FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

The #1 prescribed TRK inhibitor for *NTRK* gene fusion-positive solid tumors[25,a]

[a]Based on medical claims and prescription data claims for the period January 2019 through January 2024. Validated by IQVIA in March 2024.

Click on a cancer type to learn more
about NCCN Category 2A recommendations for larotrectinib.

2A

- Biliary Tract Cancers
- Breast Cancer
- CNS Cancers
- Cervical Cancer
- Colon Cancer
- Esophageal and Esophagogastric Junction Cancers
- Gastric Cancer
- Gastrointestinal Stromal Tumors
- Head and Neck Cancers
- Hepatocellular Carcinoma
- Histiocytic Neoplasms
- Melanoma: Cutaneous
- Non-small Cell Lung Cancer
- Occult Primary
- Ovarian Cancer[b]
- Pancreatic Adenocarcinoma
- Pediatric CNS Cancers
- Rectal Cancer
- Small Bowel Adenocarcinoma
- Soft Tissue Sarcoma
- Thyroid Carcinoma
- Uterine Neoplasms
- Vulvar Cancer (SCC)

Guidelines included are current as of July 2024. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Indication[1]

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Biliary Tract Cancers[2]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option – V.3.2024

Larotrectinib is recommended for:

- Primary treatment (useful in certain circumstances) for unresectable and metastatic biliary tract disease that is *NTRK* gene fusion-positive
- Subsequent-line therapy (useful in certain circumstances) for unresectable or metastatic biliary tract cancers if disease progresses

Sample Patient Journeys

Unresectable and metastatic biliary tract disease › ***NTRK* gene fusion-positive** › **Systemic therapy option: Larotrectinib**

Unresectable or metastatic biliary tract cancers › **First-line therapy** › **Progression of biliary tract cancers** › ***NTRK* gene fusion-positive** › **Subsequent-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

The preferred assay is multi-gene NGS testing, preferably with a transcriptome-based approach. Testing for *NTRK* fusions is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA.

CCA=cholangiocarcinoma; NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next-generation sequencing; *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[2]

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.
In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

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VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Breast Cancer[3]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for treatment of appropriate patients with recurrent unresectable or stage IV breast cancer that is *NTRK* gene fusion-positive – V.4.2024

Sample Patient Journey

Recurrent unresectable or stage IV breast cancer › **_NTRK_ gene fusion-positive** › **Systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines indicate that FISH, NGS, and PCR are methods for detecting *NTRK* gene fusions.

FISH=fluorescence in situ hybridization; NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next generation sequencing; *NTRK*=neurotrophic receptor tyrosine kinase; PCR=polymerase chain reaction.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[3]

Please see Important Safety Information throughout and full Prescribing Information.

Indication[1]

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

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VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Central Nervous System Cancers[4]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option – V.1.2024

Larotrectinib is recommended as a preferred regimen for appropriate patients with:

- Brain metastases (tumor agnostic) that are *NTRK* gene fusion-positive

Larotrectinib is recommended as useful in certain circumstances for appropriate patients with:

- Recurrent or progressive adult circumscribed glioma that is *NTRK* gene fusion-positive
- Recurrent or progressive glioblastoma that is *NTRK* gene fusion-positive

Sample Patient Journeys

Brain metastases (tumor agnostic) → **_NTRK_ gene fusion-positive** → **Preferred systemic therapy option: Larotrectinib**

Recurrent or progressive brain cancers (ie, adult circumscribed glioma, glioblastoma) → **_NTRK_ gene fusion-positive** → **Systemic therapy option: Larotrectinib**

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[4]

Please see Important Safety Information throughout and full Prescribing Information.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

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VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

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NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Cervical Cancer[5]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for second-line treatment of appropriate patients with *NTRK* gene fusion-positive recurrent or metastatic SCC, adenocarcinoma, or adenosquamous carcinoma – V.3.2024

Sample Patient Journeys

Recurrent or metastatic SCC, adenocarcinoma, or adenosquamous carcinoma › **First-line treatment** › **Second-line systemic therapy option: Larotrectinib for patients who are *NTRK* gene fusion-positive**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend considering *NTRK* gene fusion testing for patients with cervical sarcoma.

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma.

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Please see Important Safety Information throughout and full Prescribing Information.

Indication

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

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NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Colon Cancer[6]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option for second- or subsequent-line treatment of appropriate patients with advanced or metastatic colon cancer that is *NTRK* gene fusion-positive – V.4.2024

Sample Patient Journeys

Advanced or metastatic colon cancer → **First-line therapy** → ***NTRK* gene fusion-positive** → **Second- or subsequent-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

Data support limiting the subpopulation of colorectal cancers that should be tested for *NTRK* fusions to those with wild-type KRAS, NRAS, *BRAF*, and arguably to those that are MMR deficient (dMMR)/MSI-H. IHC, FISH, DNA-based and RNA-based NGS testing can be used to detect *NTRK* fusions. Positive IHC tests should be confirmed by RNA-based NGS.

BRAF=proto-oncogene B-Raf; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; KRAS=Kirsten rat sarcoma virus; MMR=mis-match repair; MSI-H=high levels of microsatellite instability; NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next generation sequencing; NRAS=N-ras oncogene; *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[6]

Please see Important Safety Information throughout and full Prescribing Information.

- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

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[b]Includes fallopian tube cancer and primary peritoneal cancer.

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LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Esophageal and Esophagogastric Junction Cancers[7]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for second- or subsequent-line treatment of appropriate patients with unresectable, locally advanced, recurrent, or metastatic esophageal and esophagogastric junction cancers that are *NTRK* gene fusion-positive – V.3.2024

Sample Patient Journeys

Unresectable locally advanced, recurrent, or metastatic esophageal or esophagogastric junction cancer (where local therapy is not indicated) › **First-line treatment** › ***NTRK* gene fusion-positive** › **Second- or subsequent-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend IHC, ISH, and targeted PCR be considered first to identify *NTRK* gene fusions, followed by NGS. If limited tissue is available or the patient is unable to undergo a traditional biopsy, a validated NGS assay performed in a CLIA-approved laboratory should be considered as sequential testing will exhaust the sample.

Liquid biopsy is increasingly used in patients with advanced disease, especially those unable to have a clinical biopsy for disease surveillance and management. For patients with metastatic or advanced esophageal and esophagogastric junction cancers who may be unable to undergo a traditional biopsy, or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. Negative results do not exclude the presence of tumor mutations or amplifications and should be interpreted with caution.

CLIA=Clinical Laboratory Improvement Amendments; IHC=immunohistochemistry; NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next generation sequencing; *NTRK*=neurotrophic receptor tyrosine kinase; PCR=polymerase chain reaction

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[7]

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and sleep disorders were observed in 42% with Grades 3–4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

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LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Gastric Cancer[8]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for second- or subsequent-line treatment of appropriate patients with unresectable locally advanced, recurrent, or metastatic gastric cancer that is *NTRK* gene fusion-positive – V.2.2024

Sample Patient Journeys

Unresectable locally advanced, recurrent, or metastatic gastric cancer (where local therapy is not indicated) › **First-line treatment** › ***NTRK* gene fusion-positive** › **Second- or subsequent-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend IHC, ISH, and targeted PCR be considered first to identify *NTRK* gene fusions, followed by NGS. If limited tissue is available or the patient is unable to undergo a traditional biopsy, a validated NGS assay performed in a CLIA-approved laboratory should be considered as sequential testing will exhaust the sample.

Liquid biopsy is increasingly used in patients with advanced disease, especially those unable to have a clinical biopsy for disease surveillance and management. For patients with metastatic or advanced gastric cancer who may be unable to undergo a traditional biopsy, or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. Negative results do not exclude the presence of tumor mutations or amplifications and should be interpreted with caution.

CLIA=Clinical Laboratory Improvement Amendments; IHC=immunohistochemistry; ISH=in situ hybridization; NGS=next generation sequencing; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; PCR=polymerase chain reaction

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[8]

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CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

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FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Gastrointestinal Stromal Tumors (GIST)[9]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option – V.1.2024

Larotrectinib is useful in certain circumstances for:

- Neoadjuvant therapy for treatment of appropriate patients with resectable GIST with significant morbidity and *NTRK* gene fusion-positive tumors
- First-line therapy for treatment of appropriate patients with unresectable, progressive, or metastatic GIST and *NTRK* gene fusion-positive tumors

Sample Patient Journeys

Resectable GIST with significant morbidity › ***NTRK* gene fusion-positive** › **Neoadjuvant therapy** › **Systemic therapy option: Larotrectinib**

Unresectable, progressive, or metastatic GIST › ***NTRK* gene fusion-positive** › **First-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend testing for alternative driver mutations for tumors that are negative for KIT or *PDGFRA* mutations, including NGS for *NTRK* gene fusions.

KIT=KIT proto-oncogene receptor tyrosine kinase; NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next generation sequencing; *NTRK*=neurotrophic receptor tyrosine kinase; *PDGFRA*=platelet-derived growth factor receptor alpha.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[9]

Please see Important Safety Information throughout and full Prescribing Information.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

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FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

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NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Head and Neck Cancers[10]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for treatment of appropriate patients with recurrent or metastatic salivary gland tumors (with no surgery or radiotherapy option) that are *NTRK* gene fusion-positive – V.4.2024

- The choice of systemic therapy should be individualized based on patient characteristics (eg, performance status, goals of therapy)

Sample Patient Journeys

Recurrent, unresectable, or metastatic salivary gland tumors (with no surgery or RT option) › **_NTRK_ gene fusion-positive** › **Systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend NGS and other biomarker tests to evaluate AR, *NTRK*, *HRAS*, *PIK3CA*, TMB, and *HER2* status.

AR=androgen receptor; *HER2*=human epidermal growth factor receptor 2; *HRAS*=Harvey rat sarcoma; NGS=next generation sequencing; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RT=radiation therapy; TMB=tumor mutational burden.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[10]

Please see Important Safety Information throughout and full Prescribing Information.

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

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In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

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FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

The #1 prescribed TRK inhibitor for *NTRK* gene fusion-positive solid tumors[25,a]

[a]Based on medical claims and prescription data claims for the period January 2019 through January 2024.

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Hepatocellular Carcinoma[11]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option – V.2.2024

- Larotrectinib is recommended as an option for subsequent-line treatment for hepatocellular carcinoma that is *NTRK* gene fusion-positive where there is disease progression.

Sample Patient Journeys

Hepatocellular carcinoma › **First-line therapy** › **Disease progression** › ***NTRK* gene fusion-positive** › **Subsequent-line systemic therapy option: Larotrectinib**

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[11]

Please see Important Safety Information throughout and full Prescribing Information.

Indication[1]

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

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NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Histiocytic Neoplasms[12]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances – V.2.2024

Larotrectinib is recommended as a systemic therapy option useful in certain circumstances for first- or subsequent-line treatment of appropriate patients with

- Multisystem or pulmonary LCH with *NTRK* gene fusion-positive tumors
- LCH CNS lesions with *NTRK* gene fusion-positive tumors
- Erdheim-Chester disease with *NTRK* gene fusion-positive tumors
- Rosai-Dorfman disease with *NTRK* gene fusion-positive tumors

Sample Patient Journeys

Multisystem or pulmonary LCH	›	***NTRK* gene fusion-positive**	›	**First- or subsequent-line systemic therapy option: Larotrectinib**
LCH CNS Lesions	›	***NTRK* gene fusion-positive**	›	**First- or subsequent-line systemic therapy option: Larotrectinib**
Erdheim-Chester Disease	›	***NTRK* gene fusion-positive**	›	**First- or subsequent-line systemic therapy option: Larotrectinib**
Rosai-Dorfman Disease	›	***NTRK* gene fusion-positive**	›	**First- or subsequent-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend RNA-based molecular panels in testing for *NTRK* gene fusion in LCH and Erdheim-Chester disease.

CNS=central nervous system; FISH=fluorescence in situ hybridization; LCH=Langerhans cell histiocytosis; MAPK=mitogen-activated protein kinase; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[12]

Please see Important Safety Information throughout and full Prescribing Information.

(NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Melanoma: Cutaneous[13]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for second-line or subsequent treatment of appropriate patients with metastatic or unresectable cutaneous melanoma that is *NTRK* gene fusion-positive – V.2.2024

Sample Patient Journey

Metastatic or unresectable disease › **First-line treatment** › **Second-line or subsequent systemic therapy option: Larotrectinib for patients with *NTRK* gene fusion-positive tumors**

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[13]

Please see Important Safety Information throughout and full Prescribing Information.

Thyroid Carcinoma | Uterine Neoplasms | Vaginal Cancer | Vulvar Cancer (SCC)

Guidelines included are current as of May 2024. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Indication[1]

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN 25 NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-26]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Non-small Cell Lung Cancer (NSCLC)[14]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option for first- (preferred) or subsequent-line (based on timing of *NTRK* gene fusion discovery) treatment of appropriate patients with advanced or metastatic NSCLC that is *NTRK*1/2/3 gene fusion-positive – V.7.2024

Sample Patient Journeys

Advanced or metastatic NSCLC → ***NTRK*1/2/3 gene fusion-positive** → **First- or subsequent-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* 1/2/3 Gene Fusion†

NCCN Guidelines recommend FISH, IHC, PCR, and NGS to detect *NTRK* gene fusions.

- False negatives may occur
- IHC methods may be complicated by baseline expressions in some tissues
- FISH may require 3 probe sets for a full analysis
- DNA-based NGS may under-detect *NTRK*1 and *NTRK*3
- Consider RNA-based NGS to maximize detection of fusion events

FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next generation sequencing; *NTRK*=neurotrophic receptor tyrosine kinase; PCR=polymerase chain reaction.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[14]

†The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories.[14]

Please see Important Safety Information throughout and full Prescribing Information.

confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

The #1 prescribed TRK inhibitor for *NTRK* gene fusion-positive solid tumors[25,a]

[a]Based on medical claims and prescription data claims for the period January 2019 through January 2024. Validated by IQVIA in March 2024.

Click on a cancer type to learn more

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Occult Primary[15]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for occult primary squamous cell cancers and adenocarcinomas that are *NTRK* gene fusion-positive – V.2.2024

Sample Patient Journeys

Occult primary › **Squamous cell disease** › ***NTRK* gene fusion-positive** › **Systemic therapy option: Larotrectinib**

Occult primary › **Adenocarcinoma** › ***NTRK* gene fusion-positive** › **Systemic therapy option: Larotrectinib**

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[15]

Please see Important Safety Information throughout and full Prescribing Information.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer[16]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for treatment of appropriate patients with recurrent epithelial ovarian (including LCOC), fallopian tube, or primary peritoneal cancer that is *NTRK* gene fusion-positive – V.3.2024

Sample Patient Journeys

Recurrent ovarian, fallopian tube, or primary peritoneal cancer › **_NTRK_ gene fusion-positive** › **Systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend tumor molecular analysis in the recurrence setting to identify potential benefit from targeted therapeutics where *NTRK* gene fusions are found.

LCOC=less common ovarian cancers; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[16]

Please see Important Safety Information throughout and full Prescribing Information.

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Pancreatic Adenocarcinoma[17]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances – V.2.2024

Larotrectinib is recommended as a systemic therapy option useful in certain circumstances for

- First-line treatment of appropriate patients with locally advanced pancreatic adenocarcinoma that is *NTRK* gene fusion-positive and good or intermediate performance status
- First-line treatment of appropriate patients with metastatic pancreatic adenocarcinoma that is *NTRK* gene fusion-positive and good, intermediate, or poor performance status

Larotrectinib is recommended as a systemic therapy preferred regimen for:

- Subsequent treatment of appropriate patients with locally advanced/metastatic pancreatic adenocarcinoma that is *NTRK* gene fusion-positive and good or poor performance status
- First-line or subsequent treatment of appropriate patients with recurrent pancreatic adenocarcinoma that is *NTRK* gene fusion-positive and good or poor performance status

Sample Patient Journeys

Locally advanced pancreatic adenocarcinoma	**Good/ intermediate performance status**	***NTRK* gene fusion-positive**	**First-line systemic therapy option: Larotrectinib**
Metastatic pancreatic adenocarcinoma	**Good/ intermediate/ poor performance status**	***NTRK* gene fusion-positive**	**First-line systemic therapy option: Larotrectinib**
Locally advanced/ metastatic pancreatic adenocarcinoma	**Good/poor performance status**	***NTRK* gene fusion-positive**	**Subsequent systemic therapy option: Larotrectinib**
Recurrent pancreatic adenocarcinoma	**Good/poor performance status**	***NTRK* gene fusion-positive**	**First-line or subsequent systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend gene profiling for *NTRK* gene fusion and other somatic findings in patients with locally advanced or metastatic pancreatic adenocarcinoma.

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[17]

Please see Important Safety Information throughout and full Prescribing Information.

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Pediatric CNS Cancers[18]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option for treatment of pediatric diffuse high-grade gliomas that are *TRK* gene fusion-positive – V.1.2024

Larotrectinib is a systemic therapy option useful in certain circumstances as:

- Adjuvant therapy for appropriate pediatric patients with diffuse high-grade glioma that is *TRK* gene fusion-positive

Larotrectinib is another recommended regimen as:

- Adjuvant therapy for appropriate pediatric patients <3 years of age with diffuse high that is *TRK* gene fusion-positive

Larotrectinib is a preferred regimen as:

- Adjuvant therapy for appropriate pediatric patients with recurrent or progressive diffuse high-grade glioma that is *TRK* gene fusion-positive

Sample Patient Journeys

Pediatric diffuse high-grade glioma › ***TRK* gene fusion-positive** › **Adjuvant therapy** › **Systemic therapy option: Larotrectinib**

Recurrent or progressive pediatric diffuse high-grade glioma › ***TRK* gene fusion-positive** › **Adjuvant therapy** › **Systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines indicate that broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas and recommend NGS with fusion detection for *NTRK*1/2/3 gene fusions and other actionable findings.

NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next generation sequencing; *NTRK*=neurotrophic receptor tyrosine kinase; *TRK*=tropomyosin receptor kinase

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[18]

Please see Important Safety Information throughout and full Prescribing Information.

and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

The #1 prescribed TRK inhibitor for *NTRK* gene fusion-positive solid tumors[25,a]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Rectal Cancer[19]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option for second- or subsequent-line treatment of appropriate patients with advanced or metastatic rectal cancer that is *NTRK* gene fusion-positive - V.3.2024

Sample Patient Journeys

Advanced or metastatic rectal cancer › **First-line therapy** › ***NTRK* gene fusion-positive** › **Second- or subsequent-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

Data support limiting the subpopulation of colorectal cancers that should be tested for *NTRK* fusions to those with wild-type KRAS, NRAS, *BRAF*, and arguably to those that are MMR deficient (dMMR)/MSI-H. IHC, FISH, DNA-based and RNA-based NGS testing can be used to detect *NTRK* fusions. Positive IHC tests should be confirmed by RNA-based NGS.

BRAF=proto-oncogene B-Raf; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; KRAS=Kirsten rat sarcoma virus; MMR=mis-match repair; MSI-H=high levels of microsatellite instability; MSS=microsatellite stable; NCCN=National Comprehensive Cancer Network® (NCCN®); NGS=next generation sequencing; *NRAS*=N-ras oncogene; *NTRK*=neurotrophic receptor tyrosine kinase; *POLE/POLD1*=DNA polymerase epsilon, catalytic subunit

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[19]

Please see Important Safety Information throughout and full Prescribing Information.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Small Bowel Adenocarcinoma (SBA)[20]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option for treatment of appropriate patients with advanced or metastatic SBA that is *NTRK* gene fusion-positive – V.4.2024

Sample Patient Journeys

Advanced or metastatic SBA › **Initial therapy** › ***NTRK* gene fusion-positive** › **Second-line and subsequent systemic therapy option: Larotrectinib**

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[20]

Please see Important Safety Information throughout and full Prescribing Information.

Thyroid Carcinoma | Uterine Neoplasms | Vaginal Cancer | Vulvar Cancer (SCC)

Guidelines included are current as of May 2024. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Indication[1]

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Soft Tissue Sarcoma[21]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy preferred regimen for first-line treatment of appropriate patients with advanced or metastatic *NTRK* gene fusion-positive soft tissue sarcomas – V.1.2024

Sample Patient Journeys

Advanced or metastatic soft tissue sarcoma › **_NTRK_ gene fusion-positive** › **First-line systemic therapy option: Larotrectinib**

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.
*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[21]

Please see Important Safety Information throughout and full Prescribing Information.

Thyroid Carcinoma | Uterine Neoplasms | Vaginal Cancer | Vulvar Cancer (SCC)

Guidelines included are current as of May 2024. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Indication[1]

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.
In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.
[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Thyroid Carcinoma[22]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option for treatment of appropriate patients with locally recurrent, advanced, and/or metastatic, *NTRK* gene fusion-positive differentiated thyroid carcinoma† not amenable to RAI therapy and metastatic, *NTRK* gene fusion-positive anaplastic carcinoma – V.3.2024

Sample Patient Journey

Locally recurrent, advanced, or metastatic thyroid carcinoma† not amenable to RAI therapy › **_NTRK_ gene fusion-positive** › **Systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend genomic testing to identify actionable mutations, including *NTRK*, for advanced, progressive, or threatening thyroid carcinoma.

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; RAI=radioactive iodine.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[22]

†For follicular, oncocytic, and papillary.

Please see Important Safety Information throughout and full Prescribing Information.

- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Uterine Neoplasms[23]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option – V.2.2024

Larotrectinib is

- Useful in certain circumstances for second-line or subsequent treatment of appropriate patients with recurrent endometrial carcinoma that is *NTRK* gene fusion-positive
- Useful in certain circumstances as a first-line treatment for appropriate patients with advanced, recurrent/metastatic, or inoperable uterine sarcoma that is *NTRK* gene fusion-positive

Sample Patient Journeys

Recurrent endometrial carcinoma › **First-line therapy** › ***NTRK* gene fusion** › **Second-line systemic therapy option: Larotrectinib**

Advanced, recurrent/metastatic, or inoperable uterine sarcoma › ***NTRK* gene fusion** › **First-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend considering *NTRK* gene fusion testing for metastatic or recurrent endometrial carcinoma and testing of at least *NTRK*, MSI, and TMB proteins in uterine sarcoma.

MSI=microsatellite instability; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; TMB=tumor mutational burden.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[23]

Please see Important Safety Information throughout and full Prescribing Information.

and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

Please see Important Safety Information throughout and full Prescribing Information.

VITRAKVI® (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION

FOR ADULT AND PEDIATRIC PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SOLID TUMORS[1]

LAROTRECTINIB (VITRAKVI®) IS RECOMMENDED IN [23] NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)[2-24]

NCCN Guidelines® Recommended Use of Larotrectinib (VITRAKVI) in Vulvar Cancer (Squamous Cell Carcinoma)[24]

NCCN Guidelines recommend larotrectinib (VITRAKVI) as a Category 2A* systemic therapy option useful in certain circumstances for second-line treatment of appropriate patients with advanced or recurrent/metastatic vulvar cancer that is *NTRK* gene fusion-positive – V.4.2024

Sample Patient Journey

Advanced or recurrent metastatic cancer › **First-line therapy** › ***NTRK* gene fusion** › **Second-line systemic therapy option: Larotrectinib**

Biomarker Testing for *NTRK* Gene Fusion

NCCN Guidelines recommend considering *NTRK* gene fusion testing for patients with advanced, recurrent, or metastatic vulvar cancer.

NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase.

*Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.[24]

Please see Important Safety Information throughout and full Prescribing Information.

Indication[1]

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

CNS=central nervous system; NCCN=National Comprehensive Cancer Network® (NCCN®); *NTRK*=neurotrophic receptor tyrosine kinase; SCC=squamous cell carcinoma; TRK=tropomyosin receptor kinase.

[b]Includes fallopian tube cancer and primary peritoneal cancer.

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Important Safety Information[1]

Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

Cognitive impairment occurred in 11% of patients. The median time to onset of cognitive impairment was 5.6 months (range: 2 days to 41 months). Cognitive impairment occurring in ≥ 1% of patients included memory impairment (3.6%), confusional state (2.9%), disturbance in attention (2.9%), delirium (2.2%), cognitive disorders (1.4%), and Grade 3 cognitive adverse reactions occurred in 2.5% of patients. Among the 30 patients with cognitive impairment, 7% required a dose modification and 20% required dose interruption.

Mood disorders occurred in 14% of patients. The median time to onset of mood disorders was 3.9 months (range: 1 day to 40.5 months). Mood disorders occurring in ≥1% of patients included anxiety (5%), depression (3.9%), agitation (2.9%), and irritability (2.9%). Grade 3 mood disorders occurred in 0.4% of patients.

Dizziness occurred in 27% of patients, and Grade 3 dizziness occurred in 1.1% of patients. Among the 74 patients who experienced dizziness, 5% of patients required a dose modification and 5% required dose interruption.

Sleep disturbances occurred in 10% of patients. Sleep disturbances included insomnia (7%), somnolence (2.5%), and sleep disorder (0.4%). There were no Grade 3-4 sleep disturbances. Among the 28 patients who experienced sleep disturbances, 1 patient each (3.6%) required a dose modification or dose interruption.

Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.

Skeletal Fractures: Among 187 adult patients who received VITRAKVI across clinical trials, fractures were reported in 7% and among 92 pediatric patients, fractures were reported in 9% (N=279; 8%). Median time to fracture was 11.6 months (range 0.9 to 45.8 months) in patients followed per fracture. Fractures of the femur, hip or acetabulum were reported in 4 patients (3 adult, 1 pediatric). Most fractures were associated with minimal or moderate trauma. Some fractures were associated with radiologic abnormalities suggestive of local tumor involvement. VITRAKVI treatment was interrupted due to fracture in 1.4% patients.

Promptly evaluate patients with signs or symptoms of potential fracture (e.g., pain, changes in mobility, deformity). There are no data on the effects of VITRAKVI on healing of known fractures or risk of future fractures.

Hepatotoxicity: Hepatotoxicity including drug induced liver injury (DILI) has been reported in patients taking VITRAKVI.

In patients who received VITRAKVI, increased AST of any grade occurred in 52% of patients and increased ALT of any grade occurred in 45%. Grade 3-4 increased AST or ALT occurred in 3.1% and 2.5% of patients, respectively. The median time to onset of increased AST was 2.1 months (range: 1 day to 4.3 years). The median time to onset of increased ALT was 2.3 months (range: 1 day to 4.2 years). Increased AST and ALT leading to dose modifications occurred in 1.4% and 2.2% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 3 (1.1%) of patients.

There have been reports in adult patients from clinical studies and post-marketing cases of Grade ≥ 2 increases in ALT and/or AST with increases in bilirubin ≥ 2 x ULN.

Obtain liver function tests (ALT, AST, ALP and bilirubin) before initiation of VITRAKVI and monitor every 2 weeks during the first two months of treatment, then monthly thereafter, or more frequently following the occurrence of Grade 2 or greater AST or ALT elevation. Temporarily withhold, reduce the dose, or permanently discontinue VITRAKVI based on severity.

Embryo-Fetal Toxicity: VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the last dose of VITRAKVI.

Adverse Reactions

The most common adverse reactions (≥20%), including laboratory abnormalities, were: increased AST (52%), increased ALT (45%), anemia (42%), musculoskeletal pain (42%), fatigue (36%), hypoalbuminemia (36%), neutropenia (36%), increased alkaline phosphatase (34%), cough (32%), leukopenia (28%), constipation (27%), diarrhea (27%), dizziness (27%), hypocalcemia (25%), nausea (25%), vomiting (25%), pyrexia (24%),lymphopenia (22%) and abdominal pain (21%)..

Drug Interactions

Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John's wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs. For coadministration with moderate CYP3A4 inhibitors, monitor for adverse reactions more frequently and reduce the dosage based on severity. For coadministration with moderate CYP3A4 inducers, modify dose as recommended.

Use in Specific Populations

Lactation: Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the last dose.

For important risk and use information about VITRAKVI, please see the full Prescribing Information.

References: 1. VITRAKVI [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; November 2023. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Biliary Tract Cancers V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed July 12, 2024. To view the most recent version of the guideline, go online to NCCN.org. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed July 12, 2024. To view the most recent version of the guideline, go online to NCCN.org. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers V.1.2024. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed July 12, 2024. 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