

Nivolumab and hyaluronidase-nvhy

An HCP Tool from AIM with Immunotherapy

Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig) for subcutaneous injection is a combination agent with nivolumab, an anti-programmed death receptor-1 (PD-1) monoclonal antibody, and hyaluronidase, an endoglycosidase. The addition of the hyaluronidase allows the primary active agent, nivolumab, to be administered as a subcutaneous injection. This is different from nivolumab, which is typically administered intravenously. The initial approval for the subcutaneous injection of nivolumab and hyaluronidase-nvhy occurred in 2024.

It is indicated for use (with specific caveats on recurrence, respectability and tumor sizes) in: colorectal cancer, esophageal cancer, gastric cancer, gastroesophageal junction cancer, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma.

Molecular biology and pharmacology for nivolumab and hyaluronidase-nvhy

Nivolumab is a PD-1-targeting antibody that binds to PD-1, a checkpoint control. PD-1 is a negative regulator of T-cell activation and proliferation, which is exploited by cancer cells. This means that PD-1 engagement will turn the immune response off, essentially acting as a brake to an immune reaction. Cancer cells thriving in the presence of immune cells have exploited this biological mechanism for their survival.

The ability to shut off an immune response exists to prevent an allergic reaction (e.g. from dust, pollen, or insect stings) from killing the organism by way of a cytokine storm and immune overreaction. However, cancer cells use the shut off inappropriately for their benefit. For this reason, nivolumab-containing agents are known as immune checkpoints or immune checkpoint inhibitors.

The hyaluronidase is an endoglycosidase component co-administered with nivolumab. It is used to increase the dispersion and absorption of the drug when administered subcutaneously. This addition of hyaluronidase with nivolumab constitutes this product as a different drug than classic nivolumab, which is administered intravenously.

Note: The indications for the subcutaneous injection of nivolumab and hyaluronidase-nvhy are approved under accelerated approval based on overall response rate and duration of response. For the continued approval of this agent, it requires verification and proof of clinical benefit in confirmatory trials.

DRUG DOSAGE AND ADMINISTRATION

Nivolumab and hyaluronidase-nvhy is a subcutaneous injection, administered only by a healthcare professional in the abdomen or thigh. The injection is administered over 3-5 minutes.

The recommended dosage varies depending on the indication, but is either 600 mg/10,000 units (600 mg nivolumab and 10,000 units hyaluronidase per 5 mL) every 2 weeks, 900 mg/15,000 units every 3 weeks, or 1,200 mg/20,000 units every 4 weeks.

Monotherapy Dosages (mg nivolumab / units hyaluronidase):

All monotherapies are 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks

- Colorectal cancer: given until disease progression of unacceptable toxicity
- Esophageal squamous cell carcinoma: given until disease progression of unacceptable toxicity
- Esophageal resected (adjuvant): given until disease recurrence or unacceptable toxicity for up to 1 year
- Gastroesophageal junction cancer (adjuvant): given until disease recurrence or unacceptable toxicity for up to 1 year
- Hepatocellular carcinoma: given until disease progression of unacceptable toxicity
- Melanoma (adjuvant): given until disease recurrence or unacceptable toxicity for up to 1 year
- Melanoma (unresectable or metastatic): given until disease progression of unacceptable toxicity
- Non-small cell lung cancer: given until disease progression of unacceptable toxicity
- Renal cell carcinoma: given until disease progression of unacceptable toxicity
- Squamous cell carcinoma of the head and neck:
- Urothelial carcinoma (adjuvant): given until disease recurrence or unacceptable toxicity for up to 1 year
- Urothelial carcinoma (locally advanced or metastatic): given until disease progression of unacceptable toxicity

Dosages when given in combination with other therapies

Significant variations exist and protocol updates are possible, depending on evolving data from clinical trials. Refer to each therapeutic agent administered in combination with nivolumab and hyaluronidase-nvhy. As a general guideline, most often nivolumab and hyaluronidase-nvhy will be administered at the standard doses listed above, either 600 mg/10,000 units every 2 weeks, 900 mg/15,000 units every 3 weeks, or 1,200 mg/20,000 units every 4 weeks.

The variation occurs with the combined agent. For example, when administered for advanced renal cell carcinoma, nivolumab and hyaluronidase-nvhy is given with cabozantinib (40 mg) once daily without food. For this same indication, whereas nivolumab and hyaluronidase-nvhy is given until disease progression, unacceptable toxicity or up to 2 years, cabozantinib is given until disease progression or unacceptable toxicity.

Modifications

There is no dose reduction recommended. General guidelines are to withhold nivolumab and hyaluronidase-nvhy for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue to drug for Grade 4 and recurrent severe Grade 3 immune-mediated reactions that require systemic immunosuppressive treatment of the inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiation.

Immune-mediated adverse events are possible with immune checkpoint inhibitors that amplify the immune response. Any organ system may be attacked by the immune system. The following are dosage modifications.

Management of dosage with notable side effects or adverse reactions

Adverse event	Common management guidance
Pneumonitis	<u>Grade 2</u> : Withhold <u>Grade 3 or 4</u> : Permanently discontinue
Colitis	<u>Grade 2 or 3</u> : Withhold <u>Grade 4</u> : Permanently discontinue
Dermatologic Conditions	<u>Suspected SJS, TEN, or DRESS</u> : Withhold <u>Confirmed SJS, TEN, or DRESS</u> : Permanently discontinue
Endocrinopathies	<u>Grade 3 or 4</u> : Withhold until clinically stable or permanently discontinue depending on severity
Hepatitis w/no tumor involvement of the liver	<u>Withhold</u> : Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases to > 3 times the upper limit normal (ULN) and ≤ 8 times the ULN or total bilirubin increases to > 1.5 and ≤ 3 times ULN. <u>Permanently discontinue</u> : ALT or AST increases to > 8 times ULN or total bilirubin increases to more than 3 times the ULN.
Hepatitis with tumor involvement of the liver	<u>Withhold</u> : Baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is >1 and ≤ 3 times ULN and increases to >5 and ≤ 10 times ULN or baseline AST/ALT is >3 and ≤ 5 times ULN and increases to >8 times and ≤ 10 times ULN. <u>Permanently discontinue</u> : ALT or AST increases to > 10 times ULN or total bilirubin increases to more than 3 times the ULN.
Intestinal Perforation	<u>Any Grade</u> : Permanently discontinue
Myocarditis	<u>Grade 2, 3 or 4</u> : Permanently discontinue
Nephritis with Renal Dysfunction	<u>Grade 2 or 3 increased blood creatinine</u> : Withhold <u>Grade 4 increased blood creatinine</u> : Permanently discontinue
Neurological Toxicities	<u>Grade 2</u> : Withhold <u>Grade 3 or 4</u> : Permanently discontinue

SIDE EFFECTS AND MANAGEMENT

The safety of this agent is based on that of the intravenous version of nivolumab. There are many indications and the specific side effects will vary. When administering nivolumab and hyaluronidase-nvhy, the most common adverse reactions ($\geq 10\%$) as [monotherapy in patients with Renal Cell Carcinoma](#) were abdominal pain, cough, diarrhea, fatigue, hypothyroidism, musculoskeletal pain, pruritus, and rash.

In [other indications when used as monotherapy](#), the most common adverse reactions of nivolumab and hyaluronidase-nvhy included abdominal pain, asthenia, arthralgia, back pain, constipation, cough, decreased appetite, diarrhea, dyspnea, fatigue, headache, musculoskeletal pain, nausea, pruritus, pyrexia, rash, upper respiratory tract infection, urinary tract infection, and vomiting.

Additional adverse reactions can occur with [combinations](#) between nivolumab and hyaluronidase-nvhy with drugs used for other indications. There are four notable examples of this.

- [Esophageal cancer and gastric cancer](#) with 5-FU and platinum-containing chemotherapy: abdominal pain, constipation, decreased appetite, diarrhea, fatigue, musculoskeletal pain, nausea, peripheral neuropathy, stomatitis, and vomiting.
- Advanced [renal cell carcinoma with cabozantinib](#): abdominal pain, cough, decreased appetite, diarrhea, dysgeusia, fatigue, hepatotoxicity, hypertension, hypothyroidism, musculoskeletal pain, nausea, palmar-plantar erythrodysesthesia syndrome, rash, stomatitis, and upper respiratory tract infection.
- Neoadjuvant treatment of [NSCLC](#) with platinum-doublet chemotherapy: constipation, decreased appetite, fatigue, nausea, and rash.
- [Urothelial cancer](#) with cisplatin and gemcitabine: constipation, decreased appetite, fatigue, musculoskeletal pain, nausea, peripheral neuropathy, rash, and vomiting.

Warnings and Precautions

There are three warnings and a precaution associated with nivolumab and hyaluronidase-nvhy injection. These are for immune-mediated adverse reactions, complications of allogeneic HSCT (hematopoietic stem cell transplantation or allo-HSCT), embryo-fetal toxicity, and a precaution for multiple myeloma patients.

Immune-Mediated Adverse Reactions

Due to the risk for infusion-mediated adverse reactions the drug should only be administered by clinical professionals. Reactions have the potential to be severe or even fatal and can occur in any organ system. Dose reductions are included in the table in the previous section. Patients need to be monitored for an early indication of an immune-mediated adverse reaction. The creatine, liver enzymes, and thyroid function should be evaluated at baseline and then periodically during treatment.

Complications of allogeneic HSCT

In patients treated with agents that block PD-1/PD-L1 interactions, serious and fatal complications can occur among patients who receive allogeneic HSCT.

Embryo-Fetal Toxicity

Females of reproductive potential should be made aware that this agent can cause fetal harm. Abortion and premature infant death occurred in animal studies. Females should be advised to use effective contraception.

Patients with Multiple Myeloma

Treatment in patients with multiple myeloma comes with a precaution. The use of nivolumab and hyaluronidase in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled trials.

QUESTIONS & ANSWERS

Q. How long can patients receive nivolumab and hyaluronidase-nvhy?

A. This largely depends on the indication for which it was prescribed. For some indications, nivolumab and hyaluronidase-nvhy are administered until disease progression or unacceptable toxicity. For other indications, the agent may be administered for up to 1 or 2 years from the first dose.

Q. What kind of medical conditions should you ask your patients about prior to prescribing nivolumab and hyaluronidase-nvhy?

A. Before your patients receive an administration of nivolumab and hyaluronidase-nvh, there are medical conditions that suggest an immune system concern like Crohn's disease, ulcerative colitis, or lupus. It is also important to know if patients have received an organ transplant, a stem cell transplant that has used donor stem cells, radiation treatment to the chest area, a condition impacting the nervous system (e.g., Guillain-Barre syndrome or myasthenia gravis), females that are pregnant or planning to become pregnant, females that are breastfeeding or plan to breastfeed.

In addition, due to interactions between agents, providers must know all of the medications or active ingredients from ingested products a patient consumes. This includes prescription medications as well as over-the-counter medicines, such as supplements (e.g. herbals, traditional Chinese medicine, vitamins, probiotics, etc.) and all other homeopathic or natural remedies that may have been consumed or ingested.

Q. What is the most important thing for patients to know about nivolumab and hyaluronidase-nvhy?

A. Because the drug may cause adverse reactions associated with the immune system, patients need to be monitored closely. The problems can be severe or fatal and happen at anytime during treatment or after the completion of treatment. Patients may also experience more than one problem at the same time, especially when this agent is used in combination with another therapy.

Q. How do you modify the dose of nivolumab and hyaluronidase-nvhy for an adverse event?

A. There is no dose reduction or modification recommended for nivolumab and hyaluronidase-nvhy. Depending on the type of reaction that occurs, the drug might be withheld or permanently discontinued. Early and immediate identification and management of immune-mediated adverse reactions are essential for the use of this agent. Monitor patients closely for symptoms and signs of underlying adverse reactions.

ADDITIONAL RESOURCE

OPDIVO QVANTIG™ (nivolumab and hyaluronidase-nvhy) injection [prescribing information]. Bristol Myers Squibb. Princeton, NJ 08543. Available at: https://packageinserts.bms.com/pi/pi_opdivo-qvantig.pdf. Accessed 6.24. 2025. Revised 5.2025.

PATIENT RESOURCES

ADDITIONAL INFORMATION RESOURCES

AIM at Melanoma

Information and facts about melanoma, detection, treatment, clinical trials, etc

<https://www.aimatmelanoma.org/>

American Cancer Society

Patient programs, services, 24/7 hotline, etc

<https://www.cancer.org/>

FINANCIAL ASSISTANCE

BMS Access Support

1 (800) 861-0048

<http://www.bmsaccesssupport.bmscustomerconnect.com/patient>

Cancer Financial Aid Coalition

Facilitates communication, educates and advocates for patients.

www.cancerfac.org

Centers for Medicare and Medicaid Services (CMS)

Apply to determine if you are eligible for government assistance.

www.cms.gov or www.medicare.gov

800-633-4227

Lazarex Foundation

Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.

www.lazarex.org

Needymeds

Database to search for free or low-cost medications, help with medical transportation and other resources.

www.needymeds.org

Patient Advocate Foundation

Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.

www.patientadvocate.org

800-532-5274

The Sam Fund for Young Adult Survivors of Cancer

Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.

www.thesamfund.org

info@thesamfund.org

PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation

Helps with the cost of medication. Availability of funds for patients with specific cancers is subject to availability.

www.cancercarecopay.org

1-866-552-6729

Medicine Assistance Tool

Database to search for patient assistance resources offered by pharmaceutical companies.

www.medicineassistancetool.org/

Patient Advocate Foundation Co-Pay Relief

Provides direct financial support to patients who medically qualify. Funds subject to availability.

<https://copays.org>

1-866-512-3861

Good Days

Provides assistance with insurance co-pays, and prescription medications. Funds subject to availability.

www.mygooddays.org

Health Well Foundation

For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Funds for patients subject to availability. Patient must also meet eligibility for financial assistance.

www.healthwellfoundation.org or grants@healthwellfoundation.org

1-800-675-8416

The Assistance Fund, Inc

Provides prescription copay and financial assistance, including health insurance premiums. Funds subject to availability.

www.theassistancefund.org

<https://tafcares.org>

1-855-845-3663

PAN Foundation

Provides financial assistance to cover out-of-pocket treatment costs. Funds subject to availability.

www.panfoundation.org

1-866-316-PANF (7263)

Patient Assistance Program

Comprehensive database of patient assistance programs offering free medications.

www.rxassist.org

info@rxassist.org

HOUSING

American Cancer Society – Hope Lodge

Provides free housing during treatment appointments. Requires a referral from your social worker.

www.cancer.org/

1-800-227-6333.

American Cancer Society – Extended Stay America

Partnership to offer discounted rooms for patients who have to be away from home for cancer treatment.

<https://www.cancer.org/about-us/our-partners/extended-stay-america.html>

1-800-227-2345

Healthcare Hospitality Network

Connects patients and their caregivers looking for lodging near their healthcare provider

<https://members.hhnetwork.org/locate-a-house>

1-800-318-8861

Joe’s House

Helping patients with cancer find lodging throughout the U.S.

<https://www.joeshouse.org/lodging?state=0>

1-877-563-7468

National Council of State Housing Agencies

Emergency rental assistance programs available by state. Federal grants still available in some areas.

<https://www.ncsha.org/emergency-housing-assistance/>

TRANSPORTATION (AIR AND GROUND)

Air Charity Network

Provides access for people in need who are seeking free air transportation to specialized health care facilities

<http://aircharitynetwork.org/>

1-877-621-7177

Corporate Angel Network

Nonprofit organization that helps cancer patients by arranging free travel on corporate aircraft

<https://www.corpangelnetwork.org/>

info@corpangelnetwork.org

1-914-328-1313

Medicaid

Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.

1-877-633-8747

Mercy Medical Angels

Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.

www.mercymedical.org/

Pilots for Patients

Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.

www.pilotsforpatients.org

318-322-5112