U.S. FOOD & DRUG ADMINISTRATION

BARACLUDE: Updates to Adverse Reactions from Long-Term Observational Study

November 8, 2019

FDA recently approved changes to the BARACLUDE® (entecavir) tablets and oral solution product labeling. The revisions are in response to a post marketing commitment related to a large simple safety study to assess the major clinical outcomes of death, progression of liver disease, and cancer in a broad population of HBV-infected patients using entecavir compared to standard of care over a period of 5 to 10 years of follow-up.

Section 6.2 Postmarketing Experience was updated to include the following

Data from Long-Term Observational Study

Study AI463080 was a randomized, global, observational, open-label Phase 4 study to assess long-term risks and benefits of BARACLUDE (0.5 mg/day or 1 mg/day) treatment as compared to other standard-of-care HBV nucleos(t)ide analogues in subjects with chronic HBV infection.

A total of 12,378 patients were treated with BARACLUDE (n=6,216) or other HBV nucleos(t)ide treatment [non-entecavir (ETV)] (n=6,162). Patients were evaluated at baseline and subsequently every 6 months for up to 10 years. The principal clinical outcome events assessed during the study were overall malignant neoplasms, liver-related HBV disease progression, HCC, non-HCC malignant neoplasms, and death. The study showed that BARACLUDE was not significantly associated with an increased risk of malignant neoplasms compared to other standard-of-care HBV nucleos(t)ides, as assessed by either the composite endpoint of overall malignant neoplasms or the individual endpoint of non-HCC malignant neoplasms. The most commonly reported malignancy in both the BARACLUDE and non-ETV groups was HCC followed by gastrointestinal malignancies. The data also showed that long-term BARACLUDE use was not associated with a lower occurrence of HBV disease progression or a lower rate of death overall compared to other HBV nucleos(t)ides. The principal clinical outcome event assessments are as follows.

Table 6: Principal Analyses of Time to Adjudicated Events - Randomized Treated Subjects

Endpoint[c]	Number of Subjects with Events		Hazard Ratio [BARACLUDE:Non-ETV] (CI[a])
	BARACLUDE N=6,216	Non-ETV N=6,162	
Primary Endpoints			
Overall malignant neoplasm	331	337	0.93 (0.800, 1.084)
Liver-related HBV disease progression	350	375	0.89 (0.769, 1.030)
Death	238	264	0.85 (0.713, 1.012)
Secondary Endpoints			
Non-HCC malignant neoplasm	95	81	1.10 (0.817, 1.478)
HCC	240[b]	263	0.87 (0.727, 1.032)

Analyses were stratified by geographic region and prior HBV nucleos(t)ide experience.
[a] 95.03% CI for overall malignant neoplasm, death, and liver-related HBV disease progression; 95% CI for non-HCC malignant neoplasm and HCC.
[b] One subject had a pre-treatment HCC event and was excluded from the analysis.
[c] Overall malignant neoplasm is a composite event of HCC or non-HCC malignant neoplasm. Liver-related HBV disease progression is a composite event of liver-related death, HCC, or non-HCC HBV disease progression.
CI = confidence interval; N = total number of subjects.

Limitations of the study included population changes over the long-term follow-up period and more frequent post-randomization treatment changes in the non-ETV group. In addition, the study was underpowered to demonstrate a difference in the non-HCC malignancy rate because of the lower than expected background rate.

The updated label will soon be available at Drugs@FDA or DailyMed

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