。有害事象を少なくとも1件発現した被験者は，LCIG投与群で37名中35名（94.6%），経口LC投与群で34名全員（100%）であった。発現率が最も高かったのは，医療機器挿入合併症に関連した有害事象であった。医療機器挿入合併症は，投与群を通じて被験者71名中36名（50.7%）から報告され，群別ではLCIG投与群で37名中21名及び経口LC投与群で34名中15名から報告された。次いで発現率が高かった有害事象は，腹痛を含む胃腸関連の有害事象であった。腹痛は，治療群を通じて被験者71名中30名（42.3%）から報告され，群別ではLCIG投与群で37名中19名及び経口LC投与群で34名中11名から報告された
S187-3-004 Phase III (米国，カナダ，オーストラリア，ニュージーランド，EU，イスラエル，ロシア，タ	354名 最適に調整された既存のPD治療薬では十分なコントロールが得られない運動症状の日内	非盲検 長期投与試験	〈主な有効性の評価〉 標準化されたOFF時間の減少は，ベースラインの6.77時間から54週エンドポイントの2.32時間に減少した（–4.44時間，$P < 0.001$）。日常生活に支障のあるジスキネジアを伴う平均ON時間では統計学的に有意な減少が各来院時に認められ（$P < 0.05$），ベースラインからエンドポイントまでの平均減少量は0.36時間であった（$P = 0.023$）。
			〈主な有害事象の割合〉 91.2%（323/354名）の被験者に有害事象が発現した。30.5%

<table>
<tr><th>試験番号
フェーズ
（実施国）</th><th>被験者数
対象</th><th>試験
デザイン</th><th>試験成績</th></tr>
<tr><td>イ）</td><td>変動を有する進行期PD患者</td><td></td><td>（108/354 名）の被験者で重篤な有害事象が報告されたが，重篤な有害事象の大部分は回復し，被験者は治験薬の投与を継続した。有害事象により 7.6%（27/354 名）の被験者が中止した。被験者の5%以上に報告された有害事象は以下の通りである。
<table>
<tr><th>器官別大分類</th><th>基本
（MedDRA 14.0）</th><th>全被験者
N = 354
n (%)</th></tr>
<tr><td>有害事象</td><td></td><td>323 (91.2)</td></tr>
<tr><td>胃腸障害</td><td></td><td></td></tr>
<tr><td></td><td>腹痛</td><td>102 (28.8)</td></tr>
<tr><td></td><td>便秘</td><td>57 (16.1)</td></tr>
<tr><td></td><td>下痢</td><td>27 (7.6)</td></tr>
<tr><td></td><td>消化不良</td><td>24 (6.8)</td></tr>
<tr><td></td><td>悪心</td><td>62 (17.5)</td></tr>
<tr><td></td><td>気腹</td><td>19 (5.4)</td></tr>
<tr><td></td><td>嘔吐</td><td>33 (9.3)</td></tr>
<tr><td>一般・全身障害および投与部位の状態</td><td></td><td></td></tr>
<tr><td></td><td>医療機器挿入合併症</td><td>123 (34.7)</td></tr>
<tr><td>感染症および寄生虫症</td><td></td><td></td></tr>
<tr><td></td><td>術後創感染</td><td>50 (14.1)</td></tr>
<tr><td></td><td>尿路感染</td><td>38 (10.7)</td></tr>
<tr><td>傷害，中毒および処置合併症</td><td></td><td></td></tr>
<tr><td></td><td>転倒</td><td>51 (14.4)</td></tr>
<tr><td></td><td>切開部位紅斑</td><td>43 (12.1)</td></tr>
<tr><td></td><td>切開部位痛</td><td>21 (5.9)</td></tr>
<tr><td></td><td>処置後分泌物</td><td>26 (7.3)</td></tr>
<tr><td></td><td>処置による疼痛</td><td>67 (18.9)</td></tr>
<tr><td></td><td>処置後局所反応</td><td>32 (9.0)</td></tr>
<tr><td>臨床検査</td><td></td><td></td></tr>
<tr><td></td><td>血中ホモシステイン増加</td><td>20 (5.6)</td></tr>
<tr><td></td><td>ビタミン B_6 減少</td><td>20 (5.6)</td></tr>
<tr><td></td><td>体重減少</td><td>36 (10.2)</td></tr>
<tr><td>代謝および栄養障害</td><td></td><td></td></tr>
<tr><td></td><td>食欲減退</td><td>19 (5.4)</td></tr>
<tr><td>筋骨格系および結合組織障害</td><td></td><td></td></tr>
<tr><td></td><td>背部痛</td><td>26 (7.3)</td></tr>
<tr><td></td><td>筋骨格痛</td><td>19 (5.4)</td></tr>
<tr><td></td><td>四肢痛</td><td>19 (5.4)</td></tr>
<tr><td>神経系障害</td><td></td><td></td></tr>
<tr><td></td><td>浮動性めまい</td><td>18 (5.1)</td></tr>
<tr><td></td><td>ジスキネジー</td><td>32 (9.0)</td></tr>
<tr><td></td><td>頭痛</td><td>31 (8.8)</td></tr>
<tr><td></td><td>パーキンソン病</td><td>33 (9.3)</td></tr>
</table>
</td></tr>
</table>

試験番号 フェーズ (実施国)	被験者数 対象	試験 デザイン	試験成績

精神障害	
不安	41 (11.6)
うつ病	29 (8.2)
幻覚	18 (5.1)
不眠症	67 (18.9)
睡眠発作	25 (7.1)
呼吸器，胸郭および縦隔障害	
口腔咽頭痛	25 (7.1)
皮膚および皮下組織障害	
過剰肉芽組織	52 (14.7)
血管障害	
起立性低血圧	29 (8.2)

相互参照：S187-3-004 試験 CSR Table 14.3__1.2.1.4

被験者の 10%以上に報告された有害事象は医療機器挿入合併症（34.7%），腹痛（28.8%），処置による疼痛（18.9%），不眠症（18.9%），悪心（17.5%），便秘（16.1%），過剰肉芽組織（14.7%），転倒（14.4%），術後創感染（14.1%），切開部位紅斑（12.1%），不安（11.6%），尿路感染（10.7%）及び体重減少（10.2%）であった。

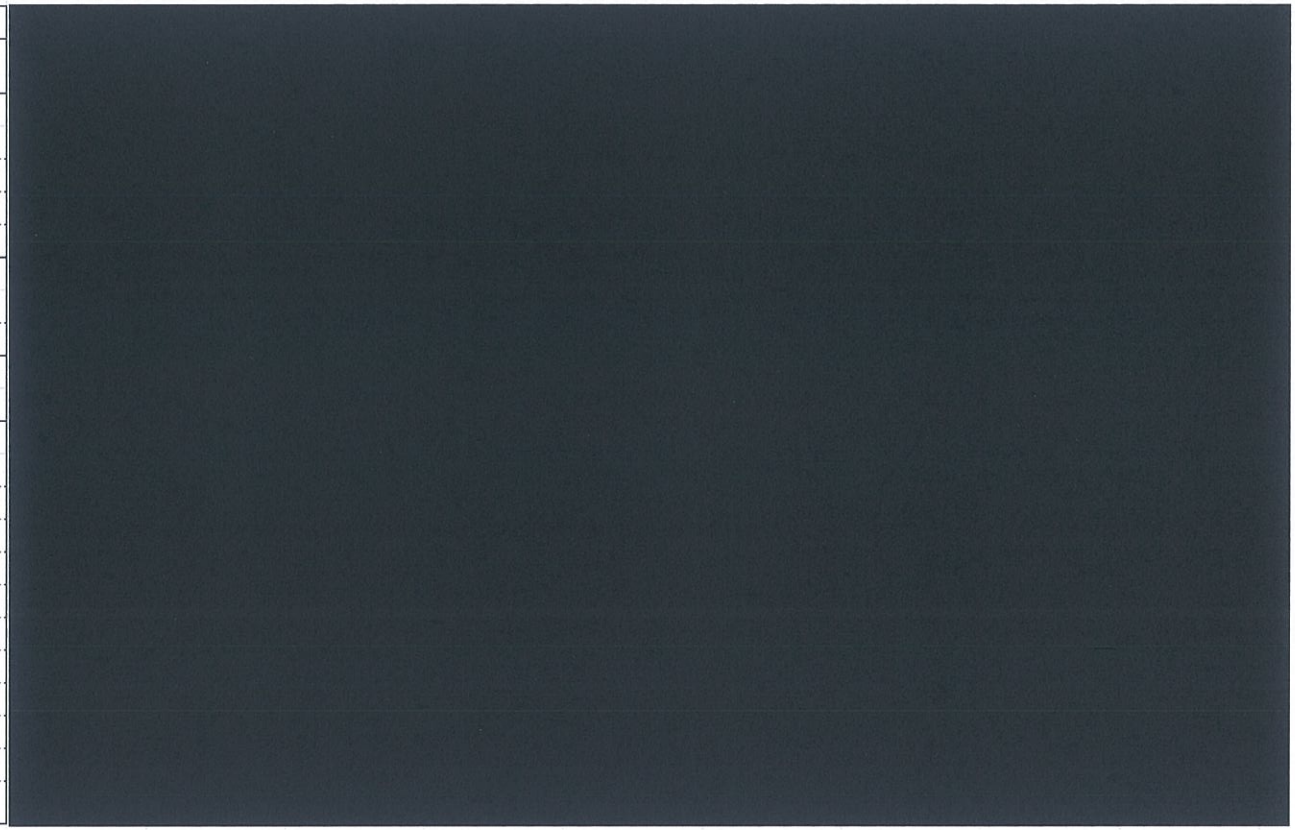
国内外の臨床第 III 相試験で得られた安全性プロファイルから，LCIG による治療は概して安全で忍容性に優れていると言える。LCIG の海外第 III 相長期オープン試験で報告された事象は，手技に関するもの，処置及び機器に関連する有害事象を除いては，海外ピボタルの実薬対照試験で報告された事象と一貫しており，また，経口 LC 製剤で確立された安全性プロファイル及び根本として存在する PD に関連した症状と一貫したものであり，新たなあるいは LCIG の組成に関連した異なるパターンの重篤な影響を示唆するものはなかった。概して，殆どの有害事象は，重症度においては，軽度あるいは中等度と評価されるものであった。

LCIG 治療システムでは，薬剤及び医療機器に関連する有害事象の発現率が用量調整期に最もリスクが高く，その後時間の経過とともに低下した。また，中止に至った有害事象の発現率も低かった。投与中止率も低い。逆に，用量調整期の終了時やそれに続く一年間の継続治療の間に，運動症状の日内変動の改善や日常運動動作の改善が認められることで，生活の質に良い影響を与えることが示されている。

国内外において実施された臨床試験で得られた知見を統計学的に有意でかつ臨床的に意味のある効果を示すこと及び安全性の知見を全般的に考慮すると，進行期 PD 患者における LCIG システムのリスク・ベネフィットはベネフィットが勝ると言える。

開発の経緯図

試験名		
構造決定，物性並びに規格及び試験方法		
安定性		
原薬	レボドパ	
	カルビドパ	
製剤		
薬物動態		
吸収・分布代謝排泄		
その他		
毒性		
臨床試験		
Phase I		
	S187.1.002	海外・参考
Phase II		
	M12-925	国内・評価
Phase III		
	M12-921	アジア・評価
	M12-923	アジア・評価
	S187.3.001/002	海外・評価
	S187.3.003	海外・参考
	S187.3.004	海外・評価
	S187.3.005	海外・参考



1.6 外国における使用状況等に関する資料

1.6.1 外国における使用状況

外国における承認状況（2016年2月時点）については表1.6-1のとおり。

表 1.6-1. 外国の承認状況

国・地域	販売名	承認年月
アルバニア	Duodopa	2009 年 3 月
オーストラリア	Duodopa	2008 年 2 月
オーストリア	Duodopa	2004 年 11 月
ベルギー	Duodopa	2005 年 11 月
ボスニア・ヘルツェゴビナ	Duodopa	2011 年 12 月
ブルガリア	Duodopa	2006 年 11 月
カナダ	Duodopa	2007 年 3 月
クロアチア	Duodopa	2006 年 11 月
キプロス共和国	Duodopa	2005 年 10 月
チェコ共和国	Duodopa	2005 年 11 月
デンマーク	Duodopa	2004 年 10 月
エストニア	Duodopa	2005 年 11 月
フィンランド	Duodopa	2005 年 1 月
フランス	Duodopa	2004 年 9 月
ドイツ	Duodopa	2005 年 10 月
ギリシャ	Duodopa	2005 年 11 月
ハンガリー	Duodopa	2005 年 11 月
アイスランド	Duodopa	2005 年 11 月
アイルランド	Duodopa	2005 年 11 月
イスラエル	Duodopa	2010 年 5 月
イタリア	Duodopa	2005 年 11 月
ラトビア	Duodopa	2005 年 10 月
リヒテンシュタイン	Duodopa	2005 年 10 月
リトアニア	Duodopa	2005 年 11 月
ルクセンブルグ	Duodopa	2005 年 11 月
マケドニア	Duodopa	2010 年 1 月
マルタ共和国	Duodopa	2005 年 10 月
オランダ	Duodopa	2004 年 11 月
ニュージーランド	Duodopa	2015 年 5 月
ノルウェー	Duodopa	2004 年 10 月
ポーランド	Duodopa	2005 年 11 月
ポルトガル	Duodopa	2004 年 7 月
ルーマニア	Duodopa	2006 年 12 月

国・地域	販売名	承認年月
ロシア	Duodopa	2015 年 6 月
セルビア共和国	Duodopa	2015 年 6 月
スロヴァキア	Duodopa	2005 年 10 月
スロヴェニア	Duodopa	2005 年 10 月
サウスアフリカ	Duodopa	2013 年 10 月
スペイン	Duodopa	2005 年 10 月
スウェーデン	Duodopa	2004 年 1 月
スイス	Duodopa	2006 年 12 月
タイ	Duodopa	2011 年 7 月
トルコ	Duodopa	2012 年 3 月
ウクライナ	Duodopa	2010 年 8 月
英国	Duodopa	2005 年 11 月
米国	Duopa	2015 年 1 月
韓国	Duodopa	2015 年 4 月
クウェート	Duodopa	2015 年 10 月

1.6.2 外国における添付文書

1.6.2.1 米国における添付文書

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUOPA safely and effectively. See full prescribing information for DUOPA.

DUOPA (carbidopa and levodopa) enteral suspension
Initial U.S. Approval: 1975

INDICATIONS AND USAGE

DUOPA is a combination of carbidopa (an aromatic amino acid decarboxylation inhibitor) and levodopa (an aromatic amino acid) indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease (1)

DOSAGE AND ADMINISTRATION

- The maximum recommended daily dose of DUOPA is 2000 mg of levodopa (i.e., one cassette per day) administered over 16 hours (2.1)
- Prior to initiating DUOPA, convert patients from all forms of levodopa to oral immediate-release carbidopa-levodopa tablets (1:4 ratio) (2.2)
- Titrate total daily dose based on clinical response for the patient (2.2)
- Administer DUOPA into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) with the CADD®-Legacy 1400 portable infusion pump (2.3)

DOSAGE FORMS AND STRENGTHS

Enteral Suspension: 4.63 mg carbidopa and 20 mg levodopa per mL (3)

CONTRAINDICATIONS

DUOPA is contraindicated in patients taking nonselective monoamine oxidase (MAO) inhibitors (4)

WARNINGS AND PRECAUTIONS

- Gastrointestinal procedure-related complications may result in serious outcomes, such as need for surgery or death (5.1)
- May cause falling asleep during activities of daily living (5.2)
- Monitor patients for orthostatic hypotension, especially after starting DUOPA or increasing the dose (5.3)
- Hallucinations/Psychosis/Confusion: May respond to dose reduction in levodopa (5.4)
- Impulse Control Disorders: Consider dose reductions or stopping DUOPA (5.5)
- Monitor patients for depression and suicidality (5.6)
- Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion (5.7)
- May cause or exacerbate dyskinesia: Consider dose reduction (5.8)
- Monitor patients for signs and symptoms of peripheral neuropathy (5.9)

ADVERSE REACTIONS

Most common adverse reactions for DUOPA (DUOPA incidence at least 7% greater than oral carbidopa-levodopa incidence) were: complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, and incision site erythema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Selective MAO-B inhibitors: May cause orthostatic hypotension (7.1)
- Antihypertensive drugs: May cause symptomatic postural hypotension. Dosage adjustment of the antihypertensive drug may be needed (7.2)
- Dopamine D2 receptor antagonists, isoniazid, iron salts, and high-protein diet may reduce the effectiveness of DUOPA (7.3, 7.4, 7.5)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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2.1 DUOPA Daily Dose
2.2 Initiation and Titration Instructions
2.3 Administration Information
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DUOPA is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease.

2 DOSAGE AND ADMINISTRATION

2.1 DUOPA Daily Dose

DUOPA is administered over a 16-hour infusion period. The daily dose is determined by individualized patient titration and composed of:

- A Morning Dose
- A Continuous Dose
- Extra Doses

The maximum recommended daily dose of DUOPA is 2000 mg of the levodopa component (i.e., one cassette per day) administered over 16 hours. At the end of the daily 16-hour infusion, patients will disconnect the pump from the PEG-J and take their night-time dose of oral immediate-release carbidopa-levodopa tablets.

Treatment with DUOPA is initiated in 3 steps *[see Dosage and Administration (2.2)]*:

1. Conversion of patients to oral immediate-release carbidopa-levodopa tablets in preparation for DUOPA treatment.
2. Calculation and administration of the DUOPA starting dose (Morning Dose and Continuous Dose) for Day 1.
3. Titration of the dose as needed based on individual clinical response and tolerability.

Extra Doses

DUOPA has an extra dose function that can be used to manage acute "Off" symptoms that are not controlled by the Morning Dose and the Continuous Dose administered over 16 hours. The extra dose function should be set at 1 mL (20 mg of levodopa) when starting DUOPA. If the amount of the extra dose needs to be adjusted, it is typically done in 0.2 mL increments. The extra dose frequency should be limited to one extra dose every 2 hours. Administration of frequent extra doses may cause or worsen dyskinesias.

Once no further adjustments are required to the DUOPA Morning Dose, Continuous Dose, or Extra Dose, this dosing regimen should be administered daily. Over time, additional changes may be necessary based on the patient's clinical response and tolerability.

2.2 Initiation and Titration Instructions

Prepare for DUOPA Treatment

Prior to initiating DUOPA, convert patients from all other forms of levodopa to oral immediate-release carbidopa-levodopa tablets (1:4 ratio). Patients should remain on a stable dose of their concomitant medications taken for the treatment of Parkinson's disease before initiation of DUOPA infusion.

Healthcare providers should ensure patients take their oral Parkinson's disease medications the morning of the PEG-J procedure.

Determine the DUOPA Starting Dose for Day 1

The steps for determining the initial DUOPA daily dosing (Morning Dose and Continuous Dose) for Day 1 are outlined below.

Step 1: Calculate and administer the DUOPA Morning Dose for Day 1	
a.	Determine the total amount of levodopa (in milligrams) in the first dose of oral immediate-release carbidopa-levodopa that was taken by the patient on the previous day.
b.	Convert the oral levodopa dose from milligrams to milliliters by multiplying the oral dose by 0.8 and dividing by 20 mg/mL. This calculation will provide the Morning Dose of DUOPA in milliliters.
c.	Add 3 milliliters to the Morning Dose to fill (prime) the intestinal tube to obtain the Total Morning Dose.
d.	The Total Morning Dose is usually administered over 10 to 30 minutes.
e.	Program the pump to deliver the Total Morning Dose.
Step 2: Calculate and administer the DUOPA Continuous Dose for Day 1	
a.	Determine the amount of oral immediate-release levodopa that the patient received from oral immediate-release carbidopa-levodopa doses throughout the previous day (16 waking hours), in milligrams. Do not include the doses of oral immediate-release carbidopa-levodopa taken at night when calculating the levodopa amount.
b.	Subtract the first oral levodopa dose in milligrams taken by the patient on the previous day (determined in Step 1 (a)) from the total oral levodopa dose in milligrams taken over 16 waking hours (determined in Step 2 (a)). Divide the result by 20 mg/mL. This is the dose of DUOPA administered as a Continuous Dose (in mL) over 16 hours.
c.	The hourly infusion rate (mL per hour) is obtained by dividing the Continuous Dose by 16 (hours). This value will be programmed into the pump as the continuous rate.
d.	If persistent or numerous "Off" periods occur during the 16-hour infusion, consider increasing the Continuous Dose or using the Extra Dose function. If dyskinesia or levodopa-related adverse reactions occur, consider decreasing the Continuous Dose or stopping the infusion until the adverse reactions subside.

DUOPA Titration

The daily dose of DUOPA can be titrated as needed, based on the patient's individual clinical response and tolerability after Day 1 of DUOPA treatment and until a stable daily dose is maintained. Adjustments to concomitant Parkinson's disease medications may be needed. In the controlled trial, the average number of titration days required to establish a stable Morning and

Continuous Dose was 5 days. Additional dose adjustments may be necessary over time based on the patient level of activity and disease progression.

The recommendations for adjusting the DUOPA Morning and Continuous Doses are provided below.

Morning Dose Adjustment

If there was an inadequate clinical response within 1 hour of the Morning Dose on the preceding day, adjust the Morning Dose (excluding the 3 mL to fill the tube) as follows:

- If the Morning Dose on the preceding day was less than or equal to 6 mL, increase the Morning Dose by 1 mL.
- If the Morning Dose on the preceding day was greater than 6 mL, increase the Morning Dose by 2 mL.

If the patient experienced dyskinesias or levodopa-related adverse reactions within 1 hour of the Morning Dose on the preceding day, decrease the Morning Dose by 1 mL.

Continuous Dose Adjustment

Consider increasing the Continuous Dose based on the number and volume of Extra Doses of DUOPA (i.e., total amount of levodopa component) that was needed for the previous day and the patient's clinical response.

Consider decreasing the Continuous Dose if the patient experienced troublesome dyskinesia, or other troublesome DUOPA-related adverse reactions on the preceding day:

- For troublesome adverse reactions lasting for a period of one hour or more, decrease the Continuous Dose by 0.3 mL per hour.
- For troublesome adverse reactions lasting for two or more periods of one hour or more, decrease the Continuous Dose by 0.6 mL per hour.

2.3 Administration Information

- DUOPA should be used at room temperature. Take one DUOPA cassette out of the refrigerator and out of the carton 20 minutes prior to use; failure to use the product at room temperature may result in the patient not receiving the right amount of medication.
- DUOPA is delivered as a 16-hour infusion through either a naso-jejunal tube for short-term administration or through a PEG-J for long-term administration.
- The cassettes are for single-use only and should not be used for longer than 16 hours, even if some drug product remains.
- An opened cassette should not be re-used.
- The PEG-J should be disconnected from the pump at the end of the daily 16-hour administration period and flushed with room temperature potable water with a syringe.

Long-term administration of DUOPA requires placement of a PEG-J outer transabdominal tube and inner jejunal tube by percutaneous endoscopic gastrostomy. DUOPA is dispensed from medication cassette reservoirs that are specifically designed to be connected to the CADD®-Legacy 1400 pump.

Establishment of the transabdominal port should be performed by a gastroenterologist or other healthcare provider experienced in this procedure. See Table 1 for the recommended tubing sets for PEG-J administration.

For short-term, temporary administration of DUOPA prior to PEG-J tube placement, treatment may be initiated by a naso-jejunal tube with observation of the patient's clinical response. See Table 2 for the recommended tubing sets for naso-jejunal administration.

Table 1. Recommended Tubing Sets for Long-Term PEG-J DUOPA Administration

Product Name	Manufacturer
AbbVie™ PEG 15 and 20 Fr	AbbVie Inc.
AbbVie™ J	AbbVie Inc.
EndoVive™ Standard PEG Kit – Pull Method	Boston Scientific Corp.
EndoVive™ Two-Port Through the PEG Jejunal Feeding Tube Kit	Boston Scientific Corp.

Table 2. Recommended Tubing Sets for Short-Term Naso-Jejunal DUOPA Administration

Product Name	Manufacturer
AbbVie™ NJ	AbbVie Inc.
NJFT-10	Wilson-Cook Medical, Inc.
Kangaroo™ Naso-Jejunal Feeding Tube	Covidien
Kangaroo™	Covidien

2.4 Discontinuation of DUOPA

Avoid sudden discontinuation or rapid dose reduction in patients taking DUOPA.

If patients need to discontinue DUOPA, the dose should be tapered or patients should be switched to oral immediate-release carbidopa-levodopa tablets *[see Warnings and Precautions (5.7)]*.

When using a PEG-J tube, DUOPA can be discontinued by withdrawing the tube and letting the stoma heal. The removal of the tube should only be performed by a qualified healthcare provider.

3 DOSAGE FORMS AND STRENGTHS

Enteral suspension: 4.63 mg carbidopa and 20 mg levodopa per mL in a single-use cassette. Each cassette contains approximately 100 mL of suspension.

4 CONTRAINDICATIONS

DUOPA is contraindicated in patients who are currently taking a nonselective monoamine oxidase (MAO) inhibitor (e.g., phenelzine and tranylcypromine) or have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently *[see Drug Interactions (7.1 and 7.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal and Gastrointestinal Procedure-Related Risks

Because DUOPA is administered using a PEG-J or naso-jejunal tube, gastrointestinal complications can occur.

These complications include bezoar, ileus, implant site erosion/ulcer, intestinal hemorrhage, intestinal ischemia, intestinal obstruction, intestinal perforation, pancreatitis, peritonitis, pneumoperitoneum, and post-operative wound infection. These complications may result in serious outcomes, such as the need for surgery or death.

Instruct patients to notify their healthcare provider immediately if they experience abdominal pain, prolonged constipation, nausea, vomiting, fever, or melanotic stool *[see Patient Counseling Information (17)]*.

5.2 Falling Asleep During Activities of Daily Living and Somnolence

Patients treated with levodopa, a component of DUOPA, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on levodopa, some perceived that they had no warning signs (sleep attack), such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported more than one year after initiation of treatment.

Falling asleep while engaged in activities of daily living usually occurs in patients experiencing preexisting somnolence, although patients may not give such a history. For this reason, prescribers should reassess patients for drowsiness or sleepiness in DUOPA-treated patients, especially since some of the events occur well after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients who have already experienced somnolence or an episode of sudden sleep onset should not participate in these activities while taking DUOPA.

Before initiating treatment with DUOPA, advise patients about the potential to develop drowsiness and specifically ask about factors that may increase the risk for somnolence with DUOPA such as the use of concomitant sedating medications or the presence of sleep disorders. Consider discontinuing DUOPA in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating). If DUOPA is continued, they should be advised to avoid driving and other potentially dangerous activities that might result in harm if the patient becomes somnolent.

5.3 Orthostatic Hypotension

DUOPA-treated patients were more likely to experience a decline in orthostatic blood pressure than patients treated with oral immediate-release carbidopa-levodopa in the controlled clinical study. Orthostatic systolic hypotension (≥30 mm Hg decrease) occurred in 73% of DUOPA-treated patients compared to 68% of patients treated with oral immediate-release carbidopa-levodopa in the controlled clinical study. Orthostatic diastolic hypotension (≥20 mm Hg decrease) occurred in 70% of DUOPA-treated patients compared to 62% of patients treated with

oral immediate-release carbidopa-levodopa. Inform patients about the risk for hypotension and syncope. Monitor patients for orthostatic hypotension, especially after starting DUOPA or increasing the dose.

5.4 Hallucinations/Psychosis/Confusion

There is an increased risk for hallucinations and psychosis in patients taking DUOPA. In the controlled clinical trial, hallucinations occurred in 5% of DUOPA-treated patients compared to 3% of patients treated with oral immediate-release carbidopa-levodopa. Confusion occurred in 8% of DUOPA-treated patients compared to 3% of patients treated with oral immediate-release carbidopa-levodopa, and psychotic disorder occurred in 5% of DUOPA-treated patients compared to 3% of patients treated with oral immediate-release carbidopa-levodopa.

Hallucinations associated with levodopa may present shortly after the initiation of therapy and may be responsive to dose reduction in levodopa. Confusion, insomnia, and excessive dreaming may accompany hallucinations. Abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychosis, disorientation, aggressive behavior, agitation, and delirium.

Because of the risk of exacerbating psychosis, patients with a major psychotic disorder should not be treated with DUOPA. In addition, medications that antagonize the effects of dopamine used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of DUOPA *[see Drug Interactions (7.3)]*.

5.5 Impulse Control/Compulsive Behaviors

Patients may experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including DUOPA, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued.

Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with DUOPA. Consider reducing the dose or discontinuing DUOPA if a patient develops such urges.

5.6 Depression and Suicidality

In the controlled clinical trial, 11% of DUOPA-treated patients developed depression compared to 3% of oral immediate-release carbidopa-levodopa-treated patients.

Monitor patients for the development of depression and concomitant suicidal tendencies.

5.7 Withdrawal-Emergent Hyperpyrexia and Confusion

A symptom complex that resembles neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or

changes in dopaminergic therapy. Avoid sudden discontinuation or rapid dose reduction in patients taking DUOPA. If DUOPA is discontinued, the dose should be tapered to reduce the risk of hyperpyrexia and confusion *[see Dosage and Administration (2.4)]*.

5.8 Dyskinesia

DUOPA may cause or exacerbate dyskinesias. In the controlled clinical trial, dyskinesia occurred in 14% of DUOPA-treated patients compared to 12% of patients treated with oral immediate-release carbidopa-levodopa. The occurrence of dyskinesias may require a dosage reduction of DUOPA or other medications used to treat Parkinson's disease.

5.9 Neuropathy

In clinical studies, 19 of 412 (5%) patients treated with DUOPA developed a generalized polyneuropathy. The onset of neuropathy could be determined in 13 of 19 patients. Most cases (12/19) were classified as subacute or chronic in onset. The neuropathy was most often characterized as sensory or sensorimotor. Electrodiagnostic testing performed in 16 patients was most often (15/16) consistent with an axonal polyneuropathy, and one patient was classified as having a demyelinating neuropathy. There was insufficient information to determine the potential role of vitamin deficiencies in the etiology of neuropathy associated with DUOPA.

Patients should have clinical assessments for the signs and symptoms of peripheral neuropathy before starting DUOPA. Monitor patients periodically for signs of neuropathy after starting DUOPA, especially in patients with pre-existing neuropathy and in patients taking medications or those who have medical conditions that are also associated with neuropathy.

5.10 Cardiovascular Ischemic Events

In clinical studies, myocardial infarction and arrhythmia were reported in patients taking carbidopa-levodopa. Ask patients about symptoms of ischemic heart disease and arrhythmia, especially those with a history of myocardial infarction or cardiac arrhythmias.

5.11 Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2 to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear. In the clinical studies, 2 of 416 (0.5%) DUOPA-treated patients developed melanoma.

Appropriately qualified health care providers (e.g., dermatologists) should perform periodic skin examinations to monitor for melanoma in patients receiving DUOPA.

5.12 Laboratory Test Abnormalities

DUOPA may increase the risk for elevated (above the upper limit of normal for the reference range) blood urea nitrogen (BUN) and creatine phosphokinase (CPK). In the controlled clinical trial, the shift from a low or normal value at baseline to an increased BUN value was greater for DUOPA-treated patients (13%) than for patients treated with oral immediate-release carbidopa-levodopa (4%). The shift from a low or normal value at baseline to an increased CPK value was

greater for DUOPA-treated patients (17%) than for patients treated with oral immediate-release carbidopa-levodopa (7%). The incidence of patients with a markedly increased BUN (≥10 mmol/L; ≥28 mg/dL) was greater for patients treated with DUOPA (11%) than that for patients treated with oral immediate-release carbidopa-levodopa (0%). The incidence of patients with an increased CPK (>3 times the upper limit of normal) was greater for patients treated with DUOPA (9%) than that for patients treated with oral immediate-release carbidopa-levodopa (0%).

Patients taking levodopa or carbidopa-levodopa may have increased levels of catecholamines and their metabolites in plasma and urine giving false positive results suggesting the diagnosis of pheochromocytoma in patients on levodopa and carbidopa-levodopa.

5.13 Glaucoma

Carbidopa-levodopa may cause increased intraocular pressure in patients with glaucoma. Monitor intraocular pressure in patients with glaucoma after starting DUOPA.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in labeling:

- Gastrointestinal and Gastrointestinal Procedure-Related Risks *[see Warnings and Precautions (5.1)]*
- Falling Asleep During Activities of Daily Living and Somnolence *[see Warnings and Precautions (5.2)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.3)]*
- Hallucinations/Psychosis/Confusion *[see Warnings and Precautions (5.4)]*
- Impulse Control/Compulsive Behaviors *[see Warnings and Precautions (5.5)]*
- Depression and Suicidality *[see Warnings and Precautions (5.6)]*
- Withdrawal-Emergent Hyperpyrexia and Confusion *[see Warnings and Precautions (5.7)]*
- Dyskinesia *[see Warnings and Precautions (5.8)]*
- Neuropathy *[see Warnings and Precautions (5.9)]*
- Cardiovascular Ischemic Events *[see Warnings and Precautions (5.10)]*
- Melanoma *[see Warnings and Precautions (5.11)]*
- Laboratory Test Abnormalities *[see Warnings and Precautions (5.12)]*
- Glaucoma *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical studies are run under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical studies, 416 patients with advanced Parkinson's disease received DUOPA. 338 patients were treated with DUOPA for more than 1 year, 233 patients were treated with DUOPA for more than 2 years, and 162 patients were treated with DUOPA for more than 3 years.

In a 12-week, active-controlled clinical trial (Study 1), a total of 71 patients with advanced Parkinson's disease were enrolled and had a PEG-J procedure. Of these, 37 patients received DUOPA and 34 received oral immediate-release carbidopa-levodopa.

The most common adverse reactions for DUOPA (incidence at least 7% greater than oral immediate-release carbidopa-levodopa) were: complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, and incision site erythema.

Table 3 lists the incidence of adverse reactions occurring in the DUOPA-treated group (requiring at least 2 patients in this group) in Study 1 when the incidence was numerically greater than that for oral immediate-release carbidopa-levodopa.

Table 3. Adverse Reactions in Study 1 for DUOPA in Patients with Advanced Parkinson's disease

Preferred Term	**DUOPA (n = 37) %**	**Oral immediate-release carbidopa-levodopa[a] (n = 34) %**
Complication of device insertion	57	44
Nausea	30	21
Constipation	22	21
Incision site erythema	19	12
Dyskinesia	14	12
Depression	11	3
Post procedural discharge	11	9
Peripheral edema	8	0
Hypertension	8	0
Upper respiratory tract infection	8	0
Oropharyngeal pain	8	0
Atelectasis	8	0
Confusional state	8	3
Anxiety	8	3
Dizziness	8	6
Hiatal hernia	8	6
Postoperative ileus	5	0
Sleep disorder	5	0
Pyrexia	5	0
Excessive granulation tissue	5	0
Rash	5	0
Bacteriuria	5	0
White blood cells urine positive	5	0
Hallucination	5	3
Psychotic disorder	5	3

Preferred Term	DUOPA (n = 37) %	Oral immediate-release carbidopa-levodopa[a] (n = 34) %
Diarrhea	5	3
Dyspepsia	5	3
[a]All patients in the clinical trial regardless of treatment arm received a PEG-J.		

Procedure and Device- Related Adverse Reactions

The most common adverse reactions associated with complications due to naso-jejunal (NJ) insertion were: oropharyngeal pain, abdominal distention, abdominal pain, abdominal discomfort, pain, throat irritation, gastrointestinal injury, esophageal hemorrhage, anxiety, dysphagia, and vomiting.

The most common adverse reactions associated with complications due to PEG-J insertion were: abdominal pain, abdominal discomfort, abdominal distension, flatulence, or pneumoperitoneum.

Additional adverse reactions that were co-reported with complication of naso-jejunal and PEG-J insertion included upper abdominal pain upper, duodenal ulcer, duodenal ulcer hemorrhage, erosive duodenitis, erosive gastritis erosive, gastrointestinal hemorrhage, peritonitis, post-operative abscess, and small intestine ulcer.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase (MAO) Inhibitors

The use of nonselective MAO inhibitors with DUOPA is contraindicated *[see Contraindications (4)]*. Discontinue use of any nonselective MAO inhibitors at least two weeks prior to initiating DUOPA.

The use of selective MAO-B inhibitors (e.g., rasagiline and selegiline) with DUOPA may be associated with orthostatic hypotension. Monitor patients who are taking these drugs.

7.2 Antihypertensive Drugs

The concurrent use of DUOPA with antihypertensive medications can cause symptomatic postural hypotension. A dose reduction of the antihypertensive medication may be needed after starting or increasing the dose of DUOPA.

7.3 Dopamine D2 Receptor Antagonists and Isoniazid

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide, papaverine) and isoniazid may reduce the effectiveness of levodopa. Monitor patients for worsening Parkinson's symptoms.

7.4 Iron Salts

Iron salts or multi-vitamins containing iron salts can form chelates with levodopa, carbidopa, and can cause a reduction in the bioavailability of DUOPA. If iron salts or multi-vitamins containing

iron salts are co-administered with DUOPA, monitor patients for worsening Parkinson's symptoms.

7.5 High-Protein Diet

Because levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be decreased in patients on a high-protein diet. Advise patients that a high-protein diet may reduce the effectiveness of DUOPA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate or well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. In animal studies, carbidopa-levodopa has been shown to be developmentally toxic (including teratogenic effects) at clinically relevant doses. DUOPA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When administered to pregnant rabbits throughout organogenesis, carbidopa-levodopa caused both visceral and skeletal malformations in fetuses at all doses and ratios of carbidopa-levodopa tested. No teratogenic effects were observed when carbidopa-levodopa was administered to pregnant mice throughout organogenesis.

There was a decrease in the number of live pups delivered by rats receiving carbidopa-levodopa during organogenesis.

8.3 Nursing Mothers

Carbidopa is excreted in rat milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human milk was reported. Caution should be exercised when DUOPA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In the controlled clinical trial, 49% of patients were 65 years and older, and 8% were 75 years and older. In patients 65 years and older, there was an increased risk for elevation of BUN and CPK (above the upper limit of the normal reference range for these laboratory analytes) during treatment with DUOPA compared to the risk for patients less than 65 years.

10 OVERDOSAGE

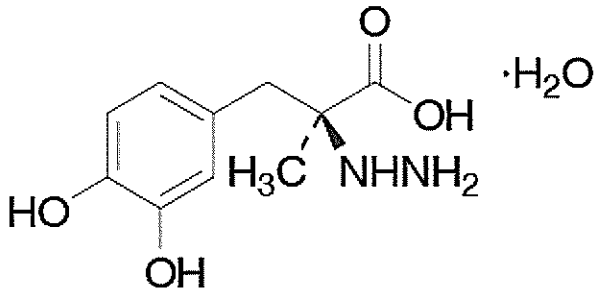
Management of acute overdosage with DUOPA is the same as management of acute overdosage with levodopa. Pyridoxine is not effective in reversing the actions of oral immediate-release carbidopa-levodopa.

In the event of an overdosage with DUOPA, the infusion should be stopped and the pump disconnected immediately. Administer intravenous fluids and maintain an adequate airway. Patients should receive electrocardiographic monitoring for arrhythmias and hypotension.

11 DESCRIPTION

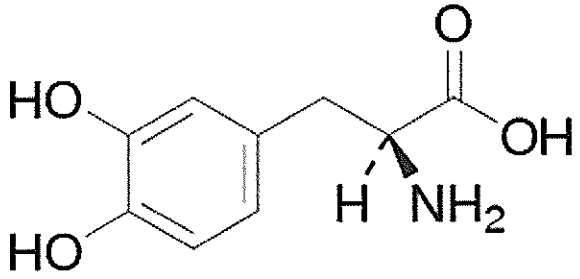
DUOPA is a combination of carbidopa, an inhibitor of aromatic amino acid decarboxylation, and levodopa, an aromatic amino acid.

Carbidopa is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-(α-hydrazino-(α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$, and its structural formula is:



The content of carbidopa in DUOPA is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3. The 4.63 mg/mL of anhydrous carbidopa is equivalent to 5.0 mg/mL of carbidopa.

Levodopa is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$, and its structural formula is:



The inactive ingredients in DUOPA are carmellose sodium and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carbidopa

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for delivery to the brain.

Levodopa

Levodopa is the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa treats the symptoms of Parkinson's disease.

12.2 Pharmacodynamics

Because its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available to the brain. The addition of carbidopa to levodopa reduces the peripheral effects (e.g., nausea and vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa.

12.3 Pharmacokinetics

The pharmacokinetics of carbidopa and levodopa with 16-hour intrajejunal infusion of DUOPA was evaluated in 18 patients with advanced Parkinson's disease who had been on DUOPA therapy for 30 days or longer. Patients remained on their individualized DUOPA doses.

The plasma concentrations versus time profile for levodopa with DUOPA 16-hour intrajejunal infusion is presented in Figure 1.

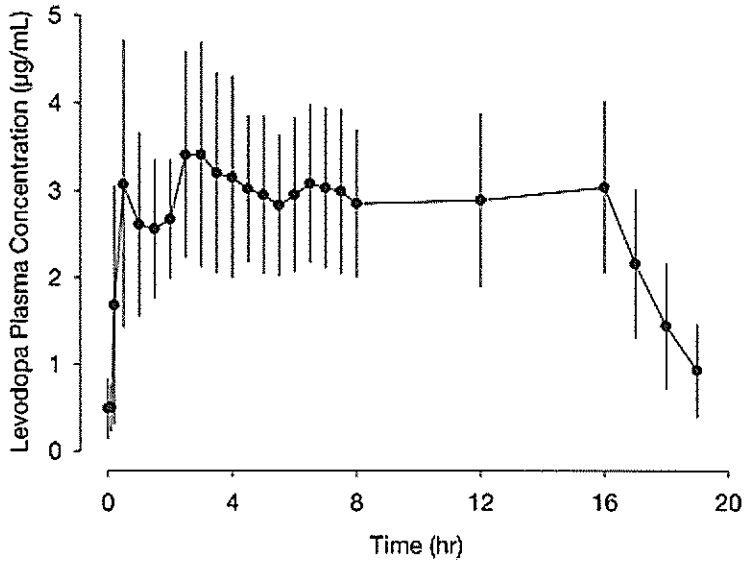


Figure 1. Plasma Concentrations (mean ± standard deviation) versus Time Profile of Levodopa with DUOPA (levodopa, 1580 ± 403 mg; carbidopa, 366 ± 92 mg) 16-Hour Infusion

Absorption and Bioavailability

Following 16-hour intrajejunal infusion of DUOPA, peak plasma levels of levodopa is reached at 2.5 hours. The absorption of levodopa may be decreased in patients on a high-protein diet because levodopa competes with certain amino acids for transport across the gut wall. The gastric emptying rate does not influence the absorption of DUOPA since it is administered by continuous intestinal infusion. In a cross-study population pharmacokinetic analysis, DUOPA had comparable bioavailability to the oral immediate-release carbidopa-levodopa (25/100 mg) tablets (over-encapsulated tablets). The estimated bioavailability for levodopa from DUOPA relative to oral immediate-release carbidopa-levodopa tablets was 97% (95% confidence interval; 95% to 98%).

In the controlled clinical trial, the intra-subject variability in carbidopa and levodopa plasma concentrations were lower for patients treated with DUOPA (N=33, 25% and 21%, respectively) than in patients treated with oral immediate-release carbidopa-levodopa (25/100 mg) tablets (N=28, 39% and 67%, respectively).

Distribution

Carbidopa is approximately 36% bound to plasma proteins. Levodopa is approximately 10-30% bound to plasma proteins.

Metabolism and Elimination

Carbidopa

Carbidopa is metabolized to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion. The elimination half-life of carbidopa is approximately 2 hours.

Levodopa

Levodopa is mainly eliminated via metabolism by the aromatic amino acid decarboxylase (AAAD) and the catechol-O-methyl-transferase (COMT) enzymes. Other routes of metabolism are transamination and oxidation. The decarboxylation of levodopa to dopamine by AAAD is the major enzymatic pathway when no enzyme inhibitor is co-administered. O-methylation of levodopa by COMT forms 3-O-methyldopa. When administered with carbidopa, the elimination half-life of levodopa is approximately 1.5 hours (see Figure 1).

Drug Interaction Studies

COMT Inhibitors

Systemic exposure of levodopa is expected to increase in the presence of entacapone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In rat, oral administration of carbidopa-levodopa for two years resulted in no evidence of carcinogenicity. DUOPA contains hydrazine, a degradation product of carbidopa. In published studies, hydrazine has been demonstrated to be carcinogenic in multiple animal species. Increases in liver (adenoma, carcinoma) and lung (adenoma, adenocarcinoma) tumors have been reported with oral administration of hydrazine in mouse, rat, and hamster.

Mutagenesis

Carbidopa was positive in the *in vitro* Ames test, in the presence and absence of metabolic activation, and the *in vitro* mouse lymphoma *tk* assay in the absence of metabolic activation but was negative in the *in vivo* mouse micronucleus assay.

In published studies, hydrazine was reported to be positive in *in vitro* genotoxicity (Ames, chromosomal aberration in mammalian cells, and mouse lymphoma *tk*) assays and in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

In reproduction studies, no effects on fertility were observed in rats receiving carbidopa - levodopa.

14 CLINICAL STUDIES

The efficacy of DUOPA was established in a randomized, double-blind, double-dummy, active-controlled, parallel group, 12-week study (Study 1) in patients with advanced Parkinson's disease who were levodopa-responsive and had persistent motor fluctuations while on treatment with oral immediate-release carbidopa-levodopa and other Parkinson's disease medications.

Patients were eligible for participation in the studies if they were experiencing 3 hours or more of "Off" time on their current Parkinson's disease drug treatment and they demonstrated a clear responsiveness to treatment with levodopa. Seventy-one (71) patients enrolled in the study and 66 patients completed the treatment (3 patients discontinued treatment because of adverse reactions, 1 patient for lack of effect, and 1 patient for non-compliance).

Patients enrolled in this study had a mean age of 64 years and disease duration of 11 years. Most patients (89%) were taking at least one concomitant medication for Parkinson's disease (e.g., dopaminergic agonist, COMT-inhibitor, MAO-B inhibitor) in addition to oral immediate-release carbidopa-levodopa. Thirty nine percent of patients were taking two or more of such concomitant medications.

Patients were randomized to either DUOPA and placebo capsules or placebo suspension and oral immediate-release carbidopa-levodopa 25/100 mg capsules. Patients in both treatment arms had a PEG-J device placement. DUOPA or placebo-suspension was infused over 16 hours daily through a PEG-J tube via the CADD®-Legacy 1400 model ambulatory infusion pump. The mean daily levodopa dose was 1117 mg/day in the DUOPA group and 1351 mg/day in the oral immediate-release carbidopa-levodopa group.

The clinical outcome measure in Study 1 was the mean change from baseline to Week 12 in the total daily mean "Off" time, based on a Parkinson's disease diary. The "Off" time was normalized to a 16-hour awake period, based on a typical person's waking day and the daily infusion duration of 16 hours. The mean score decrease (i.e., improvement) in "Off" time from baseline to Week 12 for DUOPA was significantly greater (p=0.0015) than for oral immediate-release carbidopa-levodopa. Additionally, the mean score increase (i.e., improvement) in "On" time without troublesome dyskinesia from baseline to Week 12 was significantly greater (p=0.0059) for DUOPA than for oral immediate-release carbidopa-levodopa. The treatment difference (DUOPA – oral immediate release carbidopa-levodopa) for decrease in "Off" time was approximately 1.9 hours and the treatment difference for the increase in "On" time without troublesome dyskinesia was approximately 1.9 hours. Results of Study 1 are shown in Table 4.

Table 4. Change from Baseline to Week 12 in "Off" Time and in "On" Time Without Troublesome Dyskinesia in Patients with Advanced Parkinson's Disease

Treatment Group	Baseline (hours)	LS Mean Change from Baseline at Week 12 (hours)
"Off" time		
Oral immediate-release carbidopa-levodopa	6.9	-2.1
DUOPA	6.3	-4.0*

Treatment Group	Baseline (hours)	LS Mean Change from Baseline at Week 12 (hours)
"On" time without troublesome dyskinesia		
Oral immediate-release carbidopa-levodopa	8.0	2.2
DUOPA	8.7	4.1*
LS Mean Change from Baseline based on Analysis of Covariance (ANCOVA). *=Statistically Significant.		

Figure 2 shows results over time according to treatment for the efficacy variable (change from baseline in "Off" time) that served as the clinical outcome measure at the end of the trial at 12 weeks.

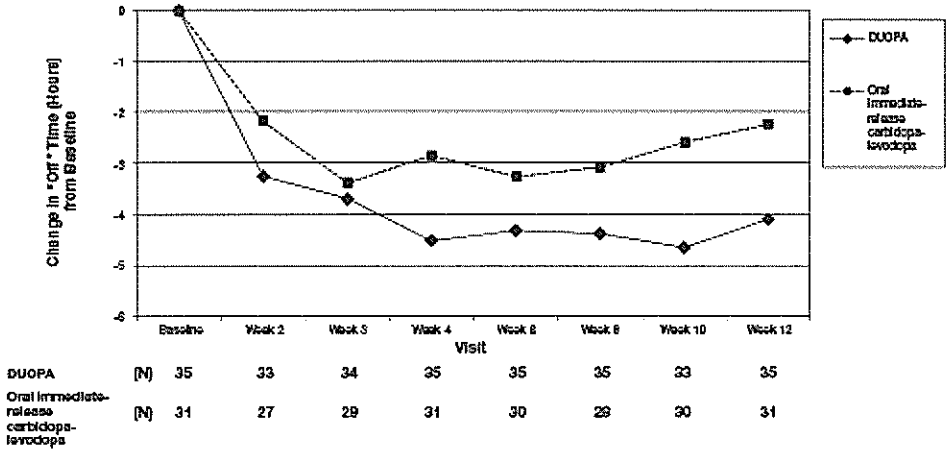


Figure 2. Change in "Off" Time Over 12 Weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Single-use cassettes containing 4.63 mg carbidopa (as 5 mg of the monohydrate) and 20 mg levodopa per mL of enteral suspension. Each cassette contains approximately 100 mL of suspension.

Carton of 7 DUOPA cassettes: NDC 0074-3012-07

16.2 Storage and Handling

Store in freezer at -20°C (-4°F). Thaw in refrigerator at 2°C to 8°C (36°F to 46°F) prior to dispensing. Cassettes should be protected from light and kept in the carton prior to use.

Thawing instructions for pharmacies

- Assign a 12 week "Use By" date based on the time the cartons are put into the refrigerator to thaw.
- Fully thaw DUOPA in the refrigerator prior to dispensing.
- In order to ensure controlled thawing of DUOPA, take the cartons containing the seven individual cassettes out of the transport box and separate the cartons from each other.
- Thawing may take up to 96 hours when the cartons are taken out of the transport box.
- Once the product has thawed, the individual cartons may be packed in a closer configuration within the refrigerator.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Information

Ask patients if they have had any previous surgery in the upper part of their abdomen that may lead to difficulty in performing the gastrostomy or jejunostomy *[see Dosage and Administration (2.3)]*.

Advise patients that foods that are high in protein may reduce the effectiveness of DUOPA *[see Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

Interruption of DUOPA Infusion

If the patient anticipates disconnecting the pump for a short period of time (less than 2 hours such as to swim, shower, or short medical procedure), no supplemental oral medication is needed, but the patient may be advised to take an extra-dose of DUOPA before disconnecting. Instruct the patient to stop the continuous rate, turn off the pump, clamp the cassette tube, disconnect the tubing, and replace the red cap on the cassette tube. The DUOPA cassette can remain attached to the pump until the tubing is reconnected. Refer the patient to the Patient Instructions for Use for additional information (i.e., changing the DUOPA Cassette: disconnecting Steps 1-5 and reconnecting Steps 10-16).

Advise the patient to contact their healthcare provider and to take oral carbidopa-levodopa until the patient is able to resume DUOPA infusion, if the patient will have prolonged interruption of therapy lasting more than 2 hours *[see Dosage and Administration (2.4)]*.

Gastrointestinal and Gastrointestinal Procedure-Related Risks

Inform patients of the gastrointestinal procedure-related risks including bezoar, ileus, implant site erosion/ulcer, intestinal hemorrhage, intestinal ischemia, intestinal obstruction, intestinal perforation, pancreatitis, peritonitis, pneumoperitoneum, post-operative wound infection and sepsis. Advise patients of the symptoms of the above listed complications and instruct them to contact their healthcare provider if they experience any of these symptoms *[see Warnings and Precautions (5.1)]*.

Falling Asleep during Activities of Daily Living and Somnolence

Alert patients to the potential sedating effects caused by DUOPA, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Because somnolence is a common adverse reaction with potentially serious consequences, patients should not drive a car, operate machinery, or engage in other potentially dangerous activities until they have gained sufficient experience with DUOPA to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., conversations, eating, driving a motor vehicle, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician.

Advise patients of possible additive effects when patients are taking other sedating medications, alcohol, or other central nervous system depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with DUOPA or when taking a concomitant medication that increases plasma levels of levodopa *[see Warnings and Precautions (5.2)]*.

Orthostatic Hypotension

Advise patients that they may experience syncope and may develop hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating while taking DUOPA. Accordingly, caution patients against standing rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with DUOPA *[see Warnings and Precautions (5.3)]*.

Hallucinations/Psychosis/Confusion

Inform patients that they may experience hallucinations (unreal visions, sounds, or sensations) and other symptoms of psychosis can occur while taking DUOPA. Tell patients to report hallucinations, abnormal thinking, psychotic behavior or confusion to their healthcare provider promptly should they develop *[see Warnings and Precautions (5.4)]*.

Impulse Control/Compulsive Behaviors

Advise patients that they may experience impulse control and/or compulsive behaviors while taking DUOPA. Advise patients to inform their physician or healthcare provider if they develop new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with DUOPA *[see Warnings and Precautions (5.5)]*.

Depression and Suicidality

Inform patients that they may develop depression or experience worsening of depression while taking DUOPA. Instruct patients to contact their healthcare provider if they experience depression, worsening of depression, or suicidal thoughts *[see Warnings and Precautions (5.6)]*.

Withdrawal-Emergent Hyperpyrexia and Confusion

Advise patients to contact their healthcare provider before stopping DUOPA. Tell patients to inform their healthcare provider if they develop withdrawal symptoms such as fever, confusion, or severe muscle stiffness *[see Warnings and Precautions (5.7)]*.

Dyskinesia

Inform patients that DUOPA may cause or exacerbate pre-existing dyskinesias *[see Warnings and Precautions (5.8)]*.

Neuropathy

Inform patients that neuropathy may develop or they may experience worsening neuropathy on DUOPA, and to contact their healthcare provider if they develop any symptoms or features suggesting neuropathy *[see Warnings and Precautions (5.9)]*.

Melanoma

Advise patients with Parkinson's disease that they have a higher risk of developing melanoma. Advise patients to have their skin examined on a regular basis by a qualified healthcare provider (e.g., dermatologist) when using DUOPA *[see Warnings and Precautions (5.11)]*.

Nursing Mothers

Because of the possibility that carbidopa or levodopa may be excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother *[see Use in Specific Populations (8.3)]*.

AbbVie Inc.
North Chicago, IL 60064, USA

03-A939 January 2015

MEDICATION GUIDE

DUOPA (Do-oh-pa)

(carbidopa and levodopa) enteral suspension

Read this Medication Guide before you start using DUOPA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about DUOPA?

DUOPA can cause serious side effects, including:

- **Stomach and intestine (gastrointestinal) problems and problems from the procedure you will need to have to receive DUOPA (gastrointestinal procedure-related problems).**
  Some of these problems may require surgery and may lead to death.
  - a blockage of your stomach or intestines (bezoar)
  - stopping movement through intestines (ileus)
  - drainage, redness, swelling, pain, feeling of warmth around the small hole in your stomach wall (stoma)
  - bleeding from stomach ulcers or your intestines
  - inflammation of your pancreas (pancreatitis)
  - air or gas in your abdominal cavity
  - skin infection around the intestinal tube, infection in your blood or abdominal cavity may occur, after surgery
  - stomach pain, nausea or vomiting
- **Tell your healthcare provider right away if you have any of the following symptoms of stomach and intestine problems and gastrointestinal procedure-related problems:**
  - stomach (abdominal) pain
  - constipation that does not go away
  - nausea or vomiting
  - fever
  - blood in your stool or a dark tarry stool (melanotic stool)

You will need to have a procedure to make a small hole (called a "stoma") in your stomach wall to place a gastro-jejunostomy tube (called a PEG-J tube) in an area of your small intestine called the jejunum. DUOPA is delivered directly to your small intestine through this tube. Your healthcare provider will talk to you about the stoma procedure. Before the stoma procedure, tell

your healthcare provider if you have ever had a surgery or problems with your stomach.

Talk to your healthcare provider about what you need to do to care for your stoma. After the procedure, you and your healthcare provider will need to regularly check the stoma for any signs of infection.

If your PEG-J tube becomes kinked, knotted, or blocked this may cause you to have worsening of your Parkinson's symptoms or recurring movement problems (motor fluctuations). Call your healthcare provider if your Parkinson's symptoms get worse or you have slow movement while you are treated with DUOPA.

What is DUOPA?

DUOPA is a prescription medicine used for treatment of advanced Parkinson's disease. DUOPA contains 2 medicines, carbidopa and levodopa.

DUOPA should not be given to children (younger than 18 years).

Who should not use DUOPA?

Do not use DUOPA if you:

- take a medicine called a nonselective Monoamine Oxidase (MAO) Inhibitor (such as phenelzine or tranylcypromine) or have taken a nonselective MAO Inhibitor within the last 14 days.
  Ask your healthcare provider or pharmacist if you are not sure if you take an MAO Inhibitor.

What should I tell my healthcare provider before using DUOPA?

Before you use DUOPA, tell your healthcare provider if you:

- have or have had stomach ulcers or stomach surgery
- have low blood pressure (hypotension) or if you feel dizzy or faint, especially when getting up from sitting or lying down
- have had problems with fainting (syncope)
- feel sleepy or have fallen asleep suddenly during the day
- have or have had depression (feelings of hopelessness or sadness) or any mental problems
- drink alcohol. Alcohol can increase the chance that DUOPA will make you feel sleepy or fall asleep when you should be awake
- have trouble controlling your muscles (dyskinesia)
- have nerve problems (peripheral neuropathy)
- have or have had heart problems, an abnormal heart rate or have had a heart attack in the past
- have or have had a type of skin cancer called melanoma
- have or have had high blood pressure (hypertension)

- have eye problems that cause increased pressure in your eye (glaucoma)
- have a history of attacks of suddenly falling asleep and without warning
- have any other medical conditions
- are pregnant or planning to become pregnant. It is not known if DUOPA will harm your unborn baby
- are breastfeeding or plan to breastfeed. DUOPA can pass into your milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take DUOPA

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements.

Using DUOPA with certain other medicines may affect each other and cause serious side effects.

Especially tell your healthcare provider if you take:

- medicines used to treat high blood pressure (hypertension)
- medicines used to treat depression called nonselective Monoamine Oxidase (MAO) Inhibitor (such as phenelzine or tranylcypromine) or have taken one within the last 14 days
- dopamine D2 receptor antagonists (antipsychotics or metoclopramide), and isoniazid
- iron or multivitamins with iron

Eating high protein foods may affect how DUOPA works. Tell your healthcare provider if you change your diet.

Ask your healthcare provider or pharmacist for a list of these medicines or foods if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use DUOPA?

- Use DUOPA exactly as your healthcare provider tells you to use it.
- Your healthcare provider should show you how to use DUOPA before you use it for the first time. Ask your healthcare provider or pharmacist if you have any questions.
- Your prescribed dose of DUOPA will be programmed into your pump by a healthcare provider and should only be changed by your healthcare provider or while you are with your healthcare provider.
- **Do not** stop using DUOPA or change your dose unless you are told to do so by your healthcare provider. Tell your healthcare provider if you develop withdrawal symptoms such as fever, confusion, or severe muscle stiffness.

- Keep a supply of oral carbidopa-levodopa immediate release (IR) tablets with you in case you are unable to give your DUOPA infusion.
- DUOPA is given continuously over 16 hours through a tube that is put into your stomach called a PEG-J. A small pump (CADD-Legacy 1400) is used to move DUOPA from the medication cassette through your PEG-J tube.
- Your DUOPA dose has three parts:
  - a morning dose
  - a continuous dose
  - extra doses
- DUOPA can also be given for a short time (short-term) through a tube put into your nose called a naso-jejunal (NJ) tube.
- The CADD-Legacy 1400 portable infusion pump should be used to give DUOPA through your PEG-J tube. See the **Instructions for Use** that comes with your CADD-Legacy 1400 portable infusion pump for complete instructions on how to use the pump.
- DUOPA comes in a small plastic container (cassette) that you connect to the pump to get your medicine.
  - Each cassette can only be used **1** time. An opened cassette should not be reused.
  - The cassette should not be used for longer than **16** hours.
  - The cassette should be thrown away at the end of the infusion, even if there is some medicine still in the cassette.
- Disconnect the pump from your PEG-J tube after the **16** hour dosing time is finished. Use a syringe filled with room temperature water to flush your PEG-J tube. See the "**Instructions for Use**" for more information about how to flush your PEG-J tube with a syringe.
- After your daily DUOPA infusion, you should take your usual night-time dose of oral carbidopa-levodopa tablets as prescribed.
- If you stop your DUOPA infusion for more than 2 hours during your **16** hour dosing time for any reason, call your healthcare provider and take oral carbidopa-levodopa as prescribed until you are able to restart your DUOPA infusion.
- If you stop your DUOPA infusion for less than 2 hours, you do not need to take oral carbidopa-levodopa, but your healthcare provider may tell you to take an extra dose of DUOPA.

What should I avoid while using DUOPA?

- **Do not** drive, operate machinery, or do other activities until you know how DUOPA affects you. Sleepiness and falling asleep suddenly caused by DUOPA can happen as late as 1 year after you start your treatment.

What are the possible side effects of DUOPA?

DUOPA may cause serious side effects, including:

- **See "What is the most important information I should know about DUOPA?"**
- **Falling asleep during normal daily activities.** DUOPA may cause you to fall asleep while you are doing daily activities such as driving, talking with other people, or eating.
  - You could fall asleep without any warning.
  - Some people using DUOPA have had car accidents because they fell asleep while driving.
    Do not drive or operate machinery until you are sure how DUOPA affects you.
    Tell your healthcare provider if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.
- **Low blood pressure when you sit or stand up quickly.** After you have been sitting or lying down, stand up slowly until you know how DUOPA affects you. This may help reduce the following symptoms while you are using DUOPA:
  - dizziness
  - nausea
  - sweating
  - fainting
- **Seeing things that are not there, hearing sounds or feeling sensations that are not real (hallucinations).** Hallucinations can happen in people who use DUOPA. Tell your healthcare provider if you have hallucinations.
- **Unusual urges.** Some people taking certain medicines to treat Parkinson's disease, including DUOPA, have reported problems, such as gambling, compulsive eating, compulsive shopping, and increased sex drive.
  If you or your family members notice that you are having unusual urges or behaviors, talk to your healthcare provider.
- **Depression and suicide.** DUOPA can cause depression or make your depression worse. Pay close attention to sudden changes in your mood, behavior, thoughts, or feelings. Call your healthcare provider right away if you feel depressed or have thoughts of suicide.
- **Uncontrolled sudden movements (dyskinesia).** If you have new dyskinesia, or your dyskinesia gets worse, tell your healthcare provider. This may be a sign that your dose of DUOPA or other medicines to control your Parkinson's disease may need to be adjusted.
- **Progressive weakness or numbness or loss of sensation in the fingers or feet (neuropathy).**

- **Heart attack or other heart problems. Tell your healthcare provider if you have experienced increased blood pressure, a fast or irregular heartbeat or chest pain.**
- **Skin cancer (melanoma).** Parkinson's disease may be associated with a higher chance of having melanoma than people who do not have Parkinson's disease. It is not known if the chance of having melanoma is higher because of the medicines used to treat Parkinson's disease, like DUOPA, or from the Parkinson's disease. People who use DUOPA should have their skin checked regularly for melanoma by a qualified healthcare professional.
- **Abnormal blood tests.** DUOPA may cause chances in certain blood tests, especially certain hormone and kidney function blood tests.
- **Worsening of the increased pressure in your eyes (glaucoma).** The pressure in your eyes should be checked after starting DUOPA.
- **The most common side effects of DUOPA include:**
  - swelling of legs and feet
  - nausea
  - high blood pressure (hypertension)
  - depression
  - mouth and throat pain

Call your healthcare provider or get medical care right away if you have any of the above symptoms. Your healthcare provider will tell you if you should stop treatment with DUOPA and if needed, tell you how to discontinue DUOPA.

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of DUOPA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DUOPA?

- Store DUOPA in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not freeze.
- Use at room temperature. Take one DUOPA cassette out of the carton and out of the refrigerator 20 minutes prior to use. Use the product at room temperature or you may not get the right amount of medication.
- Protect the cassette from light and keep it in the carton before using.
- Use DUOPA before the expiration date printed on the cassette.

Keep DUOPA and all medicines out of the reach of children.

General information about the safe and effective use of DUOPA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DUOPA for a condition for which it was not prescribed. Do not give DUOPA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about DUOPA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about DUOPA that was written for healthcare professionals.

For more information go to www.DUOPA.com or call 1-844-386-4968.

What are the ingredients in DUOPA?

Active ingredients: carbidopa and levodopa

Inactive ingredients: carmellose sodium and purified water

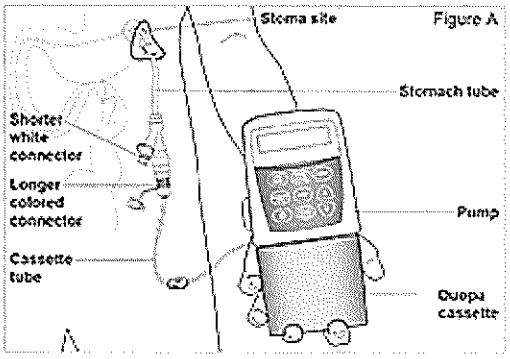
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
AbbVie Inc.
North Chicago, IL 60064, USA

03-A939 Revised: January 2015

INSTRUCTIONS FOR USE

DUOPA
(carbidopa and levodopa) enteral suspension



These instructions are for use along with any other instructions your healthcare provider gives you. Please read the Medication Guide before you start using DUOPA and each time you get a refill.

For questions or problems, call DUOPA support toll free at 1-844-386-4968.

The CADD-Legacy® 1400 pump is used for delivery of DUOPA through a tube into your stomach attached to the longer colored connector. Enteral nutrition should only be given by the shorter white connector **(see Figure A)**.

This Instructions for Use provides information for the CADD-Legacy® model 1400 pump only. There are other CADD-Legacy® pump models available. Read the label on the back of the pump to make sure it is a model 1400 pump.

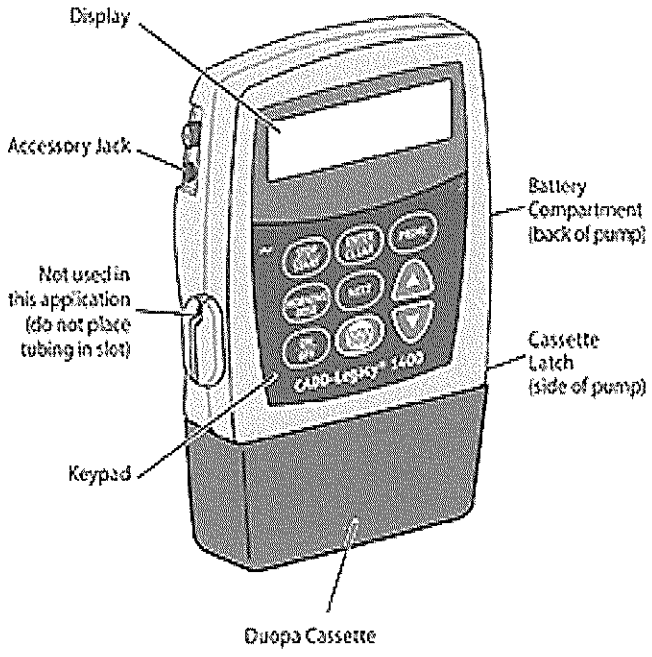
Your healthcare provider prescribed DUOPA for you. Your healthcare provider programs your prescription into the CADD-Legacy® 1400 pump. The CADD-Legacy® 1400 pump is approved for use with DUOPA. DUOPA is provided as medication inside cassettes that connect to the CADD-Legacy® 1400 pump.

The pump delivers DUOPA in **3** ways:
- Continuous Rate: Steady delivery of DUOPA delivered throughout the day while pump is on
- Morning Dose: A large dose of DUOPA given each morning
- Extra Dose: A small dose of DUOPA given as needed during the day

You will need the following items to complete these steps:
- Pump
- DUOPA cassette
- Coin, like a quarter
- Carrying bag
- Syringe
- Syringe connector
- Room temperature water

CADD-Legacy® 1400 Pump

CADD-Legacy ® 1400 Pump



Description of the Keys

- Used to start and stop the pump. Also used to silence alarms.
- Used to save new values when programming.
- Used to fill the tubing with Duopa.

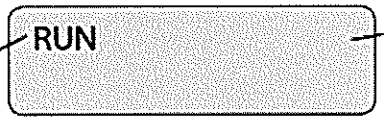
  ***NOTE:** The PRIME key is intended for use **only** by healthcare providers.*
- Used to deliver the **Morning Dose.**
- Used to advance from one screen to the next. Also used to silence alarms.
- Used to increase a value.
- Used to decrease a value.
- Used to put the pump into a low power state when not in use or back into full power.
- Used to deliver extra doses of Duopa, if allowed.

Display

The display shows programming information and messages. The main screen, which the pump displays most of the time, shows the following:

When running:

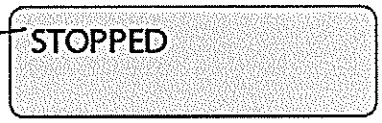
Status of pump



Battery Status (for example, LowBat appears when battery power becomes low)

When stopped:

Status of pump



DUOPA Cassette

The single-use DUOPA cassette is for use with the CADD-Legacy® 1400 pump.

Battery Compartment

Two **AA** batteries fit into the battery compartment.

Cassette Latch

The cassette latch secures the DUOPA cassette to the pump.

Failure to follow the Warnings and Cautions below could cause return of your symptoms, damage to the pump, serious injury, or may lead to death in rare cases.

WARNINGS

- Only use the pump in a manner described in this Instructions for Use, after you have received training by your healthcare provider.
- To avoid explosion hazard, **do not** use the pump near flammable explosive gases.
- Only use extension sets that are approved for use with DUOPA (See the Full Prescribing Information for DUOPA), pay attention to all warnings and cautions associated with their use.
- Always have new batteries available for replacement. If power is lost, DUOPA will not be delivered.
- If the pump is dropped or hit, the battery door or tabs may break. **Do not** use the pump if the battery door or tabs are damaged because the batteries will not be correctly secured. This may cause loss of power and DUOPA will not be delivered.
- If the pump is dropped or hit, look at the pump for damage. **Do not** use a pump that is damaged or is not functioning correctly.
- If a gap is present between the battery door and the pump housing, this means the door is not correctly latched. If the battery door becomes detached or loose, the batteries will not be correctly secured. This could cause loss of power and DUOPA will not be delivered.
- Use only DUOPA cassettes for pump accuracy and to make sure the pump works correctly. Attach the DUOPA cassette correctly. A detached or incorrectly attached DUOPA cassette could cause a problem with getting your DUOPA.

CAUTIONS

- Use only Smiths Medical accessories and replacement parts for the pump as using other brands may adversely affect the operation of the pump.
- **Do not** operate the pump at temperatures below 36°F (2°C) or above 104°F (40°C).
- **Do not** store the pump at temperatures below -4°F (-20°C) or above 140°F (60°C). **Do not** store the pump with a DUOPA cassette attached. Use the protective cassette provided when storing the pump.
- **Do not** keep the pump in humidity levels below 20% or above 90% relative humidity.
- **Do not** place the pump in cleaning fluid or water, or allow solution to soak into the pump, keypad, or battery compartment.
- **Do not** clean the pump with acetone, other plastic solvents, or abrasive cleaners.
- **Do not** use rechargeable NiCd or nickel metal hydride (NiMH) batteries. **Do not** use carbon zinc (heavy duty) batteries. They do not provide enough power for the pump to operate correctly.
- **Do not** store the pump for long periods of time with the batteries installed. Battery leakage could damage the pump.

MORNING PROCEDURE 1-3

Morning Procedure

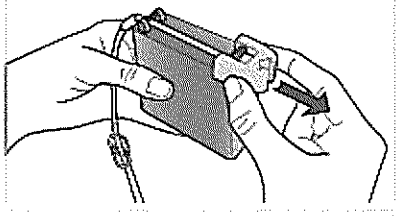
- **Take the DUOPA carton containing the DUOPA cassettes out of the refrigerator. Check the expiration date on the carton. Do not** use any of the cassettes if the expiration date has passed.
- **Take a DUOPA cassette out of the carton.** Return the carton with the remaining cassettes to the refrigerator. **Do not** use the cassette if the expiration date has passed or the cassette is damaged or empty. **Leave the DUOPA cassette at room temperature for 20 minutes before using.**
- Each DUOPA cassette may be used for up to **16** hours after removal from the refrigerator.

WARNING: Use only DUOPA cassettes to make sure the pump works correctly.

1) Remove the cassette clip (see Figure B):

- Remove the cassette tube from its slot in the clip.
- Pull the clip from cassette to slide it off of the cassette top.

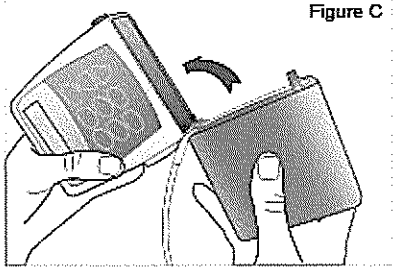
Figure B



2) Attach the DUOPA cassette to the pump (see Figure C):

- Hold the pump so the latch faces up.
- Hold the DUOPA cassette so the tube points down.
- Insert the DUOPA cassette hooks into the hinge pins at the base of the pump.

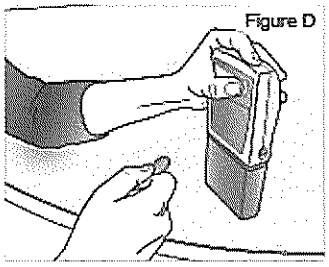
Figure C



3) Latch the DUOPA cassette into the pump:

- Hold the pump and DUOPA cassette upright against a flat surface.
- Press down on the pump, until the DUOPA cassette fits tightly against the pump (**see Figure D**).

Figure D



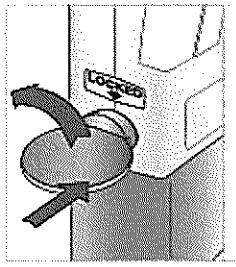
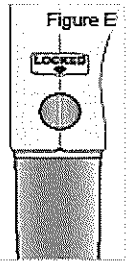


Figure E

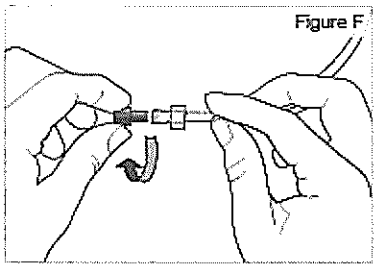


- Use a coin to twist the latch counterclockwise until the latch lines up straight with the arrow (**see Figure E**).

WARNING: Attach the DUOPA cassette correctly. A detached or incorrectly attached cassette could cause a problem with getting your DUOPA.

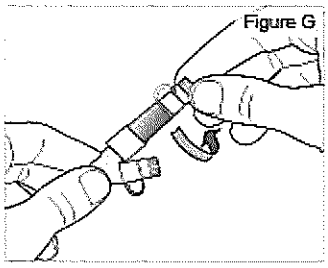
4) Remove the red cap on the end of the cassette tube (see Figure F). Save the red cap for use when you throw away the cassette.

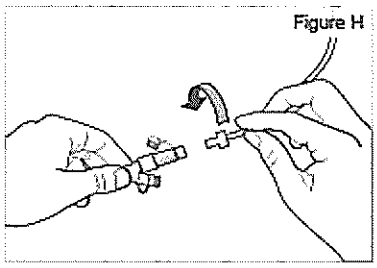
WARNING: Do not connect the red cap to the stomach tube. It will block DUOPA flow.



5) Connect the stomach tube to the cassette tube:

- While holding the stomach tube steady, twist off the white cap on the end of the longer colored connector **(see Figure G). WARNING: Do not twist the stomach tube.**





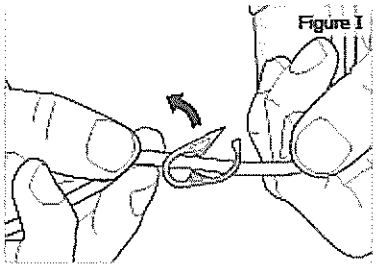
- Connect the cassette tube to the end of the longer colored connector **(see Figure H). Do not connect to the shorter white connector.**

6) Turn the pump on:

- Press and hold ON/OFF until the display turns on.
- Wait approximately **30** seconds for the pump to review settings.
- Check for STOPPED on the screen.

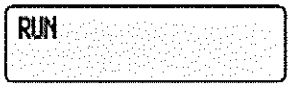
PUMP STATUS: The pump is now on but not yet delivering DUOPA.

7) Inspect the tubing for kinks or closed clamps. If needed straighten kinks or open clamps (see Figure I).



MORNING PROCEDURE 8

8) Start the pump:

- Press and **hold** (STOP START) until **3** dashes appear and then disappear from the screen.
- Wait approximately **15** seconds for the pump to start running.
- Check for 

on the display.

PUMP STATUS: The pump is now running. DUOPA delivery will begin as programmed by your healthcare provider. If the pump will not start, a message should appear on the display. Refer to the **Alarms and Messages** section on **page 22**.

It will take between 10 minutes and 30 minutes to deliver your morning dose. To start delivery of your Morning Dose you will need to press the Morning Dose key 2 times.

NOTE: If you are unable to deliver your Morning Dose, it may be too soon since the last Morning Dose to deliver another dose. You may need to wait longer. The time between Morning Doses is decided by your healthcare provider.

9) The first key press shows the Morning Dose on the display.

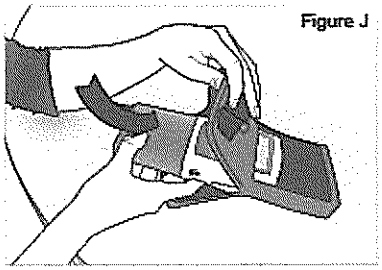
- Press MORNING DOSE.
- Check for Morning Dose x.x nl on the display. The number on your display is the Morning Dose of DUOPA your healthcare provider prescribed for you.

10) The second key press starts Morning Dose delivery.

- Press MORNING DOSE a second time to deliver the Morning Dose.
- The display Morning Dose x.x nl shows a countdown of your Morning Dose.

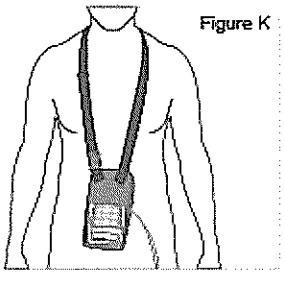
PUMP STATUS: After the Morning Dose finishes, the pump will automatically begin delivering the Continuous Rate. **RUN** will appear on the display. This completes DUOPA delivery for your Morning Procedure.

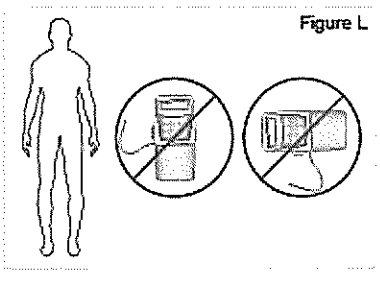
11) Insert the pump into the carrying bag (see Figure J).


Figure J

12) Wear the bag over your shoulder or neck:

- Place the bag strap over your shoulder or neck **(see Figure K)**.
- Make sure the pump is in correct position **(see Figure L)**.


Figure K

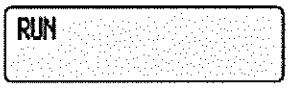

Figure L

EXTRA DOSE

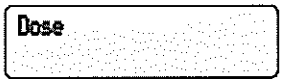
Extra Dose

1) Give an Extra Dose of DUOPA:

NOTE: If you are unable to deliver the Extra Dose, it may be too soon since the last Extra Dose to deliver another and you may need to wait longer. The time between Extra Doses and the amount of DUOPA in the Extra Dose is decided by your healthcare provider.

- Check for 

on the display.
- Press 

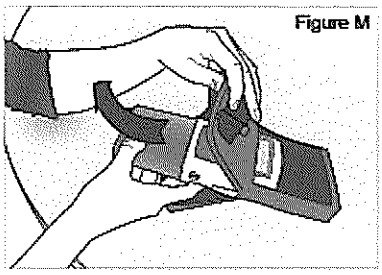
- Listen for **2** beeps.
- The display will show 

.

PUMP STATUS: The pump is now delivering the Extra Dose. When it finishes, **RUN** will appear on the display and the Continuous Rate will continue to run.

For instructions on changing a DUOPA cassette, see page 12.

Evening Procedure


Figure M

You will need:

- 1 Syringe
- 1 Syringe connector
- Room temperature water
- 1 Coin, like a quarter

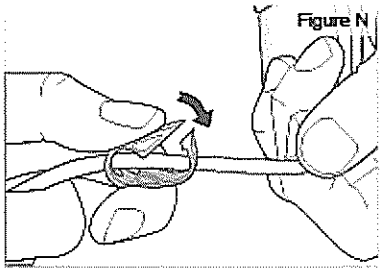
1) Remove the pump from the carrying bag (see Figure M).

2) Stop the Continuous Rate:

- Press and **hold** (STOP/START) until **3** dashes appear and then disappear from the display.
- Check for STOPPED on the display.

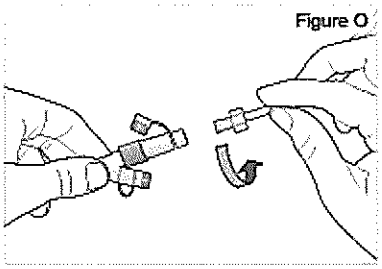
3) Turn the pump off:

- Press and **hold** (ON/OFF) until **3** sets of dots appear and then disappear from the display and the display turns off.
- Check that the display is off.


Figure N

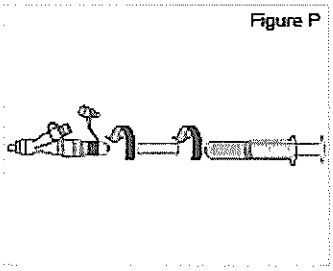
4) Clamp the cassette tube (see Figure N).

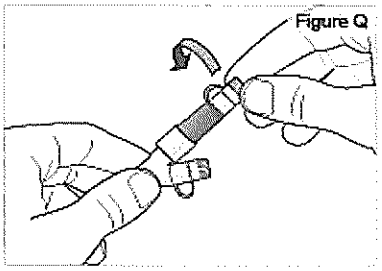
5) Disconnect the tubing:


Figure O

- Twist the cassette tube to disconnect it from the longer colored connector **(see Figure O). WARNING: Do not twist the stomach tube.**
- Replace the red cap on the cassette tube.

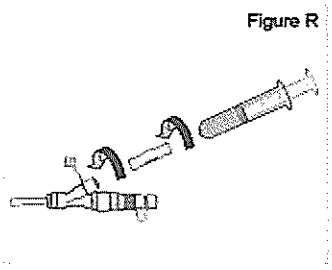
6) Flush the longer colored connector:

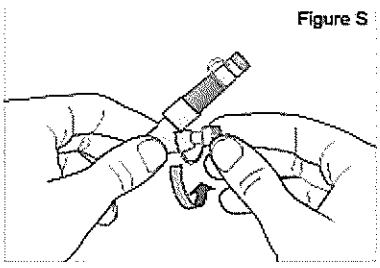




- Connect the syringe connector to the longer colored connector.
- Fill a syringe with room temperature tap or drinking water**. Do not use hot water as it could burn the wall of your stomach or intestine.**
- Connect the syringe to the syringe connector **(see Figure P)**. **Do not** over-tighten the syringe connector or it could break. **Do not** use the syringe connector if it is cracked or broken.
- Push the syringe plunger to flush the tube. **Do not** force the syringe if flushing the tube is difficult. Call your healthcare provider if you are unable or have difficulty flushing your tube.
- Remove the syringe and the syringe connector.
- Replace the white cap on the longer colored connector **(see Figure Q)**.

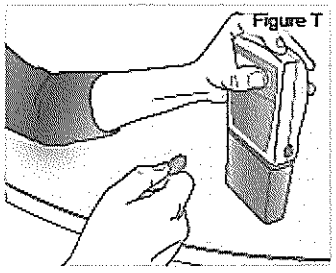
7) Flush the shorter white connector:

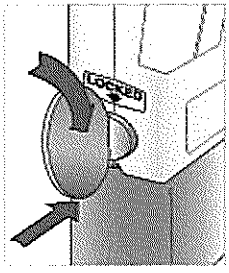


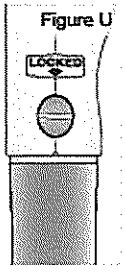


- Twist the white cap off the shorter white connector.
- Connect the syringe connector to the shorter white connector.
- Fill a syringe with room temperature tap or drinking water. **Do not use hot water as it could burn the wall of your stomach or intestine.**
- Connect the syringe to the syringe connector **(see Figure R)**. **Do not** over-tighten the syringe connector or it could break**. Do not** use the syringe connector if cracked or broken.
- Push the syringe plunger to flush the tube.
- Remove the syringe and the syringe connector. Replace the white cap on the shorter white connector **(see Figure S)**.

8) Remove the DUOPA cassette from the pump:







- Hold the pump and DUOPA cassette upright against a flat surface **(see Figure T)**.
- Use a coin to twist the latch clockwise until the latch pops out **(see Figure U)**.
- Remove the DUOPA cassette from the pump.

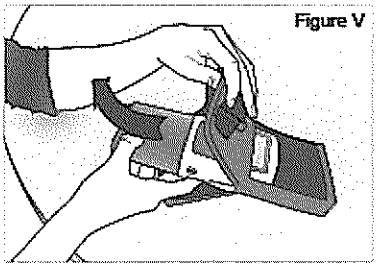
CHANGING THE DUOPA CASSETTE 1-4

Changing the DUOPA Cassette

- **Take the DUOPA carton containing the DUOPA cassette out of the refrigerator. Check the expiration date on the carton. Do not** use any of the cassettes if the expiration date has passed.
- **Take a DUOPA cassette out of the carton.** Return the carton with the remaining cassettes to the refrigerator. **Do not** use the cassette if the expiration date has passed or the cassette is damaged or empty. **Leave the DUOPA cassette at room temperature for 20 minutes before using.**
- Each DUOPA cassette may be used for up to **16** hours after removal from the refrigerator.

WARNING: Use only DUOPA cassettes to make sure the pump works correctly.

1) Remove the pump from the carrying bag (see Figure V).


Figure V

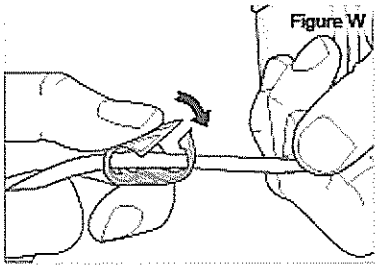
2) Stop the Continuous Rate:

- Press and **hold** (STOP START) until **3** dashes appear and then disappear from the display.
- Check for STOPPED on the display.

3) Turn the pump off:

- Press and **hold** (ON OFF) until **3** sets of dots appear and then disappear from the display and the display turns off.
- Check that the display is off.

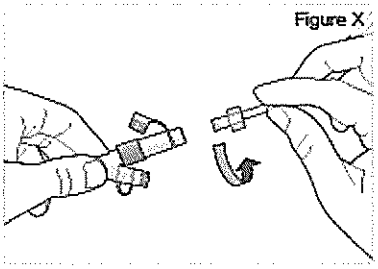
4) Clamp the cassette tube (see Figure W).


Figure W

5) Disconnect the tubing:

- Twist the cassette tube to disconnect it from the longer colored connector **(see Figure X)**. **WARNING: Do not twist the stomach tube.**
- Replace the red cap on the cassette tube.

Figure X



6) Remove the DUOPA cassette from the pump:

- Hold the pump and DUOPA cassette upright against a flat surface **(see Figure Y).**
- Use a coin to twist the latch clockwise until the latch pops out **(see Figure Z)**.
- Remove the DUOPA cassette from the pump.

Figure Y

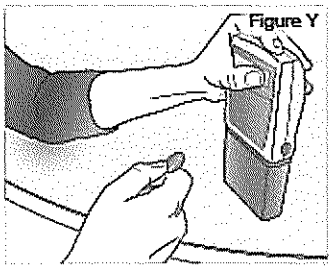
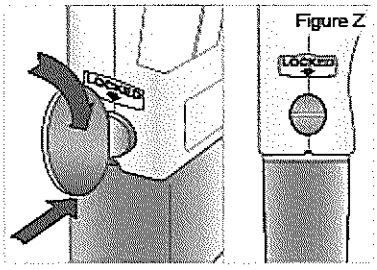


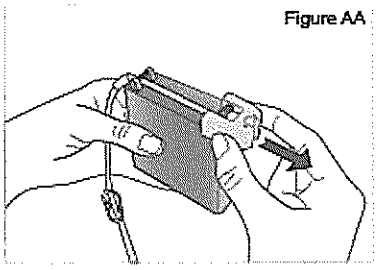
Figure Z



7) Remove the cassette clip on the new DUOPA cassette (see Figure AA):

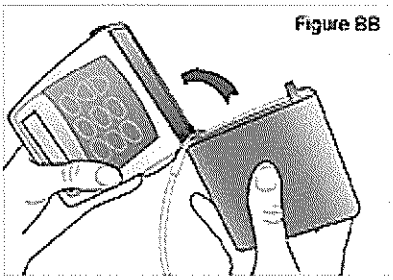
- Remove the cassette tube from its secured slot in the clip.
- Pull the clip from the cassette to slide it off of the cassette top.

Figure AA



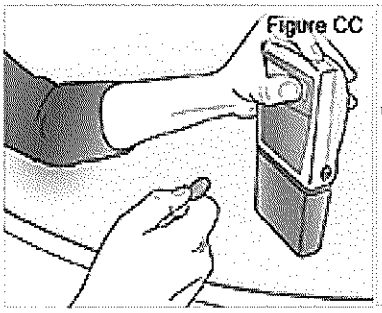
CHANGING THE DUOPA CASSETTE 8-11

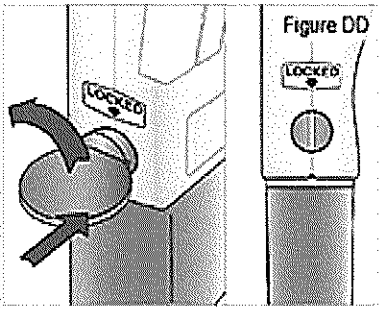
8) Attach the new DUOPA cassette to the pump (see Figure BB):



- Hold the pump so that the latch faces up.
- Hold the DUOPA cassette so that the tube points down.
- Insert the DUOPA cassette hooks into the hinge pins at the base of the pump.

9) Latch the new DUOPA cassette into the pump:

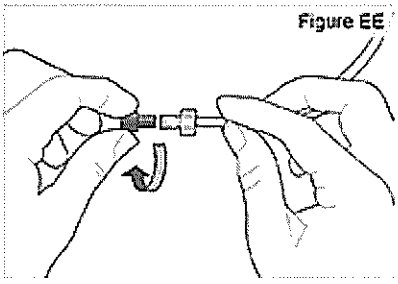




- Hold the pump and DUOPA cassette upright against a flat surface.
- Press down on the pump until the DUOPA cassette fits tightly against the pump **(see Figure CC)**.
- Use a coin to twist the latch counterclockwise until the latch lines up straight with the arrow **(see Figure DD)**.

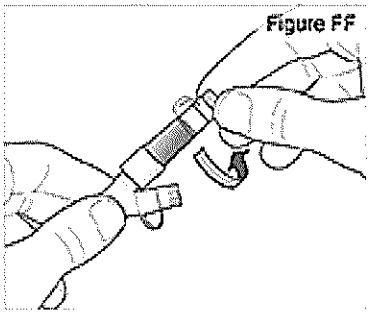
WARNING: Attach the DUOPA cassette correctly. A detached or incorrectly attached cassette could cause a problem with getting your DUOPA.

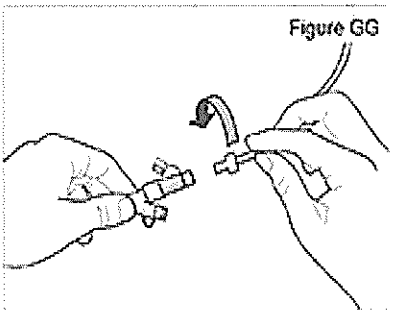
10) Remove the red cap on the end of the cassette tube (see Figure EE).
Save the red cap to use when discarding the cassette.



WARNING: Do not connect the red cap to the stomach tube as it will block DUOPA flow.

11) Connect the stomach tube to the cassette tube:





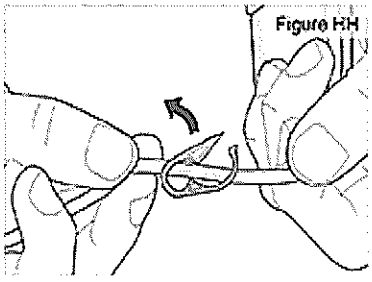
- While holding the stomach tube steady, twist off the white cap on the end of the longer colored connector **(see Figure FF). WARNING: Do not twist the stomach tube.**
- Connect the cassette tube to the end of the longer colored connector **(see Figure GG). Do not connect to the shorter white connector**.

12) Turn the pump on:

- Press and **hold** (ON/OFF) until the display turns on.
- Wait approximately **30** seconds for the pump to review settings.
- Check for STOPPED on the display.

PUMP STATUS: The pump is now on but not delivering DUOPA.

13) Inspect the tubing for kinks or closed clamps. If needed straighten kinks or open clamps (see Figure HH).

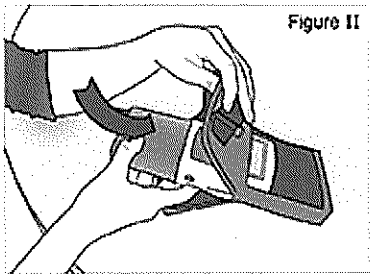


14) Start the pump:

- Press and **hold** (STOP/START) until **3** dashes appear and then disappear from the display.
- Wait approximately **15** seconds for pump to start running.
- Check for RUN on the display.

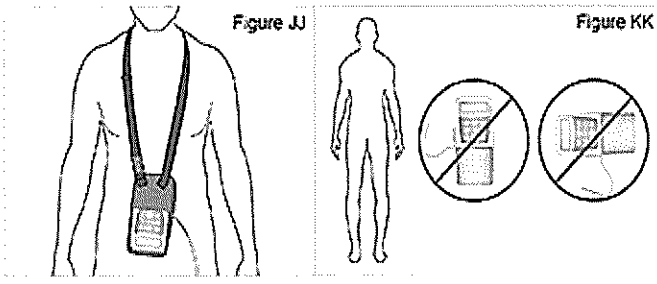
PUMP STATUS: The pump is now running.

15) Insert the pump into the carrying bag (See Figure II).



16) Wear the bag on your shoulder or neck:

- Place the bag strap over your shoulder or neck **(see Figure JJ)**.
- Make sure the pump is in correct position **(see Figure KK)**.



CHANGING THE BATTERIES 1-3

Changing the Batteries:

If you see **LowBat** or **Battery Depleted** on the display, change the batteries. Use **2** new **AA** alkaline batteries such as DURACELL® or EVEREADY® ENERGIZER®. The pump keeps all the important information when the batteries are removed.

WARNING:

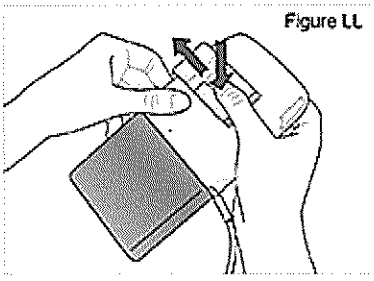
- **Always have new batteries available for replacement.** If power is lost, DUOPA will not be delivered.
- **If the pump is dropped or hit, the battery door or tabs may break. Do not** use the pump if the battery door or tabs are damaged because the batteries will not be correctly secured. This may lead to loss of power and DUOPA will not be delivered.
- **If a gap is present anywhere between the battery door and the pump housing, the door is not correctly latched.** If the battery door becomes detached or loose, the batteries will not be correctly secured. This could cause loss of power and DUOPA will not be delivered.

CAUTION:

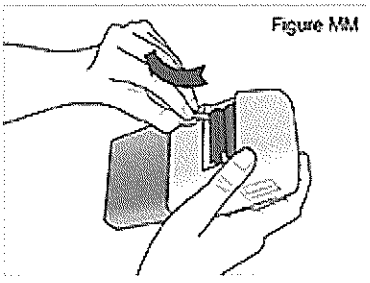
- **Do not use rechargeable NiCd or nickel metal hydride (NiMH) batteries. Do not use carbon zinc ("heavy duty") batteries.** They do not provide enough power for the pump to operate correctly.
- **Do not store the pump for prolonged periods of time with the batteries installed.** Battery leakage could damage the pump.

1) Ensure the pump is stopped.

2) Push and hold the arrow button while sliding the battery door until it comes completely off the pump (see Figure LL).


Figure LL

3) Remove the used batteries (see Figure MM).


Figure MM

4) Install new batteries into the battery compartment.

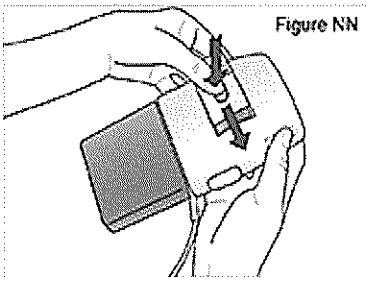
NOTE: Insert the batteries correctly based on the picture in the battery compartment. If you insert the batteries backwards, the display will remain blank. Reinsert the batteries, making sure to match the **+** and **–** markings with the battery compartment picture.

5) Listen for a beep.

PUMP STATUS: The pump is now powered. The power-up sequence will start, the pump will go through an electronic self-test, and then the pump will beep **6** times at the end of the power-up sequence. All of the display indicators, the software revision, and each setting will appear briefly.

If you do not hear a beep, and the display is off, the pump is not powered. Check that the batteries are correctly inserted.

6) Slide the battery door back onto the pump into its original closed position (see Figure NN).


Figure NN

CHANGE THE MORNING DOSE 1-3

Your healthcare provider may have set your pump to allow for dose changes to your Morning Dose and Continuous Rate (Lock Level 1). Do not change your medicine dose without approval and training from your healthcare provider.

Talk with your healthcare provider to decide when to change your Morning Dose and Continuous Rate. Do not change your Extra Dose unless your healthcare provider tells you to. If your Extra Dose requires changes, your healthcare provider will provide instructions.

Change the Morning Dose

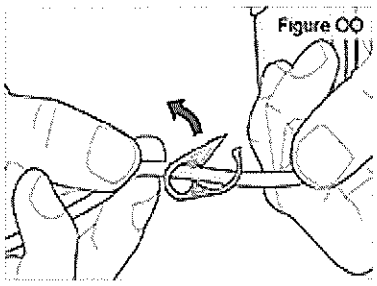
WARNING: Do not use the Prime button. Priming is for use by your healthcare provider only.

1) Turn the pump on:

- Press and **hold** (ON/OFF) until the display turns on.
- Wait approximately **30** seconds for pump to review settings.
- Check for STOPPED on the display.

PUMP STATUS: The pump is now on but not yet delivering DUOPA.

2) Inspect the tubing for kinks or closed clamps. If needed, straighten kinks or open clamps (see Figure OO).



3) Start the pump:

- Press and **hold** (STOP/START) until **3** dashes appear and then disappear from the display.
- Wait approximately **15** seconds for pump to start running.
- Check for RUN on the display.

PUMP STATUS: The pump is now running.

4) Change the Morning Dose:

a. Press MORNING DOSE **1** time.

b. Check for Morning Dose x.x nl on the display.

c. Press ▲ or ▼ to select the desired Morning Dose.

d. Press ENTER CLEAR to store the Morning Dose.

e. Make sure you see the correct Morning Dose on the display. If not, repeat **Steps 4c to 4e.**

5) Deliver the Morning Dose:

- Press MORNING DOSE **1** time.

NOTE: If you see "**Value not saved**" on the display, press **NEXT** and then repeat **Steps 4c to 4e.**

- The display Morning Dose x.x nl shows a countdown of your Morning Dose.

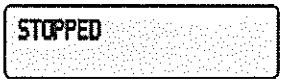
PUMP STATUS: After the Morning Dose finishes, the pump will begin delivering the Continuous Rate. **RUN** will appear on the display.

NOTE: If you are unable to deliver a Morning Dose, it may be too soon since the last Morning Dose to deliver another and you may need to wait longer. The time between Morning Doses is decided by your healthcare provider.

CHANGE THE CONTINUOUS RATE

Change the Continuous Rate

1) Stop the Continuous Rate:

- Press and hold (STOP START) until **3** dashes appear and then disappear from the display.
- Check for 

on the display.

2) Change the Continuous Rate:

a. Press (NEXT) **2** times.

b. Check for 

on the display.

c. Press (▲) or (▼) to select the desired Continuous Rate.

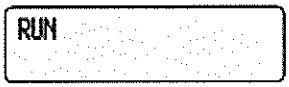
d. Press (ENTER CLEAR) to store the Continuous Rate.

e. Make sure you see the desired Continuous Rate on the display. If not, repeat **Steps 2c to 2e**.

3) Start the pump:

- Press and **hold** (STOP START) until **3** dashes appear and then disappear from the display.

NOTE: If you see "**Value not saved**" on the display, press **NEXT** and then repeat **Steps 2c to 2e.**

- Wait approximately **15** seconds for the pump to start running.
- The display will show 

PUMP STATUS: The pump is now running.

Alarms and Messages

The table below shows some of the common alarms that you may hear from the pump. With all alarms, read the display before pressing (NEXT) to silence the alarm.

What you see:	What you hear:	Meaning	Response
Error	Two-Tone Alarm	An error with the pump has occurred.	Contact your healthcare provider.
High Pressure	Two-Tone Alarm	There is pressure backed up in the tubing.	Check tubing for clamps, kinks, or blockages. Make sure the red cap has been removed from the DUOPA cassette tube. Flush connectors if necessary. If it is not possible to flush the tubes, contact your healthcare provider as your tube may be blocked.
LowBat	**3** Two-Tone Beeps Every **5** minutes	The pump batteries are low.	Change the batteries right away.
Upstream Occlusion	Two-Tone Alarm	If your healthcare provider has the Upstream Occlusion Sensor set to **ON** and a blockage in the DUOPA cassette is detected, this alarm will sound.	Detach the DUOPA cassette. Check if the DUOPA cassette is empty. If not empty, reattach the DUOPA cassette. Restart the pump to continue delivery. Contact your healthcare provider if the alarm continues.
No message on display	Two-Tone Alarm	Batteries were removed within approximately **15** seconds after stopping the pump.	Install new batteries to silence the alarm. Otherwise, the alarm will stop within a short period of time.

When you see:	What you hear:	Meaning	Response
Display shows current pump status	**2** Beeps (Long-Short)	The DUOPA cassette is not lined up with the pump or DUOPA is not flowing from the DUOPA cassette to the pumping mechanism. Very cold or extremely thick DUOPA may cause this alarm as well.	Press **NEXT** to silence the alarm. The pump continues to run. Make sure the DUOPA cassette is correctly lined up with the pump and DUOPA is flowing. Take the DUOPA cassette out of the refrigerator for **20** minutes before attaching to the pump.
Battery Depleted	Two-Tone Alarm	Batteries are dead.	Install new batteries. To continue delivery, restart the pump when completed.
Key pressed, Please release	Two-Tone Alarm	Key is being held down.	Stop pressing key. If the alarm persists, close the cassette tube clamp and remove the pump from use. Contact your healthcare provider.
No Disposable, Clamp Tubing	Two-Tone Alarm	**Disposable** refers to the DUOPA Cassette. **No Disposable** means the DUOPA cassette was removed. The pump is not sensing proper cassette attachment.	Clamp the cassette tube and disconnect it from your stomach tube. A DUOPA cassette must be correctly attached in order for the pump to run. Press **NEXT** to silence the alarm.
No Disposable, Pump won't run	Two-Tone Alarm	**Disposable** refers to the DUOPA Cassette. You have tried to start the pump without a disposable DUOPA cassette attached.	Press **NEXT** to silence the alarm. A DUOPA cassette must be correctly attached for the pump to run.
Service Due See manual	Two-Tone Alarm	The pump is scheduled for service.	Press **NEXT** to silence the alarm. The pump is still working, but contact your healthcare provider for further instructions.

FREQUENTLY ASKED QUESTIONS

What if I drop the pump or hit it against a hard surface?

Do the following right away:

- Check the DUOPA cassette latch on the side of the pump and make sure the line on the latch lines up with the arrow on the side of the pump.
- Gently twist, push, and pull on the DUOPA cassette to make sure it is still firmly attached.
- Check the battery door to make sure it is still firmly attached.

If the DUOPA cassette or the battery door is loose or damaged, do not use the pump.
Stop the pump right away, close the tubing clamp, and contact your healthcare provider.

What should I do if I drop the pump in water?

If you accidentally drop the pump in water, pick it up quickly, dry it off with a towel, and call your healthcare provider.

WARNING: If the pump is dropped or hit, look at the pump for damage. Do not use a pump that is damaged or is not working correctly.

What should I do if I need to bathe while wearing the pump?

You'll need to detach the pump before you shower, bathe, or swim. Reattach the pump to the stomach tubing afterwards and restart it.

What should I do if I need to have a medical test while wearing the pump?

The pump may need to be removed prior to certain medical tests. Be sure to talk to your doctor about your DUOPA pump before you take these tests.

Storage

- Store DUOPA in the refrigerator with the temperature between 36°F to 46°F (2°C to 8°C).
- When the DUOPA cassette has been removed from the refrigerator, DUOPA should be used within **16** hours.
- The DUOPA cassettes are for single use only and should not be used for longer than **16** hours, even if some of the medicine remains. An opened cassette should not be re-used.
- Protect the cassette from light and keep it in the carton before using.

Throwing away your DUOPA cassette or batteries

- Throw away the DUOPA cassette as your healthcare provider tells you to.
- Throw away used batteries in a manner safe for the environment, and according to any regulations that apply.

NOTES

NOTES

QUESTIONS?

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

abbvie AbbVie Inc.
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For DUOPA Support: 1-844-386-4968

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www.smiths-medical.com

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