NAME OF THE MEDICINAL PRODUCT: Aprotinin 10,000 KIU/ML Injection BP. **PRESENTATION**: Each 50ml vial contains aprotinin concentrated solution, corresponding to 500,000 KIU (Kallikrein Inhibitor Units) in sterile 0.9% sodium chloride solution. **INDICATIONS:** Aprotinin is indicated for prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery). Aprotinin should only be used after careful consideration of the benefits and risks, and the consideration that alternative treatments are available. **POSOLOGY AND METHOD OF ADMINISTRATION:** Posology: An appropriate aprotinin-specific IgG antibody test may be considered before administration of aprotinin. *Adult:* Owing to the risk of allergic/anaphylactic reactions, a 1 ml (10,000 KIU) test dose should be administered to all patients at least 10 minutes prior to the remainder of the dose. After the uneventful administration of the 1 ml test dose, the therapeutic dose may be given. A H1-antagonist and a H2-antagonist may be administered 15 minutes prior to the test dose of aprotinin. In any case standard emergency treatments for anaphylactic and allergic reactions should be readily available (see section 4.4 of Summary of Product Characteristics (SmPC)). A loading dose of 1 - 2 million KIU is administered as a slow intravenous injection or infusion over 20 - 30 minutes after induction of anaesthesia and prior to sternotomy. A further 1 - 2 million KIU should be added to the pump prime of the heart-lung machine. To avoid physical incompatibility of aprotinin and heparin when adding to the pump prime solution, each agent must be added during recirculation of the pump prime to assure adequate dilution prior to admixture with the other component. The initial bolus infusion is followed by the administration of a continuous infusion of 250,000 - 500,000 KIU per hour until the end of the operation. In general, the total amount of aprotinin administered per treatment course should not exceed 7 million KIU. *Paediatric population* - The safety and efficacy in children below 18 years of age have not been *e*stablished. Refer to SmPC for use in other specific patient populations. Aprotinin should be infused using a central venous catheter. The same lumen should not be used for the administration of any other medicinal product. When using a multi-lumen central catheter, a separate catheter is not required. Aprotinin must be given only to patients in the supine position and must be given slowly (maximum 5 - 10 ml/min) as an intravenous injection or a short infusion. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or any of the excipients. Patients with a positive aprotinin specific IgG antibody test. If no such test is possible prior to treatment, administration of aprotinin to patients with a suspected previous exposure including in fibrin sealant products during the last 12 months is contraindicated. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Aprotinin should not be used when CABG surgery is combined with another cardiovascular surgery because the benefit risk balance of aprotinin in other cardiovascular procedures has not been established.** *Laboratory monitoring of anticoagulation during cardiopulmonary bypass:* Aprotinin is not a heparin-sparing agent and it is important that adequate anticoagulation with heparin be maintained during aprotinin-therapy. Elevations in the partial thromboplastin time (PTT) and celite. Activated Clotting Time (Celite ACT) are expected in aprotinin-treated patients during surgery, and in the hours after surgery. **Therefore, the partial thromboplastin time (PTT) should not be used to maintain adequate anticoagulation with heparin. In patients undergoing cardiopulmonary bypass with aprotinin therapy, one of three methods is recommended to maintain adequate anticoagulation: Activated Clotting Time (ACT), Fixed Heparin Dosing, or Heparin Titration (see below). If activated clotting time (ACT) is used to maintain adequate anticoagulation, a minimal celite-ACT of 750 seconds or kaolin-ACT of 480 seconds, independent of the effects of haemodilution and hypothermia, is recommended in the presence of aprotinin**. Important: aprotinin is not a heparin-sparing agent. *Graft Conservation:* Blood drawn from the aprotinin central infusion line should not be used for graft preservation. *Re-exposure to aprotinin:* Administration of aprotinin, especially to patients who have received

aprotinin (including aprotinin containing fibrin sealants) in the past requires a careful risk/benefit assessment because an allergic reaction may occur. Standard emergency treatment for allergic/anaphylactic reactions should be readily available during treatment with aprotinin. *Renal impairment:* Results from recent observational studies indicate that renal dysfunction could be triggered by aprotinin, particularly in patients with pre-existing renal dysfunction. An analysis of all pooled placebo-controlled studies in patients undergoing coronary artery bypass graft (CABG) has found elevations of serum creatinine values >0.5 mg/dL above baseline in patients with aprotinin therapy. Careful consideration of the balance of risks and benefits is therefore advised before administration of aprotinin to patients with pre-existing impaired renal function or those with risk factors (such as concomitant treatment with aminoglycosides). An increase in renal failure and mortality compared to age-matched historical controls has been reported for aprotinin-treated patients undergoing cardiopulmonary bypass with deep hypothermic circulatory arrest during operation of the thoracic aorta. Adequate anticoagulation with heparin must be assured. *Mortality:* An association between aprotinin use and increased mortality has been reported in some non-randomized observational studies while other non-randomized studies have not reported such an association. In these studies, aprotinin was usually administered to patients who had more risk factors for increased mortality before surgery than patients in the other treatment groups. Most of the studies did not adequately account for these baseline differences in risk factors and the influence of these risk factors on the results is not known. Therefore, interpretation of these observational studies is limited and an association between aprotinin use and increased mortality can neither be established nor refuted. Thus, aprotinin should only be used as authorized in isolated CABG surgery, after careful consideration of the potential risks and benefits. A publication by Fergusson et al 2008 analysed data from a randomized controlled trial, Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART), and reported a higher mortality rate in aprotinin-treated patients compared to those treated with tranexamic acid or aminocaproic acid. However, due to several methodological deficiencies no firm conclusion on cardiovascular risks can be made on the BART study results. **UNDESIRABLE EFFECTS:** Refer to the Summary of Product Characteristics for full details of the safety of the product. *Summary of the safety profile:* The safety of aprotinin has been evaluated in more than forty-five phase II and phase III studies including more than 3800 patients exposed to aprotinin. In total, about 11% of aprotinin-treated patients experienced adverse reactions. The most serious adverse reaction was myocardial infarction. The adverse reactions should be interpreted within the surgical setting. *Tabulated summary of adverse reactions:* Adverse drug reactions (ADRs) based on all placebo-controlled clinical studies with aprotinin sorted by CIOMS III categories of frequency (aprotinin n=3817 and placebo n=2682; status: April 2005) are listed in the table in SmPC: Frequencies are defined as: Common: ≥ 1/100 to < 1/10; Uncommon: ≥ 1/1,000 to < 1/100; Rare: ≥ 1/10,000 to < 1/1,000; Very rare: < 1/10,000; Not known: cannot be estimated from the available data. *Uncommon*: Myocardial ischaemia, coronary occlusion/thrombosis, myocardial infarction, pericardial effusion, thrombosis, Oliguria, acute renal failure, renal tubular necrosis. *Rare*: Allergic reaction, anaphylactic/anaphylactoid reaction, Arterial thrombosis (and its organ specific manifestations that might occur in vital organs such as kidney, lung or brain). *Very rare*: Anaphylactic shock (potentially life threatening), disseminated intravascular coagulation, coagulopathy, pulmonary embolism, injection and infusion site reactions, infusion site (thrombo-) phlebitis. **BASIC NHS COST**: £79.00 for 1 vial. **LEGAL CLASSIFICATION**: POM. **MA NUMBER**: PL 40621/0020. **MA HOLDER**: Nordic Group B.V. Siriusdreef 41, 2132 WT Hoofddorp, The Netherlands. **Further information available from:** Nordic Pharma Ltd., Unit 3 Commerce Park, Brunel Road, Theale, Reading, Berkshire RG7 4AB. **DATE OF PREPARATION:** Mar 2021. Item code: APR/21/18.

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 Nordic Pharma on 0800 121 8924.