## Nexavar® (sorafenib)

**Prescribing Information** (Refer to full Summary of Product Characteristics (SmPC) before prescribing)

**Presentation:** Film-coated tablets containing 200 mg sorafenib (as tosylate). **Indication(s):** Treatment of hepatocellular carcinoma (refer to SmPC section 5.1). Renal cell carcinoma: Treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. Differentiated thyroid carcinoma: Treatment of patients with progressive, locally advanced or metastatic, differentiated papillary/follicular/ Hürthle cell) thyroid carcinoma, refractory to radioactive iodine. **Posology & method of administration:** Treatment should be supervised by a physician experienced in the use of anticancer therapies. ***Adults:*** 400 mg twice daily. Treatment should continue as long as a clinical benefit is observed or until unacceptable toxicity occurs. ***Posology adjustments:*** Temporary treatment interruption or dose reduction or discontinuation may be considered, depending on the severity of the observed adverse reactions. When dose reduction is necessary during treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the dose should be reduced to 400mg once daily. When dose reduction is necessary during the treatment of differentiated thyroid carcinoma (DTC), the dose should be reduced to 600 mg daily in divided doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart). If additional dose reduction is necessary, the dose may be reduced to 400 mg sorafenib daily in divided doses (two tablets of 200 mg twelve hours apart), and if necessary further reduced to one tablet of 200 mg once daily. After improvement of non-haematological adverse reactions, the dose may be increased. ***Children & adolescents:*** Safety and efficacy not yet established in patients <18 years. ***Elderly:*** No dose adjustment (>65 years). ***Renal impairment:*** No dose adjustment in mild, moderate or severe impairment. No data available in patients requiring dialysis. Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised. ***Hepatic impairment:*** No dose adjustment in Child Pugh A or B (mild to moderate) hepatic impairment. No data is available on Child Pugh C (severe) hepatic impairment. ***Method of administration:*** Take tablets with a glass of water, without food or with a low/moderate fat meal. With a high-fat meal, take tablets at least 1 hour before or 2 hours after. **Contra-indications:** Hypersensitivity to sorafenib or any of the excipients. **Warnings & precautions:** Hand-foot skin reaction and rash usually CTC grade 1 and 2 (generally appear during first 6 weeks of treatment). Increased incidence of arterial hypertension was observed (usually mild to moderate, early in the course of treatment). Blood pressure should be monitored regularly and treated as appropriate. In severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, consider permanent discontinuation. The risk of aneurysm and/or artery dissection should be carefully considered in patients with risk factors such as hypertension or history of aneurysm before initiating sorafenib. Increased incidence of cardiac ischaemia/infarction: consider temporary or permanent discontinuation in patients developing cardiac ischaemia and/or infarction. Increased risk of bleeding may occur: consider permanent discontinuation if any bleeding event necessitates medical intervention. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, and consider periodic monitoring (on-treatment electrocardiograms, electrolytes). Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalization have been reported. Interrupt sorafenib temporarily in cases of symptomatic hypoglycaemia, regularly monitor blood glucose levels in patients with diabetes in order to assess if anti-diabetic medicinal product's dosage need to be adjusted. Gastrointestinal perforation is reported in <1% patients; sorafenib therapy should be discontinued. Cases of tumour lysis have been reported. These patients should be monitored closely and treated promptly. Levels of sorafenib may be increased in patients with severe hepatic impairment. Infrequent bleeding events or elevations in INR have been reported in some patients taking warfarin or phenprocoumon concomitantly. Patients on such therapy should be monitored. No formal studies on wound healing have been conducted. Temporary interruption of sorafenib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. Cases of renal failure have been reported in the elderly, consider monitoring of renal function. High risk RCC patients according to MSKCC prognostic group were not included in the RCC study and benefit-risk has not been evaluated in these patients. The risk of reduced plasma concentrations of sorafenib should be considered before starting a treatment course with antibiotics. Higher mortality has been reported in patients with squamous cell carcinoma of the lung treated with sorafenib in combination with platinum-based chemotherapies. Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localized therapy prior to administering sorafenib in patients with differentiated thyroid cancer (DTC). When using sorafenib in patients with DTC, close monitoring of blood calcium level is recommended. Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes. When using sorafenib in DTC patients, close monitoring of TSH level is recommended. Prescribers should consult the SmPC in relation to other warnings and precautions. **Interactions:** Inducers of metabolic enzymes (e.g. CYP3A4 inducers such as rifampicin), may decrease sorafenib concentrations. Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 in vitro with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinically meaningful inhibition. In-vitro inhibition of UGT1A1, UGT1A9 pathway and P-gp (possible increase of P-gp substrates concentration, e.g. digoxin). Coadministration of paclitaxel and carboplatin with sorafenib with a 3-day break in sorafenib dosing: no dose adjustment required. Modest increase in capecitabine & 5-FU exposure. Increase in AUC of doxorubicin, irinotecan and active metabolite SN-38 (UGT1A1 substrate). Increase in AUC & Cmax of docetaxel. Neomycin and other antibiotics interfering with GI microorganisms with glucuronidase activity (resulting in decreased sorafenib exposure). Effects of other antibiotics have not been studied but will likely depend on their ability to interfere with microorganisms with glucuronidase activity. **Fertility, pregnancy & lactation:** No data on use in pregnant women. Studies in animals have shown reproductive toxicity including malformations. Do not use during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and risk to foetus. Effective contraception must be used during treatment. Animal studies indicate that sorafenib can impair male and female fertility. Women must not breast-feed during treatment. **Effects on ability to drive and use machines:** No studies have been performed; no evidence of impairment. **Undesirable effects:** The most important serious adverse reactions were myocardial infarction/ischaemia, gastrointestinal perforation, drug-induced hepatitis, haemorrhage and hypertension/ hypertensive crisis. *Very common:* haemorrhage (inc. gastrointestinal*, respiratory tract* and cerebral haemorrhage*), hypertension, infection, lymphopenia, anorexia, hypophosphataemia, diarrhoea, nausea, vomiting, constipation, dry skin, rash, alopecia, hand-foot skin reaction (palmar plantar erythrodysaesthesia syndrome), erythema, pruritus, arthralgia, fatigue, pain (e.g. mouth, abdominal, bone, tumour, headache), fever, weight decreased, increased amylase and lipase. *Common*:- congestive heart failure*, myocardial ischaemia/infarction*, folliculitis, leucopenia, neutropenia, anaemia, thrombocytopenia, hypothyroidism, hypocalcaemia, hypokalaemia, hyponatraemia, hypoglycaemia, depression, peripheral sensory neuropathy, dysgeusia, tinnitus, flushing, rhinorrhoea, dysphonia, stomatitis (e.g. dry mouth and glossodynia), dyspepsia, dysphagia, gastrooesophageal reflux disease, keratoacanthoma/squamous cell cancer of the skin, exfoliative dermatitis, acne, skin desquamation, hyperkeratosis, myalgia, muscle spasms, renal failure, proteinuria, erectile dysfunction, asthenia, influenza-like illness, mucosal inflammation, transient increase in transaminases. Serious: cf. *CI/W&P – in addition:* hypersensitivity reactions (e.g. skin reactions and urticaria), interstitial lung disease-like events* (e.g. pneumonitis, radiation pneumonitis, acute respiratory distress), reversible posterior leukoencephalopathy*, hypertensive crisis*, gastrointestinal perforations*, hyperthyroidism, hyperbilirubinaemia, jaundice, pancreatitis, cholecystitis, cholangitis, angioedema, anaphylactic reaction, drug induced hepatitis*, QT prolongation, Stevens-Johnson syndrome, leucocytoclastic vasculitis, toxic epidermal necrolysis*, rhabdomyolysis, nephrotic syndrome, encephalopathy, aneurysms and artery dissections. *These adverse reactions may have a life-threatening or fatal outcome: most events are either uncommon or less frequent than uncommon. Prescribers should consult the SmPC in relation to other side effects. Special precautions for storage: Do not store above 25°C. **Legal category:** POM. **Package Quantity & Basic NHS Cost:** 112 tablets, £3576.56. **MA Number:** EU/1/06/342/001, PLGB 00010/0701. **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD. Telephone: 0118 206 3000. **Date of preparation:** July 2022.

Nexavar® is a trademark of the Bayer Group.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store.
Adverse events should also be reported to Bayer plc.
Tel: 0118 206 3500, Fax: 0118 206 3703, Email: pvuk@bayer.com