

## **New Heat-Stable Norvir® (ritonavir) Tablet Approved in Europe**

The European Commission granted approval of a new tablet formulation of Abbott's antiretroviral medication Norvir® (ritonavir) on Jan. 25, 2010. The new Norvir tablets can be stored at room temperature and do not require refrigeration, making it more convenient for some patients. European approval is a critical step in Abbott's efforts to expedite registration filings for the Norvir tablet in countries around the world, including in developing countries where the majority of people with HIV live. The Norvir tablets and the Norvir soft-gelatin capsules both contain 100 mg of ritonavir. While the rate of drug absorbed is different, there is no requirement for dosage change. The Norvir tablet is the direct result of years of effort by Abbott scientists who wanted to improve this critical component of HIV treatment by making it more convenient for patients. The tablet was developed using Abbott's Meltrex® technology, a proprietary melt-extrusion process that makes it more heat-stable. This is the same technology used to develop Abbott's Kaletra® tablet, which combines lopinavir and ritonavir. Norvir is used in combination with other antiretroviral medications to treat HIV.

We hope to have this product available from mid April 2010 in the UK.

### **Prescribing Information**

**Norvir® (ritonavir) 100mg soft capsules, Norvir® 100mg film-coated tablets and Norvir® 80mg/ml oral solution**

Refer to Summary of Product Characteristics for full information

### **Presentations:**

**Norvir 100mg soft capsules:** Each soft capsule contains 100mg ritonavir.

**Norvir 100mg film-coated tablets:** Each film-coated tablet contains 100mg ritonavir.

**Norvir 80mg/ml oral solution:** Each ml of solution contains 80mg of ritonavir.

**Indication:** In combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older).

**Dosage and Administration:** Should only be administered by physicians experienced in the treatment of HIV infection. Dose escalation when initiating therapy may improve tolerance. Norvir soft capsules and Norvir oral solution should preferably be ingested with food. Norvir film-coated tablets should be ingested with food and swallowed whole and not chewed, broken or crushed.

*Ritonavir dosed as an antiretroviral agent:*

*Adults:* Norvir soft capsules: 600mg (6 capsules) twice daily. Norvir film-coated tablets: 600mg (6 tablets) twice daily. Norvir oral solution: 600mg (7.5ml) twice daily. Starting dose 300mg twice daily for 3 days, increased by 100mg twice daily up to 600mg twice daily over a period not to exceed 14 days.

*Children ≥ 2 years:* 350mg/m<sup>2</sup> twice daily. Maximum dose 600mg twice daily. Starting dose 250mg/m<sup>2</sup> twice daily increasing at 2-3 day intervals by 50mg/m<sup>2</sup> twice daily.  
*Children < 2 years:* Not recommended.

*Ritonavir dosed as a Pharmacokinetic enhancer:*

For dosage recommendations, refer to the product information of the other Protease Inhibitors approved for co-administration with ritonavir.

**Contraindications:** Known hypersensitivity to ritonavir or formulation excipients. Severe hepatic insufficiency. Do not administer with the following drugs: alfuzosin, pethidine, piroxicam, propoxyphene, amiodarone, bepridil, encainide, flecainide, propafenone, quinidine, fusidic acid, voriconazole, astemizole, terfenadine, rifabutin, clozapine, pimozide, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, lovastatin, simvastatin, Sildenafil (when used in patients with pulmonary arterial hypertension (PAH) only), clorazepate, diazepam, estazolam, flurazepam, oral midazolam, triazolam and St. Johns wort (*Hypericum perforatum*).

**Precautions and Warnings:** Impaired hepatic or renal function. Extra monitoring recommended when serious persistent vomiting and /or diarrhoea occurs. Caution should be exercised with concomitant use of sildenafil, tadalafil, vardenafil for the treatment of erectile dysfunction. . Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients. Concomitant use of ritonavir and fluticasone is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Co-administration of saquinavir/ritonavir with rifampicin is not recommended due to the risk of severe hepatotoxicity. Haemophilic patients should be informed of the possibility of increased bleeding. As somnolence and dizziness are known undesirable effects, this should be taken into account when driving and using machinery.

The oral solution contains alcohol (43%) therefore concomitant administration with disulfiram or drugs with disulfiram-like reactions (e.g metronidazole) should be avoided. Also to be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The soft capsules contain *small* amounts of alcohol, less than 100mg per maximum dose of 600mg. New onset diabetes mellitus, hyperglycaemia or exacerbation of diabetes mellitus has been reported in patients receiving protease inhibitors. Protease inhibitors may be associated with metabolic abnormalities e.g. hypertriglyceridaemia, hypercholesterolaemia. Combination antiretroviral therapy (CART) is associated with lipodystrophy in some patients. Pancreatitis. Immune reactivation syndrome may occur, especially in patients with severe immunodeficiency at initiation of CART. Cases of 20th January 2010 osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. PR interval prolongation has been reported in healthy adults receiving Norvir. Use with caution in patients receiving other drugs that can prolong the PR interval (e.g. verapamil or atazanavir). Norvir oral solution contains castor oil polyoxyl which may cause stomach upset and diarrhoea. It also contains the azo colouring agent sunset yellow (E110) which may cause allergic reactions. Please refer to Interaction section for precautions with other medicinal products.

**Interactions:** Co-administration of Norvir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. Norvir oral solution should not be co-administered with amprenavir oral solution to children due to the risk of toxicity from the excipients in the two formulations. Doses higher than 100mg twice daily of ritonavir with darunavir, saquinavir or fosamprenavir and 100mg once daily with atazanavir is not recommended. Doses of ritonavir less than 200mg twice daily should not be used with tipranavir as it might alter the efficacy of the combination. Risk of nephrolithiasis may be increased when doses of indinavir greater than 800mg twice daily are given with ritonavir. Appropriate doses for ritonavir and nelfinavir have not been established. Dosage alteration should not be necessary when co-

administering ritonavir with zidovudine or didanosine. Higher frequency of adverse events and laboratory abnormalities experienced in patients receiving 500mg ritonavir twice daily with efavirenz 600mg once daily. Ritonavir can be coadministered with maraviroc or nevirapine. Low dose ritonavir should be used in combination with delavirdine. Alfuzosin should not be co-administered with ritonavir. Dose adjustment should be considered based on the patient's clinical response to methadone therapy. Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir. Digoxin levels increase. High dose of theophylline may be required due to induction of CYP1A2. Serum concentrations of anticancer agents (vincristine and vinblastine) may be increased resulting in potential increased incidence of adverse events. Warfarin concentrations may be affected. Dose reduction of desipramine should be considered. An increase in the incidence in trazodone-related adverse events was noted. Concomitant use with fexofenadine is not recommended. Concomitant use of Salmeterol is not recommended. Serum levels should be monitored when used with atovaquone. No dose reduction of clarithromycin should be necessary in patients with normal renal function. Ketoconazole plasma levels can be markedly increased; this interaction can have serious gastrointestinal and hepatic consequences. Dose alteration of sulfamethoxazole/trimethoprim should not be necessary. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended. Caution must be exercised and reduced doses should be used if ritonavir is used concurrently with atorvastatin or rosuvastatin. Alternative methods of contraception should be considered if ethinyl estradiol is used. The recommended dose of bupropion should not be exceeded. Concomitant use with fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Cardiac and neurologic events have been reported when co-administered with disopyramide, mexiletine or nefazadone and the possibility of drug interaction cannot be excluded. Careful monitoring of therapeutic and adverse effects is recommended when amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, amphetamine, fentanyl, carbamazepine, divalproex, lamotrigine, phenytoin, loratidine, erythromycin, itraconazole, haloperidol, risperidone, thioridazine, amlodipine, diltiazem, nifedipine, cyclosporine, tacrolimus, everolimus, parenteral midazolam, alprazolam, buspirone, zolpidem, dexamethasone or prednisolone is concomitantly administered with ritonavir.

#### **Side-effects:**

#### **When ritonavir is dosed as an antiviral agent the following side-effects have been reported:**

*Very common side effects (>1/10):* Taste perversion, circumoral and peripheral paresthesia, headache, abdominal pain, nausea, diarrhoea, vomiting and asthenia.

*Common side effects (>1/100, <1/10):* Allergic reactions including urticaria, mild skin eruptions, angioedema, bronchospasm, decreased WBC, decreased haemoglobin, decreased neutrophils, increased eosinophils, dizziness, hyperaesthesia, paraesthesia, somnolence, insomnia, anxiety, vasodilatation, increased cough, pharyngitis, dyspepsia, anorexia, local throat irritation, flatulence, dry mouth, eructation, mouth ulcer, rash, pruritus, sweating, lipodystrophy, myalgia, increased CPK, fever, pain, weight loss, increased GGT, increased CPK, increased triglycerides, increased SGPT, increased SGOT, increased amylase, increased uric acid, decreased potassium, decreased free and total thyroxine.

*Potentially serious uncommon side effects (>1/1000, <1/100) and rare side effects (>1/10000, <1/1000):* Diabetic mellitus, hepatitis, rhabdomyolysis, anaphylaxis and Stevens Johnson syndrome.

*Unknown frequency:* Thrombocytopenia, hypertriglyceridaemia, hypercholesterolaemia, hyperuricaemia, seizure, syncope, orthostatic hypotension, acute renal failure and menorrhagia. Prescribers should consult the summary of product characteristics for further information on side effects.

**Use in pregnancy and lactation:** The exposure of ritonavir during pregnancy has not been fully established. If a patient becomes pregnant, ritonavir should be used only if the benefits clearly outweigh the risks to the foetus. It is not known whether this medicine is excreted in human milk. HIV infected women should not breast-feed their infants under any circumstances to avoid potential transmission of HIV.

**Overdosage:** Should be treated with gastric lavage, administration of activated charcoal and general supportive measures.

**Legal category:** POM.

**Marketing Authorisation Numbers/ presentation:** Soft Capsules: EU/1/96/016/004; One bottle containing 84 capsules £94.35. Film-Coated tablets: EU/1/96/016/005; One bottle containing 30 tablets £33.70. Oral Solution: EU/1/96/016/001; Five bottles each containing 90ml with graduated dosage cup £403.20.

Further information is available on request from Abbott Laboratories Ltd., Unit 2, Vanwall Road, Vanwall Business Park, Maidenhead, Berkshire SL6 4XE.  
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