

NEXAVAR®



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**APPROVAL OF NEXAVAR® WITH CONDITIONS FOR THE TREATMENT OF LOCALLY ADVANCED / METASTATIC RENAL CELL (CLEAR CELL) CARCINOMA IN PATIENTS WHO HAVE FAILED PRIOR CYTOKINE THERAPY OR ARE CONSIDERED UNSUITABLE FOR SUCH THERAPY.**

**July 2006**

Dear Health Care Professional,

Bayer Inc. is pleased to announce that Health Canada has granted a Notice of Compliance with Conditions (NOC/c) for NEXAVAR® (sorafenib tablets) for the treatment of locally advanced / metastatic renal cell (clear cell) carcinoma in patients who failed prior cytokine therapy or are considered unsuitable for such therapy. This authorization reflects the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit. Products approved under Health Canada's NOC/c policy have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment for the approved use.

This approval was primarily based on a surrogate endpoint, progression-free survival (PFS) evaluated in the largest Phase III, randomized, placebo-controlled trial conducted to date in locally advanced / metastatic Renal Cell Carcinoma (RCC). This pivotal trial included patients with locally advanced / metastatic RCC with low- or intermediate-risk Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score without brain metastases. The median PFS for patients randomized to NEXAVAR (167 days) was double that observed for patients randomized to placebo (84 days), representing a 56% reduction in risk of progression for patients receiving sorafenib compared to placebo ( $P < 0.000001$ ). The effect of sorafenib on PFS was consistent across patient subgroups evaluated, including patients with no prior cytokine therapy (N=137), for whom the median PFS was 172 days on NEXAVAR compared to 85 days on placebo. At an interim

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survival analysis based on 367 deaths, overall survival (OS) was longer in patients treated with NEXAVAR (median OS was 19.3 months for sorafenib-treated patients and 15.9 months for placebo patients) with a hazard ratio of 0.77. This analysis included 200 placebo patients that had crossed over to NEXAVAR treatment. The trend for longer OS in the NEXAVAR arm did not meet the criteria for statistical significance for this analysis. Additional analyses are planned as the survival data mature.

### **Indication**

NEXAVAR is indicated for treatment of locally advanced / metastatic renal cell (clear cell) carcinoma in patients who failed prior cytokine therapy or are considered unsuitable for such therapy.

### **Patients should be advised about the conditional nature of the market authorization for NEXAVAR.**

**Geriatrics (>65 years of age):** Analyses of data by age demographics suggest that no dose adjustment is required on the basis of patient age (65 years or older). No differences in safety or efficacy were observed between older and younger patients.

**Pediatrics (<18 years of age):** The safety and effectiveness of sorafenib in pediatric patients has not been established. NEXAVAR should not be used in adolescents or children.

### **Contraindications**

NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any of the excipients.

### **Dosage and Administration**

NEXAVAR is an orally administered tablet containing 200 mg sorafenib. The recommended dose of NEXAVAR is 400 mg (2 x 200 mg tablets) taken twice a day (equivalent to total daily dose of 800 mg) without food.

### **Serious Warnings and Precautions**

NEXAVAR should be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy.

NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment or patients with severe renal impairment.

Clinically significant adverse events include hypertension, hemorrhage, and cardiac ischemia / infarction.

### **Pharmacology**

NEXAVAR targets serine/threonine and receptor tyrosine kinases in both the tumour cell and tumour vasculature. Kinases are enzymes that may play a major role in transmitting the chemical signals required for critical cellular processes. NEXAVAR inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, KIT, and FLT-3) and in the tumour vasculature (CRAF, VEGFR-2, VEGFR-3, and PDGFR-β).

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RAF kinases are serine/threonine kinases whereas KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR- $\beta$  are receptor tyrosine kinases.

### **Adverse Events**

The overall safety evaluation of NEXAVAR is based on 1286 cancer patients who received NEXAVAR as monotherapy and 165 patients who received NEXAVAR concurrently with chemotherapy. A total of 346 patients were exposed to NEXAVAR monotherapy for greater than 6 months. A total of 664 RCC patients received NEXAVAR monotherapy, of whom 215 were treated for at least 6 months. A full presentation of safety information is provided in the Product Monograph.

Clinically significant adverse events included hypertension (17% for sorafenib vs 2% for placebo), hemorrhage (15% sorafenib vs 8% for placebo), and cardiac ischemia / infarction (2.9% for sorafenib vs 0.4% for placebo).

In a randomized, placebo-controlled study in locally advanced / metastatic RCC, the most common treatment-emergent adverse events reported with sorafenib vs placebo were rash (40% vs 16%), diarrhea (43% vs 13%), hand-foot skin reaction (30% vs 7%), fatigue (37% vs 28%), and hypertension (17% vs 2%). Most adverse events observed with NEXAVAR were CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Grade 1 and 2. CTCAE Grade 4 drug-related adverse events were rare, reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

### **Further Information**

The Product Monograph is available to health care professionals upon request.

For medical enquiries regarding NEXAVAR, please contact the medical information department of Bayer Inc at:

1-800-265-7382.

Original signed by:

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**Any suspected adverse drug reactions can also be reported to:**

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)  
Marketed Health Products Directorate  
HEALTH CANADA  
Address Locator: 0701C  
OTTAWA, Ontario, K1A 0K9  
Tel: (613) 957-0337 or Fax: (613) 957-0335  
Toll free for consumers and health professionals:  
Tel: 866 234-2345, Fax: 866 678-6789  
[cadrmp@hc-sc.gc.ca](mailto:cadrmp@hc-sc.gc.ca)

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.