BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

St. Paul's Hospital
613-1081 Burrard Street
Vancouver, BC
Canada V6Z 1Y6

Tel 604.806.8477
Fax 604.806.8464
www.cfenet.ubc.ca

August 13, 2012

Dear Doctor,

Complera™ and rilpivirine (Edurant™) are now approved as "extended access agents" in the BC Centre for Excellence in HIV/AIDS Drug Treatment Program (DTP). These agents are primarily indicated as an alternative to efavirenz based therapy for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-naïve adults who have demonstrated intolerance to efavirenz or are not eligible to use efavirenz.

Complera™ is a fixed-dose combination product containing rilpivirine, tenofovir and emtricitabine and can be used alone, while rilpivirine is used as part of combination therapy with a minimum of two other antiretroviral agents.

Complera™ or rilpivirine prescriptions will be reviewed as "extended access" DTP drug requests. Clinical concerns associated with use of these agents are summarized in the attached document. These include potency concerns in patients with baseline HIV-1 viral loads >100,000 copies/mL, requirements for a normal to high calorie meal around the time of drug administration and contraindications with concomitant medications that increase gastric pH or induce CYP 3A enzymes and lower rilpivine exposure.

All Complera™ or rilpivirine drug requests must specifically include the justification for use. Any requests that do not include this information will be forwarded back to the prescriber and the drug request will be held until this information is received.

Yours sincerely,

Julio S. G. Montaner, MD, DSc (hon), FRCPC, FCCP, FACP, FRSC
Professor of Medicine, Chair in AIDS Research and Head of Division of AIDS,
University of British Columbia;
Director, BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Providence Healthcare;
Founding National Co-Director, CIHR Canadian HIV Trials Network
Past-President, International AIDS Society

Valentina Montessori, MD, FRCPC
Clinical Associate Professor
Division of Infectious Diseases, UBC;
Co-Chair, Drug Evaluation & Therapy Committee
BC Centre for Excellence in HIV/AIDS

BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

St. Paul's Hospital
613-1081 Burrard Street
Vancouver, BC
Canada V6Z 1Y6

Tel 604.806.8477
Fax 604.806.8464
www.cfenet.ubc.ca

BC-CfE Recommendations for the Use of Rilpivirine and Complera®:

Summary:

Rilpivirine is available as an **"extended access agent"** from the BC-CfE to be used primarily as an alternative to efavirenz in combination with other antiretroviral agents, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-naive patients who have demonstrated intolerance to efavirenz or are not eligible to use efavirenz. Because of remaining concerns regarding potency, rilpivirine should be avoided as initial treatment if the baseline plasma viral load is above 100,000 copies/mL.

Rilpivirine is available as a single drug or in a fixed dose combination with tenofovir and emtricitabine (Truvada®) under the name of Complera®.

Treatment substitutions from efavirenz or ritonavir boosted PIs to rilpivirine may be considered among patients who are fully and consistently undetectable on first line HAART, if there are significant tolerability issues to other alternative NNRTIs. To what extent a pre-HAART baseline plasma viral load above 100,000 copies/mL will affect rilpivirine efficacy in this setting has not yet been investigated. Expert advice should therefore be sought in such cases; and careful consideration should be given to alternative treatment options with more favorable efficacy profiles in this setting.

Treatment substitution from ritonavir boosted PI based HAART to rilpivirine based HAART should not be recommended if there are any concerns that the dual nucleoside backbone may be compromised because of partial drug resistance. This is relevant given the relative lower genetic barrier and lower potency of rilpivirine in comparison to ritonavir boosted PI based HAART.

Also of note, rilpivirine is potentially more expensive than other therapeutic options. Particularly when it is considered that some of the alternatives are or soon will become generic.

In view of the above considerations, rilpivirine is an "extended access agent" within the BC-CfE Drug Treatment Program and therefore rilpivirine requests should specifically include the justification for the use of this agent. Requests for rilpivirine will be reviewed separately by the BC-CfE staff.

Rilpivirine - Background Information:

Rilpivirine is available from the BC-CfE to be used primarily as an alternative to efavirenz in combination with other antiretroviral agents, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-naive patients who have demonstrated intolerance to efavirenz or are not eligible to use efavirenz. Because of remaining concerns regarding potency, rilpivirine should be avoided as initial treatment if the baseline plasma viral load is above 100,000 copies/mL.

Rilpivirine is also available as the fixed dosed combination tablet of Complera®, containing emtricitabine + tenofovir + rilpivirine, as an alternative to Atripla® (emtricitabine + tenofovir + efavirenz), with the same caveat listed above.

As discussed below, rilpivirine and Complera® should be taken with a normal to high calorie meal, and they should not be used with PPIs or CYP3A4 inducers.

Switching to Complera:

Preliminary evidence (Cohen C, et al. EACS 2011. Abstract LBPS 10/4) suggests that individuals who are continuously virologically suppressed (confirmed HIV-1 RNA less than 40 copies/ml) on Atripla® for at least three months can be switched to Complera®. The switch is to be done in full from one day to the next. To what extent a pre-HAART baseline plasma viral load above 100,000 copies/mL will affect rilpivirine efficacy in this setting has not yet been investigated. Preliminary evidence presented at IAC 2012 suggests that switches from ritonavir boosted PI based HAART to rilpivirine based HAART also viable, however, the same caveats apply. Treatment substitution from ritonavir boosted PI based HAART to rilpivirine based HAART should not be recommended if there are any concerns that the dual nucleoside backbone may be compromised because of partial drug resistance. This is relevant given the relative lower genetic barrier and lower potency of rilpivirine in comparison to ritonavir boosted PI based HAART. Expert advice should therefore be sought in such cases; and careful consideration should be given to alternative treatment options with more favorable efficacy profiles in this setting.

At this time there is no data regarding efficacy and safety of treatment switches from other regimens (such as Raltegravir, Maraviroc or Nevirapine based regimens) to Complera®, and therefore this cannot be recommended. In circumstances where these kinds of switches are deemed necessary, expert guidance is recommended. To what extent pre-HAART baseline characteristics will affect rilpivirine efficacy in this setting has not yet been investigated. Expert advice should therefore be sought in such cases; and careful consideration should be given to alternative treatment options with better-characterized efficacy profiles in this setting.

Special Considerations when Using Rilpivirine or Complera®:

Resistance to the NNRTI class, to emtricitabine (FTC) and lamivudine (3TC) and to tenofovir was observed with increased frequency when patients had virological failure with Complera® than with Atripla®. This should be considered when selecting an initial drug regimen, as emergence of NNRTI, emtricitabine and/or tenofovir can compromise future drug options. As always, the need for full adherence and careful virological monitoring should be stressed, particularly when rilpivirine based therapy is used.

Food increases rilpivirine exposure by 57% compared to fasting. This effect is similar with a high-fat meal of approximately 1000 Cal or a standard breakfast of approximately 500 Cal.

Table: Meal Options Comprising 500-600 kcal

- 2 slices of whole wheat toast with peanut butter, fresh fruit, and 1 cup orange juice (509 calories)
- 2 eggs, 2 strips of bacon, and 2 slices of wheat toast with butter (520 calories)
- 2 toasted breakfast pastries, yogurt, and 1 cup of juice (596 calories)
- Plain bagel with 2 tbsp cream cheese, yogurt, and a banana (569 calories) - Roast beef sandwich on a hard roll with mayonnaise and cheese (582 calories)
- 2 slices of cheese pizza and 1 can of regular soda (550 calories)
- Peanut butter and jelly sandwich on wheat bread, a banana, and 1 cup skim milk (562 calories)
- Veggie burger on a bun with tomato soup and a side salad (500 calories)
- Grilled chicken Caesar salad (521 calories)
- 2 cups of spaghetti with marinara sauce and 1 slice of bread (514 calories)
- Salmon with rice and fresh vegetables (596 calories)
- Tofu and vegetable stir-fry with brown rice and a side salad (527 calories)

Therefore, rilpivirine and Complera® should be taken with a normal to high calorie meal, as illustrated in the Table above. Taking rilpivirine or Complera® with a protein supplement drink alone does not increase absorption.

Proton pump inhibitors (PPI's) reduce the exposure to Rilpivirine by at least 40%. Therefore, Rilpivirine and Complera® should not be used with PPIs, including esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole. An acceptable alternative consists of using an H_2 antagonist given at least 12h before or 4h after dosing, or to use antacids given ≥2h before or ≥4h after dosing. H_2 antagonists taken 2 hours before rilpivirine resulted in 85% reduction in rilpivirine exposure.

Rilpivirine and Complera® should not be used with CYP3A4 inducers, given that these drugs decrease the bioavailability of rilpivirine. These include:
–Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)
–Antimycobacterials (rifabutin, rifampin, rifapentine)
–St. John's Wort (Hypericum perforatum)
–Systemic glucocorticoid (i.e.: dexamethasone).

August 13, 2012