



Horizon BCBSNJ
Medical Necessity Guideline

Section Drugs
Policy Number
Effective Date 3/24/06
Review Date 11/19/07, 7/25/08,
9/26/08, 11/24/08

Subject:

BRAND NAME Nexavar
(Generic) (sorafenib)

IMPORTANT NOTE:

*The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. **Outpatient prescription drugs are not covered under all Horizon benefit plans.** If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.*

Horizon BCBSNJ pharmacy guidelines do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.

FDA-APPROVED INDICATION

Nexavar is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC). Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Medical Necessity Guideline:

1. The following questionnaire may be used to determine medical necessity of sorafenib prescriptions.

CRITERIA FOR APPROVAL			
1.	Does the patient have one of the following diagnosis: <ul style="list-style-type: none"> • advanced renal cell carcinoma (RCC)? • unresectable hepatocellular carcinoma (HCC) 	Yes	No
2.	Does the patient have a diagnosis of thyroid cancer?	Yes	No
3.	If applicable, are the physician and patient aware that this drug must not be taken if the patient is pregnant or may become pregnant?	Yes	No
4.	Is the request for Nexavar 200 mg more than the dispensing limit of 4 tablets per day?	Yes	No

Guidelines for Approval			
Duration of Approval		6 Months	
Set 1			

Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)				
1	4	2	1				
3		3	4				

Horizon BCBSNJ Pharmacy Guideline Development Process: This Horizon BCBSNJ Pharmacy Guideline (the "Pharmacy Guideline") has been developed by Horizon BCBSNJ's Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

BLACK BOX WARNINGS

None.

RATIONALE

The intent of the criteria is to ensure that patients follow selection elements established by Horizon BCBS New Jersey's medical policies. Horizon BCBSNJ will also cover the indication of thyroid cancer, based on recommendations contained in NCCN guidelines.

ADDITIONAL INFORMATION

Mechanism of Action:

Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*. Sorafenib inhibited tumor growth of the murine renal cell carcinoma, RENCA, and several other human tumor xenografts in athymic mice. A reduction in tumor angiogenesis was seen in some tumor xenograft models. Sorafenib was shown to interact with multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT- 3, VEGFR- 2, VEGFR- 3, and PDGFR- β). Several of these kinases are thought to be involved in angiogenesis.

Dosage:

The recommended daily dose of Nexavar is 400 mg (2 x 200 mg tablets) taken twice daily, without food (at least 1 hour before or 2 hours after eating). Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Nexavar therapy. When dose reduction is necessary, the Nexavar dose may be reduced to 400 mg once daily. If additional dose reduction is required, Nexavar may be reduced to a single 400 mg dose every other day. Suggested dose modifications for skin toxicity are outlined in Table 1.

Table 1: Suggested Dose Modifications for Skin Toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
----------------------------	-------------------	------------------------------------

Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with Nexavar and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1 st occurrence	Continue treatment with Nexavar and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2 nd or 3 rd occurrence	Interrupt Nexavar treatment until toxicity resolves to Grade 0-1 When resuming treatment, decrease Nexavar dose by one dose level (400 mg daily or 400 mg every other day)
	4 th occurrence	Discontinue Nexavar treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1 st or 2 nd occurrence	Interrupt Nexavar treatment until toxicity resolves to Grade 0-1 When resuming treatment, decrease Nexavar dose by one dose level (400 mg daily or 400 mg every other day)
	3 rd occurrence	Discontinue Nexavar treatment

* Adapted from Nexavar Product Information.

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

Warnings:

Pregnancy Category D

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib should be assumed to cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are no adequate and well-controlled studies in pregnant women using Nexavar. Women of childbearing potential should be advised to avoid becoming pregnant while on Nexavar. Nexavar should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Precautions:

General

Dermatologic Toxicities:

Hand-foot skin reaction and rash represent the most common adverse events attributed to Nexavar. Analysis of cumulative event rates from the clinical studies suggest that rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with Nexavar. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of Nexavar, or in severe or persistent cases, permanent discontinuation of Nexavar. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 3 of 451 Nexavar patients.

Hypertension:

In Study 1, treatment-emergent hypertension was reported in approximately 16.9% of Nexavar-treated patients and 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. Blood pressure should be monitored weekly during the first 6 weeks of Nexavar therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of Nexavar should be considered. Permanent discontinuation due to hypertension occurred in 1 of 451 Nexavar patients.

Hemorrhage:

An increased risk of bleeding may occur following Nexavar administration. In Study 1, bleeding regardless of causality was reported in 15.3% of patients in the Nexavar group and 8.2% of patients in the placebo group. The incidence of CTCAE Grade 3 and 4 bleeding events was 2% and 0%, respectively, in Nexavar patients, and 1.3%

and 0.2%, respectively, in placebo patients. There was one fatal hemorrhage in each treatment group in Study 1. If any bleeding event necessitates medical intervention, permanent discontinuation of Nexavar should be considered.

Cardiac Ischemia and/or Infarction:

In Study 1, the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the Nexavar group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of Nexavar should be considered in patients who develop cardiac ischemia and/or infarction.

Warfarin Co-administration:

Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on Nexavar therapy. Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

Wound Healing Complications:

No formal studies of the effect of Nexavar on wound healing have been conducted. Temporary interruption of Nexavar therapy is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of Nexavar therapy following major surgical intervention. Therefore, the decision to resume Nexavar therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Drug Interactions

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Substances that are inducers of CYP3A4 activity (e.g., rifampin, St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations. Caution is recommended when administering Nexavar with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g., irinotecan). Caution is recommended when administering doxorubicin with Nexavar. Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with K_i values of 6 and 1-2 μ M, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with Nexavar. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with Nexavar.

Patients with Hepatic Impairment

In vitro and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with Child-Pugh A and B hepatic impairment. Nexavar has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering Nexavar to patients with Child-Pugh A and B hepatic impairment.

Impairment of Fertility

Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

Pregnancy

Pregnancy Category D. There are no adequate and well-controlled studies in pregnant women using Nexavar. Women of childbearing potential should be advised to avoid becoming pregnant while on Nexavar.

Nursing Mothers

It is not known whether sorafenib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of sorafenib on infants have not been studied, women should be advised against breast-feeding while receiving Nexavar.

Pediatric Use

The safety and effectiveness of Nexavar in pediatric patients have not been studied.

REFERENCES

1. Nexavar Product Information. Onyx Pharmaceuticals. December 2005.
2. American Hospital Formulary Service. American Society of Health-System Pharmacists. 2007.
3. USPDI. Thomson MICROMEDEX. 2007.

4. MICROMEDEX Thomson Healthcare. MICROMEDEX Inc. Greenwood Village, CO. February 2007.

Pharmacy Guidelines can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician or pharmacist, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.

This Horizon BCBSNJ Pharmacy Guideline is proprietary. It is to be used only as authorized by Horizon BCBSNJ and its affiliates. The contents of this Pharmacy Guideline are not to be copied, reproduced or circulated to other parties without the express written consent of Horizon BCBSNJ. The contents of this Pharmacy Guideline may be updated or changed without notice, unless otherwise required by law and/or regulation. However, benefit determinations are made in the context of Pharmacy Guidelines existing at the time of the decision and are not subject to later revision as the result of a change in Pharmacy Guideline.