Prescribing Information (UK)

Vargatef® (nintedanib) 100 mg and 150 mg soft capsules

Soft capsules containing 100 mg or 150 mg nintedanib (as esilate). **Indication:** Vargatef is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. **Dose and Administration:** Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies. The recommended dose of nintedanib is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21 day docetaxel treatment cycle. Vargatef must not be taken on the same day of docetaxel chemotherapy administration (= day 1). If a dose of nintedanib is missed, administration should resume at the next scheduled time at the recommended dose. The individual daily doses of nintedanib should not be increased beyond the recommended dose to make up for missed doses. The recommended maximum daily dose of 400 mg should not be exceeded. Patients may continue therapy with nintedanib after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs. For posology, methods of administration, and dose modifications of docetaxel, please refer to the corresponding product information for docetaxel. Dose adjustments should be considered in case of adverse reactions of pre-specified severity: diarrhoea, vomiting, nausea and other non-haematological or haematological adverse reactions, and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and bilirubin elevations – as initial measure for the management of adverse reactions treatment with nintedanib should be temporarily interrupted. Please refer to the Summary of Product Characteristics (SPC) for further information including when to discontinue treatment. Paediatric population: Safety and efficacy in children aged 0-18 years have not been established. Elderly patients (≥ 65 years): No overall differences in safety and efficacy were observed for elderly patients. No adjustment of initial dosing required on the basis of a patient's age. Race and body weight: Based on population pharmacokinetic analyses, no *a priori* dose adjustments necessary. Safety data for Black and African American patients are limited. Renal impairment: Less than 1 % of a single dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy and pharmacokinetics have not been studied in patients with severe renal impairment (< 30 ml/min creatinine clearance). Hepatic impairment: Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90%). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B). No adjustment of the starting dose is needed for patients with mild hepatic impairment (Child Pugh A) based on clinical data. Limited safety data available from 9 patients with moderate hepatic impairment (Child Pugh B) are insufficient to characterize this population. The safety, efficacy and pharmacokinetics of nintedanib have not been investigated in patients with severe hepatic impairment (Child Pugh C). Treatment of patients with moderate (Child Pugh B) to severe (Child Pugh C) hepatic impairment is not recommended. The capsules must be taken orally, preferably with food, swallowed whole with water, and must not be chewed or crushed. **Contraindications:** Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients. **Warnings and Precautions:** Gastrointestinal disorders: Patients with gastrointestinal disorders including diarrhoea, nausea and vomiting may require interruption, dose reduction or discontinuation of therapy. Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide. Supportive care for nausea and vomiting

may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration. In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur. Interruption, dose reduction or discontinuation of therapy with Vargatef may be required. Neutropenia and sepsis: Combination treatment with docetaxel is associated with a higher frequency of neutropenia of CTCAE grade ≥ 3 as compared to treatment with docetaxel alone. Subsequent complications such as sepsis or febrile neutropenia have been observed (including fatal cases). Blood counts should be monitored during therapy, please refer to SPC. Hepatic function: Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A). Treatment with Vargatef is not recommended in patients with moderate or severe hepatic impairment. Cases of drug-induced liver injury have been observed with nintedanib treatment, including severe liver injury with fatal outcome. Elevation of liver enzymes (ALT, AST, blood alkaline phosphatase (ALKP), gamma-glutamyltransferase (GGT)) and bilirubin were reversible upon dose reduction or interruption in the majority of cases. Transaminase, ALKP and bilirubin levels should be investigated before initiation of combination treatment and monitoring continued as required. If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with Vargatef may be required, please refer to the SPC. Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations in liver enzymes. Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with these risk factors. Renal function: Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with nintedanib use. Patients should be monitored during nintedanib therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered. Haemorrhage: Vascular endothelial growth factor receptor (VEGFR) inhibition might be associated with an increased risk of bleeding. Vargatef is not recommended in patients with recent pulmonary bleeding (> 2.5 ml of red blood) as well as patients with centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours. In case of bleeding, dose adjustment, interruption or discontinuation should be considered based on clinical judgement. Patients taking concomitant anticoagulation, such as warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, international normalised ratio (INR), and clinical bleeding episodes. Patients with stable brain metastasis should be closely monitored for signs and symptoms of cerebral bleeding. Treatment not recommended for patients with active brain metastasis. Venous thromboembolism: Increased risk of venous thromboembolism including pulmonary embolism and deep vein thrombosis. Patients should be closely monitored for thromboembolic events. Caution should be used especially in patients with additional risk factors for thromboembolic events. Vargatef should be discontinued in patients with life-threatening venous thromboembolic reactions. Arterial thromboembolic events: Caution should be used when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia. Aneurysms and artery dissections: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Vargatef, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal perforations: Based on the mechanism of action patients treated with Vargatef may have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. Treatment should only be initiated at least 4 weeks after major surgery. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. Wound healing complication: Nintedanib may impair wound healing. Treatment should therefore only be initiated or, in case of perioperative interruption, resumed based on clinical judgement of adequate wound healing. Effect on QT interval: Caution should be exercised in patients who may develop QTc prolongation. Allergic reaction: Dietary soya-products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations. Special populations: Close monitoring is recommended in patients weighing < 50 kg. **Interactions:** Interaction studies have only been performed in adults. P-glycoprotein (P-gp): Nintedanib is a substrate of P-gp. If co-administered, potent P-gp inhibitors e.g. ketoconazole or erythromycin may increase exposure to nintedanib. Patients should be monitored closely for tolerability of nintedanib. Potent P-gp inducers e.g. rifampicin, carbamazepine, phenytoin and St. John's Wort may decrease exposure to nintedanib. Co-administration should be carefully considered. Cytochrome (CYP)- enzymes: Likelihood of drug-drug interactions with nintedanib based on CYP metabolism considered to be low. Other medicinal products: The potential for interactions with hormonal contraceptives was not explored. **Fertility, Pregnancy and Lactation:** Nintedanib may cause foetal harm in humans; women should avoid becoming pregnant while receiving this treatment and use adequate contraception during and for at least 3 months after the last dose of Vargatef. Since the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy. There is no information on the use of Vargatef in pregnant women, but preclinical studies have shown reproductive toxicity and therefore nintedanib should not be used during pregnancy unless the clinical condition requires treatment. Pregnancy testing should be conducted at least prior to treatment. Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy. If the patient becomes pregnant while receiving Vargatef, she should be apprised of the potential hazard to the foetus. Termination of the treatment with Vargatef should be considered. There is no information on the excretion of nintedanib and its metabolites in human milk. Preclinical studies showed that small amounts of nintedanib and its metabolites (≤ 0.5 % of the administered dose) were secreted into milk of lactating rats. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with Vargatef. Based on preclinical investigations there is no evidence for impairment of male fertility. There are no human or animal data on potential effects of nintedanib on female fertility available. **Undesirable effects:** The most frequently reported adverse reactions specific for nintedanib were diarrhoea, increased liver enzymes (ALT and AST) and vomiting. Very common (≥ 1/10): Neutropenia (includes febrile neutropenia), decreased appetite, electrolyte imbalance, peripheral neuropathy, bleeding, diarrhoea, vomiting, nausea, abdominal pain, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase (ALKP) increased, mucositis (including stomatitis), rash, alopecia. Common (≥ 1/100 < 1/10): Febrile neutropenia, abscesses, sepsis, thrombocytopenia, dehydration, weight decreased, headache, venous thromboembolism (cases of pulmonary embolism have been reported), hypertension, hyperbilirubinaemia, gamma-glutamyltransferase (GGT) increased, pruritus. Uncommon (≥ 1/1,000 < 1/100):

Myocardial infarction, perforation, pancreatitis, drug-induced liver injury, renal failure. Not known (cannot be estimated from the available data): aneurysms and artery dissections, colitis. Prescribers should consult the Summary of Product Characteristics for further information on side effects and recommended measures. **Pack sizes and NHS price:** 100 mg 120 capsules: £2151.10; 150mg 60 capsules: £2151.10. **Legal category:** POM. **MA numbers:** 100 mg: EU/1/14/954/002; 150 mg: EU/1/14/954/004. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in August 2020.**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).