BRITISH COLUMBIA CENTRE for EXCELLENCE in HIV/AIDS

Providence HEALTH CARE
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Pharmacovigilance Initiative
SAFETY ALERT
No.4, September 2012

Nevirapine XR (Viramune XR™) tablet remnants in stool

Sentinel event

The BC Centre for Excellence in HIV/AIDS (BC-CfE) Pharmacovigilance initiative has received several reports of patients observing nevirapine 400 mg extended release (XR) tablets (Viramune XR™) "whole" tablets and/ or tablet fragments in their stool (feces). Patients who have handled these remnants have found them to be a soft, friable mass. In BC, approximately 4% of patients treated with nevirapine XR have reported seeing tablet remnants in their stool. To date, this phenomenon has not been associated with treatment failure.

Background

- Nevirapine 400 mg XR tablets are formulated in a non-digestible cellulose-based hydrophilic polymer matrix called hypromellose, with the drug dispersed throughout the matrix. Upon contact with water in the gastrointestinal (GI) tract, the polymer becomes hydrated and drug is released by tablet erosion.[1] Nevirapine particles dissolve in GI fluid and are absorbed. Remnants of the hydrated matrix are eliminated in the stool.
- In the VERxVE and TRANxITION clinical trials, a total of 15/ 801 (1.9%) of study participants receiving nevirapine XR reported tablet remnants in their stools.[1-,3] All 15 participants achieved the primary study endpoint of sustained virologic response (< 50 copies/mL) and all had nevirapine trough plasma concentrations comparable to the overall study sample. Tablet remnants retrieved from the feces of three clinical trial participants were analyzed and found to contain nevirapine concentrations 22.8-42.2% of the original nevirapine concentration found in nevirapine XR tablets.[1]
- The Viramune XR product monograph states: "Occasionally, the inactive ingredients of Viramune extended-release tablets will be eliminated in the faeces as soft, hydrated remnants".[4] The product manufacturer acknowledges that "after swelling of the Viramune XR tablet from water absorption, the remnants may appear as 'whole' tablets".[5] However, the manufacturer also notes that under "normal" passage through the GI tract under normal physiologic conditions, the observed tablet remnants would not be expected to be whole, intact tablets containing the entire original nevirapine content.[5]
- The product manufacturer has conducted additional quality control tests on tablet samples returned from BC and found that these samples met "all product specifications for dissolution performance".[6]
- **To date, there are no known cases of treatment failure associated with nevirapine XR tablet remnants in the stool**, either in British Columbia or in the manufacturer's global database.[1-6]

Recommendations

There is currently no safety concern associated with the observation of nevirapine XR tablets or tablet fragments in the stool under normal physiological conditions. Prior to prescribing nevirapine XR tablets, consider:

- Patients who have abnormally rapid gastrointestinal transit time or other gastrointestinal pathology which could impair absorption of an extended release formulation may NOT be good candidates for nevirapine XR.
- Patients who currently take nevirapine 200 mg tablets twice daily, and who have other antiretroviral medications which must be taken twice daily may prefer to remain on the 200 mg immediate release tablets.

- Discuss the new tablet formulation with the patient and ensure that he/ she is aware of the new medication strength and the possibility that visible tablet remnants may be eliminated in the feces.
- Following a switch to nevirapine XR tablets, conduct routine HIV plasma viral load monitoring. Measure the first HIV plasma viral load within three months, or prior to the next refill, whichever is sooner.
    - If the patient experiences an HIV viral load "blip" (>40 but <250 copies/mL), consider repeating the viral load in one month.
    - If a possible loss of virologic suppression is noted (>250 copies/mL), order drug resistance testing and repeat the HIV viral load in one month.
    - More frequent monitoring may be indicated if the patient develops a gastrointestinal illness which could potentially affect medication absorption, or if the patient notes *frequent* passage of apparently "whole" nevirapine XR tablets.

References

1) Letter; Medical Affairs, Boehringer Ingelheim (Canada). July 13, 2012.

2) Gathe J, Andrade-Villanueva J, Santiago, S. et. al. Efficacy and safety of nevirapine extended-release once daily versus nevirapine immediate-release twice-daily in treatment-naïve HIV-1-infected patients. Antiviral Therapy 2011; 16:759-769.

3) Arasteh K, Ward D, Plettenberg A, et. al. Twenty-four-week efficacy and safety of switching virologically suppressed HIV-1-infected patients from nevirapine immediate release 200 mg twice daily to nevirapine extended release 400 mg once daily (TRANxITION). HIV Medicine 2012; 13(4): 236-244.

4) Viramune XR (nevirapine 400 mg extended release) product monograph. Boehringer Ingelheim (Canada). May 2011.

5) Report; Boehringer Ingelheim Global Pharmacovigilance. Safety assessment Viramune Extended-Release (XR) tablets in the stool. August 3, 2012.

6) Letter; Medical Affairs, Boehringer Ingelheim (Canada). August 23, 2012.

Thank you for reporting suspected adverse reactions to antiretroviral drugs

How to report: Complete the adverse reaction section on the HIV drug prescription request or therapy discontinuation form (available to HIV care providers) or download an adverse reaction report form at www.cfenet.ubc.ca (available to any health care provider, patient or caregiver).

Contact the BC-CfE Pharmacovigilance Initiative:
Telephone: 604-806-8663 Fax: 604-806-9044 E-mail: ADR@cfenet.ubc.ca

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