09-J2000-52

Original Effective Date: 03/15/16

Reviewed: 12/10/25

Revised: 01/15/26

Subject: Irinotecan Liposome Injection (Onivyde™)

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DESCRIPTION:

Irinotecan liposome injection (Onivyde) is a topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome. Topoisomerase 1 promotes cytotoxicity by inducing single-strand breaks in DNA and preventing re-ligation. In mice, irinotecan liposome at lower doses has demonstrated similar intratumoral exposure as compared to irinotecan hydrochloride.

Irinotecan liposome injection (Onivyde) was approved by the U.S. Food and Drug Administration (FDA) in October 2015 in combination with 5-fluorouracil (5-FU) and leucovorin (LV), for the treatment of metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine-based therapy and in February 2024 it was approved with oxaliplatin, fluorouracil, and leucovorin for the first-line treatment of metastatic pancreatic adenocarcinoma.

The efficacy of irinotecan liposome injection was evaluated in a three-arm, randomized, open-label trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression, after gemcitabine or gemcitabine-based therapy. Subjects were eligible for the trial if the Karnofsky Performance Status (KPS) was greater than or equal to 70, serum bilirubin was within normal limits, and albumin was greater than or equal to 3 g/dL. The subjects were randomized to receive irinotecan liposome injection monotherapy, irinotecan liposome injection with 5-FU/LV, or 5-FU/ LV alone. Treatment was continued until disease progression or unacceptable toxicity. The primary outcome of overall survival was improved with irinotecan liposome injection in combination with 5-FU/LV at 6.1 months as compared to 4.2 months with 5-FU/ LV alone (hazard ratio 0.68, 95%CI 0.50 – 0.93; p=0.014). There was no improvement in overall survival with irinotecan liposome injection when used as monotherapy as compared to 5-FU/ LV alone. Median progression-free survival was improved with irinotecan liposome injection in combination with 5-FU/LV at 3.1 months as compared to 1.5 months

with 5-FU/ LV alone (hazard ratio 0.55, 95%CI 0.41 – 0.75). The objective response rate (confirmed complete/partial response) was also improved with irinotecan liposome injection in combination with 5-FU/LV at a rate of 7.7% as compared to 0.8% with 5-FU/ LV alone. The most frequent adverse reactions resulting in discontinuation of with irinotecan liposome injection in combination with 5-FU/LV were diarrhea, vomiting and sepsis. Dose reductions or delays in therapy most frequently occurred due to neutropenia, diarrhea, nausea, anemia, vomiting, fatigue, and thrombocytopenia.

The National Comprehensive Cancer Network (NCCN) provides support for the use of irinotecan liposome injection (Onivyde) for metastatic, locally advanced and recurrent adenocarcinoma of the pancreas and as first-line or for disease progression in ampullary adenocarcinoma of the pancreatobiliary and mixed types.

POSITION STATEMENT:

I. Initiation of Irinotecan liposome injection (Onivyde) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when **ALL** associated criteria are met:

   A. Adenocarcinoma of the pancreas

      1. Member has **ONE** of the following:
         a. Metastatic disease
         b. Locally advanced **disease**
         c. Recurrent disease
      2. **ONE** of the following regimens:
         a. For first-line therapy in combination with oxaliplatin, fluorouracil and leucovorin
         b. For induction therapy in combination with oxaliplatin, fluorouracil and leucovorin followed by chemoradiation
         c. For disease progression in combination with fluorouracil and leucovorin after **ONE** of the following:
            i. Gemcitabine-based therapy
            ii. Fluoropyrimidine-based therapy (e.g., fluorouracil or capecitabine) if irinotecan was not previously given
      3. The dose does not exceed **ONE** of the following:
         i. 50 mg/m^2 every two weeks with oxaliplatin, fluorouracil and leucovorin
         ii. 70 mg/m^2 every two weeks with fluorouracil and leucovorin

   B. Ampullary Adenocarcinoma

      1. Member has **ONE** of the following histological subtypes of ampullary cancer:
         a. Pancreatobiliary type
         b. Mixed type
      2. **ONE** of the following:
         a. First-line therapy for metastatic disease in combination with oxaliplatin, fluorouracil and leucovorin
         b. For disease progression in combination with fluorouracil and leucovorin after **ONE** of the following:

i. Gemcitabine-based therapy

ii. Fluoropyrimidine-based therapy (e.g., fluorouracil or capecitabine) if irinotecan was not previously given

iii. Oxaliplatin-based therapy if irinotecan was not previously given

3. Dose does not exceed the maximum FDA-approved dose

C. Other FDA-approved or NCCN supported diagnosis

1. **ONE** of the following is met:

a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

b. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

2. Dose does not exceed the maximum FDA-approved dose

Duration of approval: 6 months

II. Continuation of irinotecan liposome injection (Onivyde) **meets the definition of medical necessity** for the treatment of pancreatic cancer, ampullary adenocarcinoma, or other FDA-approved or NCCN supported diagnosis when ALL of the following criteria are met:

1. The member's disease has not progressed while receiving treatment with irinotecan liposome injection (Onivyde)

2. The member has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage

3. The dose does not exceed **ONE** of the following:

i. 50 mg/m^2 every two weeks with oxaliplatin, fluorouracil and leucovorin

ii. 70 mg/m^2 every two weeks with fluorouracil and leucovorin

Duration of approval: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in combination with fluorouracil and leucovorin and in combination with oxaliplatin, fluorouracil and leucovorin as first-line treatment.
- Do not substitute irinotecan liposome injection for other drugs containing irinotecan HCl.

- The recommended dose is 50 mg/m^2 intravenous infusion over 90 minutes every two weeks with oxaliplatin, fluorouracil and leucovorin and 70 mg/m^2 intravenous infusion over 90 minutes every two weeks with fluorouracil and leucovorin.
- Premedicate with a corticosteroid and an anti-emetic 30 minutes prior.

Dose Adjustments

- The recommended starting dose in patients homozygous for UGT1A1*28 is 50 mg/m^2 every two weeks. If appropriate based on indication, increase the dose to 70 mg/m^2 as tolerated in subsequent cycles.
- There is no recommended dose for patients with serum bilirubin above the upper limit of normal.
- Dose reductions may be necessary. See prescribing information for details of adjustment in the setting of an adverse reaction by grade from the National Cancer Institute Common Terminology Criteria for Adverse Events.

Drug Availability

- Injection: 43 mg/10 mL single dose vial

PRECAUTIONS:

Boxed Warning

SEVERE NEUTROPENIA AND SEVERE DIARRHEA

- Fatal neutropenic sepsis occurred in 0.8% of patients receiving irinotecan liposome injection. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving irinotecan liposome injection in combination with fluorouracil and leucovorin. Withhold irinotecan liposome injection for absolute neutrophil count below 1500/mm3 or neutropenic fever. Monitor blood cell counts periodically during treatment.
- Severe diarrhea occurred in 13% of patients receiving irinotecan liposome injection in combination with fluorouracil and leucovorin. Do not administer to patients with bowel obstruction. Withhold for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

Contraindications

- Severe hypersensitivity reaction to irinotecan liposome injection or irinotecan HCl.

Precautions/Warnings

- **Interstitial lung disease (ILD):** Fatal ILD has occurred in patients receiving irinotecan HCl. Discontinue irinotecan liposome injection if ILD is diagnosed.
- **Severe hypersensitivity reaction:** Permanently discontinue for severe hypersensitivity reactions.
- **Embryo-fetal toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

BILLING/CODING INFORMATION:

HCPCS Coding

J9205	Injection, irinotecan liposome, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C25.0 – C25.9	Malignant neoplasm of pancreas
C24.1	Malignant neoplasm of ampulla of Vater

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) was found at the time of the guideline creation. The following Local Coverage Determination (LCD) was reviewed on the last guideline revised date: Irinotecan (L33727) located at fcso.com.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Table 1

Karnofsky Performance Status (KPS) (%)		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal	70	Cares for self; unable to carry on normal activity or to do active work.

needs; varying amount of assistance needed.	60	Requires occasional assistance but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

RELATED GUIDELINES:

Irinotecan HCL (Camptosar®) IV, 09,J0000-99

OTHER:

Table 2: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences: urgent intervention indicated
5	Death related to adverse event

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/10/25.

GUIDELINE UPDATE INFORMATION:

03/15/16	New Medical Coverage Guideline.
04/01/16	Revision to guideline consisting of adding code C9474 and deleting code C9399.
01/01/17	Revision: added HCPCS code J9205.
03/15/17	Review and revision to guideline consisting of updating position statement, program exceptions, and references.
03/15/18	Review and revision to guideline consisting of updating position statement, coding and references.
04/15/19	Review and revision to guideline consisting of updating position statement, coding and references.
06/15/20	Review and revision to guideline consisting of updating references.
05/15/21	Review and revision to guideline consisting of updating references.
11/15/22	Review and revision to guideline consisting of adding NCCN recommendations for progression of ampullary adenocarcinoma and deleting those associated with small cell lung cancer as well as updating coding and references.
01/15/24	Review and revision to guidelines consisting of updating the references.
06/15/24	Review and revision to guideline consisting of updating the position statement to include the FDA indication and NCCN recommendations for pancreatic cancer for first-line therapy or induction therapy followed by chemoradiation in combination with oxaliplatin, fluorouracil and leucovorin as well as updating dosing and references.
01/15/25	Review and revision to guideline consisting of updating references.
01/15/26	Review and revision to guideline consisting of revising the position statement to include NCCN recommendation of first-line therapy for metastatic ampullary adenocarcinoma in combination with oxaliplatin, fluorouracil and leucovorin and updating references.