BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

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Dear Doctor:

Nevirapine (Viramune®) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination antiretroviral therapy for treatment of HIV. Two strengths of nevirapine tablets are now available through the BC Centre for Excellence in HIV/AIDS (BC-CfE): The original 200 mg *immediate release (IR)* tablets and new 400 mg *extended release (XR)* tablets. The **400 mg XR tablets are the preferred dosage form** for once daily nevirapine dosing in adults for the following reasons: i) XR tablets achieve more consistent nevirapine serum levels than IR tablets, ii) XR tablets permit regimen simplification, iii) XR tablets are the only nevirapine formulation officially indicated for once daily dosing and iv) XR tablets provide a substantial cost savings.

Two clinical trials have demonstrated that nevirapine XR tablets are non-inferior to IR tablets. The **VERxVE** study randomized 1011 treatment naive patients to either nevirapine 400 mg XR once daily or 200 mg IR twice daily in combination with tenofovir and emtricitabine. All participants received nevirapine 200 mg IR daily for 14 days prior to randomization. Both groups had comparable suppression of HIV viral load, with 81.0% of XR and 75.9% of IR-treated achieving virological response at 48 weeks. Post-randomization adverse event rates were similar in both groups, with fewer hepatic events in the XR group (5.5%) compared to IR (9.1%).

In the **TRANxITION** study, 443 virologically suppressed patients treated with nevirapine 200 mg IR twice daily in combination with 2 NRTIs for > 18 weeks were randomized to either remain on IR tablets (n= 148) or switch to 400 mg XR once daily (n=295). After 24 weeks, both groups maintained virological suppression (94% of XR, 93% of IR -treated). In this un-blinded study, more patients who switched to XR reported mild gastrointestinal (20.7% XR, 4.7% IR) or mild general symptoms (9.8% XR, 5.4% IR) than those remaining on IR; however, only 3/295 (1%) XR-treated participants discontinued nevirapine due to an adverse event.

How to SWITCH patients from nevirapine IR to nevirapine XR tablets:
Adults who are currently taking a total daily dose of 400 mg nevirapine IR (either once daily or divided twice a day) are candidates for switching to 400 mg XR once daily. Pharmacists require prescriber authorization to switch between IR and XR tablets, but BC-CfE approval is not required. To facilitate the switch to nevirapine XR tablets, the BC-CfE printed refill prescriptions will include a pre-printed nevirapine medication order change which prescribers may choose to sign to authorize a switch to the XR formulation. Please discuss a potential switch to nevirapine XR with your patients.

How to INITIATE nevirapine XR therapy

Nevirapine may be used as an **alternative** to first-line antiretroviral therapy in patients who meet criteria established to minimize the risk of **serious hepatic and cutaneous adverse events** including Stevens-Johnson syndrome. Risk of these hypersensitivity reactions is greatest during the first 18 weeks of therapy, particularly the first 6 weeks.

Do NOT initiate or re-start nevirapine in the following circumstances unless potential benefit outweighs the risk:

- The patient has a history of severe rash or liver toxicity associated with nevirapine use.
- **Current HIV viral load is detectable** (> 40 copies/mL) AND **current CD4** count is **>400 cells/mL** in males OR **>250 cells/mL** in females.
  (Note: these CD4 thresholds are not applicable if the current viral load is undetectable)
- Co-infection with Hepatitis B or C, severe hepatic dysfunction or concurrent use of other drugs known to cause liver injury.

Avoid simultaneously starting nevirapine with other medications commonly associated with rash (e.g. trimethoprim-sulfamethoxazole).

Monitor hepatic enzymes (AST, ALT) and bilirubin at week 2, then monthly for the first 4 months. Instruct the patient to promptly report onset of rash. Severe rash, blisters, mucous membrane involvement or rash with systemic symptoms requires immediate medical attention.

Caution: Nevirapine has a long half-life and hypersensitivity reactions may continue to worsen even after discontinuation. Stopping nevirapine at the **first sign** of rash or liver toxicity which develop during the first 18 weeks of treatment may reduce the severity of reaction.

Dosage schedule for initiating nevirapine or re-starting after > 7 day therapy interruption:

Nevirapine dose escalation reduces the risk of rash.

- 200 mg IR tablets once daily for 14 days THEN
- 400 mg XR tablet once daily thereafter.

Dosage schedule for switching directly to nevirapine from another NNRTI:

Prior treatment with another NNRTI such as efavirenz, etravirine or rilpivirine for >14 days induces the liver enzymes that metabolize nevirapine. To ensure therapeutic serum concentrations, nevirapine is generally initiated at full dose (400 mg XR tablet once daily) when switching directly from another NNRTI.

For more information about nevirapine 400 mg XR tablets contact the St Paul's Hospital Ambulatory Pharmacy 604-806-8151 or 1-800-547-3622 (outside greater Vancouver).

Yours sincerely,

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