Nivolumab and hyaluronidase-nvhy (OPDIVO QVANTIG)
National Drug Mini-Monograph
June 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody with hyaluronidase as a fixed-combination product for subcutaneous administration. Hyaluronidase is used to increase dispersion and absorption of the drug product.
Indications Under Review[1]	Solid tumors, including: Renal cell carcinoma (RCC), melanoma, NSCLC, Squamous Cell Carcinoma (SCC) of the head & neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma (ESCC), gastroesophageal junction (GEJ) cancer, gastric cancer and esophageal adenocarcinoma
Dosage Regimen	Varies by malignancy; may be given in combination with other agents, except ipilimumab Every 2-week dosing: 600mg/10,000 units every 2 weeks Every 3-week dosing: 900mg/15,000 units every 3 weeks Every 4-week dosing: 1200mg/20,000 units every 4 weeks Administered via subcutaneous injection over 3-5 minutes in abdomen or thigh; by healthcare professional
Dosage Forms Under Review	Nivolumab 600mg and 10,000 units hyaluronidase per 5 ml (120mg/2000 units per ml) as SDV

EFFICACY CONSIDERATIONS

Trial	**CHECKMATE-67T (NCT04810078)**
Design	Multicenter, randomized, open-label, noninferiority study
Population	Advanced or metastatic clear cell RCC w/wo sarcomatoid features; received $\geq$ 2 prior systemic regimens N=495; mAge 65 yrs; 68% male; 85% white; IMDC risk: 21% favorable; 62% intermediate; 17% poor Stratified by: body weight, IMDC risk score
Exclusion	Untreated, symptomatic CNS mets, active autoimmune disease, prior checkpoint inhibitor
Intervention	Nivolumab 1200mg/hyaluronidase 20,000 units SUBQ every 4 weeks
Comparator	Nivolumab 3mg/kg IV every 2 weeks
Results	Primary objective: noninferiority of nivolumab exposure (SUBQ vs. IV) by coprimary endpoints from PK analysis; *Predefined acceptance margin for PK endpoints: lower boundary of 90% CI of GMR $\geq$ 0.8 of time-averaged serum nivolumab Cavg over 28 days (C_{avgd28}) and Cmin at steady state (C_{minss});* Results: GMR C_{avgd28} 2.098 (90% CI 2.001-2.200) and GMR C_{minss} 1.774 (90% CI 1.633-1.927) Secondary: noninferiority of efficacy tested in hierarchical fashion, as primary PK endpoints were met; *Predefined acceptance margin for ORR relative risk deemed noninferior if lower boundary of 95% CI $\geq$ 0.60* Results: overall response rate (ORR) by BICR of nivo/hyal SUBQ vs. nivo IV in patients with $\geq$ 6 mos follow up Follow-up 8 mos: ORR per BICR 24.2% (95% CI 19, 30) vs. 18.2% (95% CI 14, 24); • relative risk 1.33 (95% CI 0.94-1.87); mPFS: 7.23 vs. 5.65 mos; HR 1.06 (95% CI 0.84-1.34) Follow-up 15 mos: mPFS 6.34 vs. 5.65 mos; HR 1.06 (95% CI 0.85-1.32)
Notes	Subcutaneous nivolumab/hyaluronidase demonstrates noninferiority to IV nivolumab based on PK endpoints and ORR relative risk. FDA-approval for subcutaneous nivolumab/hyaluronidase in the following solid tumors: melanoma, NSCLC, Squamous Cell Carcinoma (SCC) of the head & neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma (ESCC), gastroesophageal junction (GEJ) cancer, gastric cancer and esophageal adenocarcinoma is based upon established evidence with IV nivolumab in these disease states along with additional PK and safety data demonstrating noninferiority

Nivolumab/hyaluronidase is NOT approved for use in combination with ipilimumab and is NOT approved for use in Hodgkin Lymphoma.

Key: IMDC International Metastatic RCC Database Consortium, CNS central nervous system, PK pharmacokinetic, GMR geometric mean ratio, BICR blinded independent central review, SUBQ subcutaneous, IV intravenous, NSCLC non-small cell lung cancer

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None
Other Warnings	• Severe and fatal immune-mediated adverse reactions • Complications of allogeneic hematopoietic stem cell transplant • Embryo-fetal toxicity • Nivolumab/hyaluronidase should not be used in combination with a thalidomide analogue and dexamethasone in the treatment of multiple myeloma outside of the clinical trial setting • Nivolumab/hyaluronidase should **not** be administered intravenously
Top 5 AEs	Varies by regimen and if given as monotherapy or in combination with other agents. Monotherapy in RCC (≥ 10%): MS pain, fatigue, pruritus, rash, hypothyroidism Monotherapy in melanoma, NSCLC, H/N, urothelial carcinoma, mCRC, HCC: fatigue, rash, MS pain, pruritus, diarrhea With cabozantinib in RCC: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash With platinum-doublet in NSCLC: nausea, constipation, fatigue, decreased appetitie, rash With cisplatin-gemcitabine in urothelial cancer: nausea, fatigue, MS pain, constipation, rash With fluoropyrimidine- and platinum- in esophageal and gastric cancer: nausea, PN, decreased appetite, fatigue, constipation

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	GUIDELINES
Nivolumab/ hyaluronidase Available as SDV 600mg/ 10,000 units in total 5ml SUBQ dose to be drawn up into a syringe SUBQ dose volume varies from 5-10ml SUBQ dose administered over 3-5 min.	NF	No	Solid tumors: RCC, melanoma, NSCLC, SCC of the head & neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, ESCC, GEJ cancer, gastric cancer and esophageal adenocarcinoma	NCCN Guidelines for the following: Gastric cancer v2.2025 Esophageal/ esophagogastric junction cancer v3.2025 Kidney cancer v3.2025 Melanoma v2.2025 Non-Small Cell Lung Cancer 3.2025 Head and Neck cancers v2.2025 Bladder cancer v1.2025 Colon cancer v3.2025 Hepatocellular carcinoma v1.2025 Includes the following statement(s), if applicable: Nivolumab/hyaluronidase is not approved for concurrent use with IV ipilimumab; it may replace IV nivolumab given as monotherapy; the SUBQ product has different dosing and administration instructions than IV
Nivolumab Available as [10mg/ml] in 4, 10, 12, 24 ml SDV Administer as IV infusion over 30 min	PA-F	Yes	RCC, melanoma, NSCLC, SCC of the head & neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, ESCC, GEJ cancer, gastric cancer, esophageal adenocarcinoma and classical Hodgkin Lymphoma	NCCN Hodgkin Lymphoma v2.2025 IV nivolumab is included; no mention of SUBQ product

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. Subcutaneous nivolumab/hyaluronidase has demonstrated noninferiority to intravenous nivolumab exposure in RCC based upon coprimary endpoints from pharmacokinetic analyses: • the time-averaged nivolumab exposure following nivolumab/hyaluronidase SUBQ was noninferior to that of nivolumab IV over the first 28 days of treatment • the minimum nivolumab exposure at steady state following nivolumab/hyaluronidase SUBQ was noninferior to that of nivolumab IV 2. Secondary endpoint of ORR relative risk was also noninferior with nivolumab/hyaluronidase SUBQ compared to nivolumab IV 3. Demonstrated noninferiority of PK endpoints evaluating serum nivolumab exposure and ORR of the nivolumab/hyaluronidase product, in addition to clinical trials demonstrating efficacy of nivolumab IV in the aforementioned solid tumors, has supported use of the subcutaneous product by the FDA and national guidelines, in most solid tumor settings (except with concomitant ipilimumab) 4. Given supportive safety and efficacy data, comparable cost and less clinic time for patients and healthcare personnel spent with nivolumab administration, nivolumab/hyaluronidase should be made available, similar to the nivolumab intravenous product. Of note, nivolumab/hyaluronidase is not approved in Hodgkin Lymphoma and should not replace nivolumab IV in this setting.

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References

1 OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) injection, for subcutaneous use [prescribing information online]. Princeton, NJ; Bristol-Myers Squibb Company. San Diego, CA; Halozyme Therapeutics, Inc. December 2024. Available at: OPDIVO QVANTIG Prescribing Information May, 2025.
2 Albiges L, Bourlon MT, Chacon M, et al. Subcutaneous versus intravenous nivolumab for renal cell carcinoma. Annals of Oncology 2025; 36: 99-107.
3 George S, et al. Oral presentation at ASCO GU Annual Meeting 2024; San Diego, CA. Presentation LBA360.