Onivyde™ (irinotecan liposome injection)
(Intravenous)

-E-

Document Number: IC-0428

Last Review Date: 05/03/2021
Chapter 1 Date of Origin: 02/2019
Dates Reviewed: 02/2019, 05/2019, 05/2020, 05/2021

I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Onivyde 43 mg/10 mL single dose vial: 4 vials per 14 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- 172 billable units per 14 days

III. Initial Approval Criteria [1,2]

Coverage is provided in the following conditions:

- Patient is 18 years of age or older; **AND**

Universal Criteria

- Patient does not have bowel obstruction; **AND**

Pancreatic Adenocarcinoma †‡

- Must be used in combination with fluorouracil and leucovorin; **AND**
- Patient has locally advanced or metastatic disease; **AND**
- Patient has good performance status (defined as an ECOG PS of 0-2); **AND**
- Used after disease progression with gemcitabine-based therapy

Recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia recommended indication

IV. Renewal Criteria [1]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe diarrhea, severe neutropenia, pulmonary toxicity (interstitial lung disease), severe hypersensitivity reactions, etc.

V. Dosage/Administration

Indication	Dose
Pancreatic Cancer	Administer 70 mg/m² intravenously, every 14 days Note: Patients homozygous for UGT1A1*28: Administer 50 mg/m² every 14 days, and may titrate up to 70 mg/m², as tolerated in subsequent cycles.

VI. Billing Code/Availability Information

HCPCS code:

- J9205 - Injection, irinotecan liposome, 1 mg: 1 billable unit = 1 mg

NDC:

- Onivyde 43 mg/10 mL single dose vial: 15054-0043-xx

VII. References (STANDARD)

1. Onivyde [package insert]. Cambridge, MA; Merrimack Pharmaceuticals, Inc.; June 2017. Accessed April 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) irinotecan liposomal. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and

NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed by Magellan Rx April 2021.

3. Wang-Gillam A, Li CP, Bodky G, NAPOLI-1 study group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016 Feb 6;387(10018):545-557. doi: 10.1016/S0140-6736(15)00986-1. Epub 2015 Nov 29.

VIII. References (ENHANCED)

1e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Pancreatic Adenocarcinoma, Version 2.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed by Magellan Rx April 2021.

2e. Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer. 2011 Jul;47(11):1676-81.

3e. Oettle H, Riess H, Stieler JM, et al. Second-Line Oxaliplatin, Folinic Acid, and Fluorouracil Versus Folinic Acid and Fluorouracil Alone for Gemcitabine-Refractory Pancreatic Cancer: Outcomes From the CONKO-003 Trial. Journal of Clinical Oncology 2014 32:23, 2423-2429.

4e. Gill S, Ko YJ, Cripps C, et al. PANCREOX: A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. Journal of Clinical Oncology 2016 34:32, 3914-3920.

5e. Heinemann V, Vehling-Kaiser U, Waldschmidt D, et al. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). Gut. 2012;62(5):751-9.

6e. Yoo C, Hwang JY, Kim JE, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. Br J Cancer. 2009;101(10):1658-63.

7e. Neuzillet C, Hentic O, Rousseau B, et al. FOLFIRI regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and platinum-salts. World J Gastroenterol. 2012;18(33):4533-41.

8e. Assaf E, Verlinde-Carvalho M, Delbaldo C, et al. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma. Oncology. 2011;80(5-6):301-6.

9e. Xiong HQ, Varadhachary GR, Blais JC, et al. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer. 2008 Oct 15;113(8):2046-52.

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11e. Portal A, Pernot S, Tougeron D, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort. Br J Cancer. 2015;113(7):989-95.

12e. Magellan Health, Magellan Rx Management. Onivyde Clinical Literature Review Analysis. Last updated April 2021. Accessed April 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C24.1	Malignant neoplasm of ampulla of Vater
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of the pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.

J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; TTF = time to treatment failure; AE = adverse event; PS = performance status

Pancreatic Adenocarcinoma

Second-line therapy for locally advanced or metastatic disease *if prior gemcitabine-based therapy*							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
5-FU + leucovorin + liposomal irinotecan	1 (if previously treated with gemcitabine-based therapies) 2A for all others	Yes	Phase 3 (NAPOLI-1), randomized (1:1), open-label	Liposomal irinotecan monotherapy or 5-FU + leucovorin	OS	After prior gemcitabine-based therapy	• Liposomal irinotecan in combination with 5-FU and leucovorin extended survival with a manageable safety profile in patients with metastatic pancreatic adenocarcinoma who previously received gemcitabine-based therapy • Liposomal monotherapy did not demonstrate superior efficacy over 5FU and leucovorin and was associated with more severe toxicity than combination, suggesting that the drug should only be used in combination.
Oxaliplatin + 5-FU + leucovorin (OFF)	2A	No	Phase 3, multi-center	Best supportive care (BSC)	----------	Second-line after prior gemcitabine monotherapy	• Although stopped prematurely, this randomized trial provided evidence for the benefit of second-line chemotherapy as compared to BSC alone. OFF significantly prolonged survival time compared to BSC alone after failure of first-line therapy with gemcitabine.
Oxaliplatin + 5-FU + leucovorin (OFF)	2A	No	Phase 3 (CONKO-003), randomized, open-label	5-FU + leucovorin (FF)	OS	Second-line after prior gemcitabine monotherapy	• Second-line OFF significantly extended the duration of overall survival when compared with FF alone in patients with

							advanced gemcitabine-refractory pancreatic cancer.
5-FU + leucovorin + oxaliplatin (FOLFOX) – mFOLFOX6 studied	2A	No	Phase 3 (PANCREOX), open-label, randomized	5FU + leucovorin	PFS	Second-line therapy after gemcitabine-based therapy	• No benefit was observed with the addition of oxaliplatin, administered as mFOLFOX6, versus infusional 5FU/LV in patients with advanced pancreatic cancer previously treated with first-line gemcitabine
Capecitabine (after prior gemcitabine + erlotinib)	2A	No	Phase 3 (AIO-PK0104), randomized	Gemcitabine (after prior capecitabine + erlotinib)	TTF	Second-line therapy	• Both treatment strategies are feasible and demonstrated comparable efficacy however no significant difference was seen in survival
5-FU + leucovorin + irinotecan (FOLFIRI) – mFOLFIRI-3	2A	No	Phase 2, randomized	mFOLFOX	6-mon OS	Second-line after prior gemcitabine-based therapy	• Both mFOLFIRI-3 and mFOLFOX regimens were tolerated with manageable toxicity and offered modest activities (6-mon OS 27%-30%) as second-line treatments for patients with advanced pancreatic cancer, previously treated with gemcitabine.
5-FU + leucovorin + irinotecan (FOLFIRI) – FOLFIRI-1 and FOLFIRI-3 studied	2A	No	Phase 2	N/A	----------	Subsequent therapy after 1-3 lines of gemcitabine- and platinum-based therapies	• FOLFIRI had an acceptable toxicity and OS efficacy of 6.6 months, limited to patients in good condition (PS 0-1).
FOLFIRINOX	2A (category 1 for first-line therapy)	No	Retrospective analysis	N/A	----------	Second-line after prior gemcitabine monotherapy	• Efficacy of FOLFIRINOX was demonstrated with an overall disease control rate of 63% in second-line treatment of metastatic pancreatic adenocarcinoma.
Capecitabine + oxaliplatin (XELOX)	2A	No	Phase 2	N/A	6-mon OS	Second-line therapy after gemcitabine-based therapy	• Combination of capecitabine and oxaliplatin is active in gemcitabine-pretreated patients with advanced pancreatic cancer with a 6-mon OS rate of 44%
Pembrolizumab (for MSI-H or dMMR tumors)	2A	Yes (for patients with MSI-H or dMMR solid	Phase 2	N/A	----------	Second-line or later	• Mismatch repair-deficient cancers, including pancreatic cancer, demonstrated sensitivity to immune checkpoint blockade with an ORR of 62%

		tumors with progression or no alternative treatment options)					
Second-line therapy for locally advanced or metastatic disease *if prior fluoropyrimidine-based therapy*							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
5-FU + leucovorin + liposomal irinotecan	2A (if no prior irinotecan)	No	No clinical trial data to support use after prior fluoropyrimidine-based therapy.				
Gemcitabine	1 (for poor performance status) 2A (for good performance status)	No	Recommendation is based on evidence in first-line therapy. No clinical trial data in second-line therapy.				
Gemcitabine + albumin-bound paclitaxel	2A (if prior fluoropyrimidine-based therapy)	No	Prospective multicenter cohort	N/A	----------	Second-line after FOLFIRINOX failure	• Nab-paclitaxel + gemcitabine has clinical activity after FOLFIRINOX failure in patients with metastatic pancreatic adenocarcinoma
Gemcitabine + erlotinib	2A	No	Recommendation is based on evidence in first-line therapy. No clinical trial data in second-line therapy.				
Pembrolizumab (for MSI-H or dMMR tumors)	2A	Yes (for patients with MSI-H or dMMR solid tumors with progression or no alternative treatment options)	Phase 2	N/A	----------	Second-line or later	• Mismatch repair-deficient cancers, including pancreatic cancer, demonstrated sensitivity to immune checkpoint blockade with an ORR of 62%
Post-resection for local or metastatic recurrence							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

5-FU + leucovorin + liposomal irinotecan	2A	No	No clinical literature to support use.