Gilead Quad Tablet Gets FDA Committee Approval Nod

May 11, 2012 By Tim Horn

An advisory committee to the U.S. Food and Drug Administration (FDA) has voted 13 to 1 in support of approval of Gilead's "Quad," the unofficial name for a fixed-dose combination tablet containing elvitegravir, cobicistat, Viread (tenofovir) and Emtriva (emtricitabine). Should the FDA follow the recommendation of its Antiviral Drugs Advisory Committee, which met at the DoubleTree Hotel in Silver Spring on May 11, the drug will be the third all-in-one regimen to be approved by the agency.

Gilead is requesting approval of the Quad for people living with HIV starting HIV treatment for the first time.

The panel's sole "no" vote was cast by Michelle Estrella, MD, of Johns Hopkins University School of Medicine. She was unable to support recommending approval, she said, because of lingering concerns about the Quad's potential effects on kidney function, along with the limited amount of data involving women participating in the clnical trials conducted to date.

The new drug application (NDA) submitted by the company marks the first time the FDA has been asked to give marketing clearance to a fixed-dose combination tablet containing two drugs that have not, individually, been reviewed and approved by the agency. Elvitegravir, the company's experimental integrase inhibitor, requires boosting to be maximally effective and to allow once-daily dosing. For this—and as a potential alternative to low-dose Norvir for use in combination with other medications—Gilead has developed cobicistat, a potent pharmacokinetic enhancer without any activity against HIV.

The approval recommendation was based primarily on the 48-week results of two, nearly identical, Phase III clinical trials: Gilead studies 102 and 103. Both studies were conducted to determine if the Quad was non-inferior—no better, no worse—to standard regimens currently used to treat HIV. Study 102, which is ongoing, compares the Quad with Atripla (efavirenz plus tenofovir and emtricitabine). Study 103, also ongoing, compares the Quad to Norvir (ritonavir)-boosted Reyataz plus Truvada (tenofovir plus emtricitabine).

A total of 1,408 were randomized in both studies; 701 were allotted to receive the Quad, 352 received Atripla and 355 received Norvir-boosted Reyataz plus Truvada. All volunteers in Study 102 were recruited in the United States, compared with 54 percent of those in Study 103.

After nearly a year of treatment, 87.6 percent of those receiving the Quad, compared with 84.1 percent of those receiving Atripla, had viral loads below 50 copies in Study 102. In study 103, 89.5 percent in the Quad group, compared with 86.8 percent of those in the Norvir-boosted Reyataz group, had undetectable viral loads.

During the advisory committee meeting, it was noted that the Quad was comparable to the other regimens regardless of gender, race, age, region, and pre-treatment viral loads and CD4 cell counts. However, the FDA noted, “the percentage of women enrolled across study arms was low, between 8 and 12 percent.”

In both studies, the Quad was well tolerated and most adverse events were mild to moderate. The most common adverse events observed were nausea, diarrhea, upper respiratory tract infection and headache.

Compared with patients taking Atripla or Norvir-boosted Reyataz, fewer people stopped therapy with the Quad because of treatment-related side effects. Discontinuation rates because of adverse events were 5.1 percent in both the Atripla and Norvir/Reyataz groups, compared with 3.7 percent in the combined Quad groups.

As for specific side effects, the FDA analysis of the data indicated that headache was more common among those receiving the Quad compared with the comparator regimens. However, more than 95 percent of the headaches reported were mild in severity. And while central nervous system complications—notably abnormal dreams and insomnia—were more common among those using the Quad compared with those using Norvir-boosted Reyataz plus Truvada, they were more likely to occur among those receiving Atripla compared with those taking the Quad.

Of particular concern to the FDA reviewers was the higher number of kidney-related complications among those taking the Quad compared with the comparator regimens. Previous studies have suggested that both cobicistat and tenofovir may independently increase the risk of kidney problems.

In both Phase III studies, eight patients in the Quad group discontinued treatment due to kidney-related side effects—three patients with kidney failure, one with Fanconi syndrome (which causes the kidneys to pass healthful substances into the urine, not into the blood) and four patients with increased creatinine levels in the blood, a potential marker of kidney disease.

One patient in the Norvir-boosted Reyataz group discontinued treatment because of a kidney-related side effect, judged to be related to his ARV regimen.

The FDA reviewers also noted higher rates of decreased estimated creatinine clearance and glomerular filtration rates (eGFR) —additional markers of potential kidney damage, based on urine and blood testing—among those in the combined Quad group, compared with those receiving the comparator regimens. Gilead, however, argued that while the cobicistat in the Quad inhibits creatinine secretion by the kidneys’ tubules, it is not actually harming kidney function. This

suggestion by the company is based on highly specific kidney function testing of patients in studies 102 and 103, as well as those in another clinical trial (Gilead study 121).

“The disproportionate number of renal adverse events leading to study drug discontinuation in the [Quad] group, combined with a higher frequency of graded serum creatinine and urine protein abnormalities, raise a question as to whether two discrete processes may be at work: a non-pathologic decrease in eGFR as [Gilead] maintains and a bone fide increased risk of renal dysfunction," the FDA reviewers noted in a pre-meeting briefing document. "The difficulty arises in assessing for and rapidly discriminating between these two events, as a modest elevation in creatinine and modest decline in eGFR is anticipated with the use of [the Quad], but prolonged use in the setting of renal injury should be avoided.

Gilead has, however, proposed kidney safety measures for patients and health care providers considering the Quad, including pre-treatment measurements of creatinine clearance and a recommendation that the Quad be discontinued if creatinine clearance falls below a specified threshold.

Gilead will also recommend routine monitoring of creatinine clearance and other kidney health measurements during treatment with the Quad and will warn against combining the Quad with other kidney-toxic medications.

The FDA is expected to decide whether or not to act on the advisory committee’s vote and discussion points on or before August 27.

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