Clinical Policy: Irinotecan Liposome Injection (Onivyde)

Reference Number: PA.CP.PHAR.304
Effective Date: 01/2018
Last Review Date: 10/2025

Description
Irinotecan liposome injection (Onivyde®) is a topoisomerase inhibitor.

FDA Approved Indication(s)
Onivyde is indicated:

- In combination with oxaliplatin, fluoruracil and leucovorin, for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma;
- In combination with fluorouracil and leucovorin, for the treatment of adult patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.

Limitation(s) of use: Onivyde is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

Policy/Criteria
It is the policy of PA Health & Wellness ® that Onivyde is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Pancreatic Adenocarcinoma (must meet all)**:**

1. Diagnosis of locally advanced, metastatic, or recurrent pancreatic adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a or b):
   a. In combination with fluorouracil, leucovorin, liposomal irinotecan, and oxaliplatin (i.e., as a component of the NALIRIFOX regimen; *see Appendix D*) as first-line;
   b. In combination with fluorouracil and leucovorin for disease progression following gemcitabine-based therapy, or fluoropyrimidine-based therapy without prior irinotecan;
5. Request meets one of the following (a, b or c):
   a. Dose does not exceed 50 mg/m^2 every 2 weeks when used as a component of the NALIRIFOX regimen;
   b. Dose does not exceed 70 mg/m^2 every 2 weeks when prescribed in combination with flurouracil and leucovorin only;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Ampullary Adenocarcinoma (off-label) (must meet all)**:**

1. Diagnosis of ampullary adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Prescribed in combination with fluorouracil and leucovorin for disease progression if previously treated with one of the following (i, ii, or iii):
      i. Gemcitabine-based therapy;
      ii. Fluoropyrimidine-based therapy without prior irinotecan;
      iii. Oxaliplatin-based therapy without prior irinotecan;
   b. For metastatic disease: Prescribed in combination with fluorouracil, leucovorin, liposomal irinotecan, and oxaliplatin (i.e., as a component of the NALIRIFOX regimen; *see Appendix D*) as first-line therapy;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

C. Other diagnoses/indications: Refer to PA.CP.PMN.53
1. Biliary tract cancers

II. Continued Approval

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b or c):
   a. Dose does not exceed 50 mg/m^2 every 2 weeks when used as a component of the NALIRIFOX regimen;
   b. Dose does not exceed 70 mg/m^2 every 2 weeks when prescribed in combination with flurouracil and leucovorin only;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies; or
2. Refer to PA.CP. PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Indication	Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Pancreatic Adenocarcinoma	Examples of gemcitabine-containing regimens: gemcitabine alone or with any of the following: capecitabine, fluorouracil and leucovorin, albumin-bound paclitaxel and/or cisplatin, erlotinib, docetaxel and capecitabine	Varies	Varies
	Examples of fluoropyrimidine-based regimens: fluorouracil with any of the following: leucovorin, irinotecan/ liposomal irinotecan, and oxaliplatin	Varies	Varies
Ampullary Adenocarcinoma	Examples of gemcitabine-based therapy: gemcitabine alone or with any of the following: albumin-bound paclitaxel, capecitabine, cisplatin, durvalumab	Varies	Varies
	Examples of fluoropyrimidine based therapy: fluorouracil with any of the following: leucovorin, oxaliplatin	Varies	Varies
	Examples of oxaliplatin-based therapy: oxaliplatin with any of the following: fluorouracil, leucovorin, capecitabine	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): severe hypersensitivity reaction to Onivyde or irinotecan HCl
- Boxed warning(s): severe neutropenia and severe diarrhea; do not administer in patients with bowel obstruction

Appendix D: NALIRIFOX
- NALIRIFOX regimen contains fluorouracil, leucovorin, liposomal irinotecan, and oxaliplatin

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Pancreatic adenocarcinoma	• 50 mg/m^2 IV every 2 weeks when used prior to leucovorin, fluorouracil, and oxaliplatin • 70 mg/m^2 IV every 2 weeks when used prior to leucovorin and fluorouracil only • If homozygous for UGT1A1*28 allele: 50 mg/m^2 IV every 2 weeks. Increase the dose to 70 mg/m^2 as tolerated in subsequent cycles	70 mg/m^2 every 2 weeks

VI. Product Availability

Single-dose vial: 43 mg/10 mL

VII. References

1. Onivyde Prescribing Information. Cambridge, MA: Merrimack Pharmaceuticals, Inc.; December 2024. Available at: https://www.onivyde.com/. Accessed July 10, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 31, 2025.
3. National Comprehensive Cancer Network. Pancreatic Adenocarcinoma Version 2.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed August 31, 2025.
4. National Comprehensive Cancer Network. Ampullary Adenocarcinoma. Version 2.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf. Accessed August 31, 2025.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9205	Injection, irinotecan liposome, 1 mg

Reviews, Revisions, and Approvals	Date
4Q 2018 annual review: removed requirement to check for contraindication bowel obstruction; added COC; summarized NCCN and FDA-approved uses for improved clarity; added specialist involvement in care; references reviewed and updated.	07/2018
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/2019
4Q 2020 annual review: added oncologist prescriber requirement; added age limit; references reviewed and updated.	10/2020

Reviews, Revisions, and Approvals	Date
4Q 2021 annual review: no significant changes; references reviewed and updated.	10/2021
4Q 2022 annual review: per NCCN and FDA label, added that disease must be locally advanced, metastatic, or recurrent and added requirement for disease progression following gemcitabine-based therapy or FOLFIRINOX; references reviewed and updated.	10/2022
4Q 2023 annual review: per NCCN compendium and Pancreatic Adenocarcinoma guidelines version 2.2023, updated "FOLFIRINOX" to "fluoropyrimidine-based therapy and no prior irinotecan" and added "component of NALIRIFOX regimen"; updated Appendix B to include examples of fluoropyrimidine-based therapy; references reviewed and updated.	10/2023
RT4: added newly FDA-approved use as first-line use when prescribed in combination with oxaliplatin, fluorouracil, and leucovorin for metastatic disease.	04/2024
4Q 2024 annual review: updated FDA approved indications section to align with prescriber information; updated continued therapy section from "pancreatic adenocarcinoma" to "all indications in Section I"; added ampullary adenocarcinoma off-label criteria as supported by NCCN compendium and guideline; references reviewed and updated.	10/2024
4Q 2025 annual review: for ampullary adenocarcinoma, added option for prescribed in combination with NALIRIFOX regimen as first-line therapy for metastatic disease per NCCN; for initial approval criteria, extended approval duration from 6 months to 12 months; references reviewed and updated.	10/2025