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Shire's Prucalopride Brings Real-World CV Safety Data To US FDA Panel, But Will It Be Enough?

by Sue Sutter

European postmarketing epidemiological study results 'reasonably exclude' a greater than three-fold increased risk of major adverse cardiovascular events with the constipation drug but, due to potential bias, cannot definitively exclude a possibly unacceptable level of risk, agency says.

The US FDA is asking its Gastrointestinal Drugs Advisory Committee whether the results from short-term clinical trials and a European postmarketing observational study, which was submitted in lieu of a premarketing safety study, are adequate to characterize the cardiovascular safety of *Shire PLC*'s *Motegrity* (prucalopride) for chronic idiopathic constipation.

In briefing documents released ahead of the Oct. 18 committee meeting, FDA suggests that while Shire has demonstrated efficacy for prucalopride, uncertainties remain about the selective serotonin type 4 (5-HT4) receptor agonist's cardiovascular (CV) safety, given the limitations of the available data and a history of CV concerns with this class of drugs.

A key question for Shire will be whether prucalopride, which was approved as *Resolor* by the European Medicines Agency in 2009, can finally come to the US market without need for a dedicated CV safety study.

A broader question for the agency – as well as a biopharma industry eager to see FDA use real-world data to support regulatory decision-making – is the

AdComm Voting Questions

- Do the clinical trial data provide substantial evidence of effectiveness of prucalopride for the treatment of adults with chronic idiopathic constipation (CIC)?

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extent to which advisory committee members are comfortable relying upon the European observational study in their safety determination.

FDA's briefing document makes clear the agency's own hesitations. Although reviewers accept the findings of the European retrospective observational study (SPD555-802) as evidence that reasonably excludes a greater than three-fold increased risk of major adverse cardiovascular events (MACE), "because of the serious potential for bias due to confounding, FDA could not use SPD555-802 to reliably bound MACE risk at levels lower than three-fold."

- Has the potential risk of cardiovascular adverse events with the use of prucalopride in adults with CIC been adequately addressed by the applicant?
- Does the risk-benefit profile of prucalopride support the approval of this application?

The agency poses three voting *questions* on efficacy, safety and overall risk-benefit. *(See box.)*

Long-Delayed NDA Relies Heavily On Foreign Data

Shire submitted the prucalopride new drug application (NDA) on Dec. 21, 2017 for treatment of chronic idiopathic constipation (CIC) in adults. (Also see "*Keeping Track: FDA Approves Novel HIV Treatment, New Dosing Regimen For Opdivo; Another Rare Pediatric Disease Designation For Prometic*" - Pink Sheet, 11 Mar, 2018.) The recommended dose is 2 mg once daily, reduced to 1 mg once daily for geriatric patients and individuals with severe renal impairment.

If approved, prucalopride "would offer a different class of drugs for the treatment of CIC compared to the currently available therapies in the US," FDA's briefing *document* states.

The drug's development for the US market was stalled for many years. Development was subject to a clinical hold due to genotoxicity and carcinogenicity concerns, and the investigational new drug application (IND) was inactive from July 2004 to September 2012, according to FDA's briefing document.

The NDA includes data from two 12-week, Phase III trials (PRU-CRC-3001 and SPD555-302) completed in 2011 and 2013, respectively, as the primary basis to demonstrate efficacy in support of FDA approval. Both trials were conducted in non-US populations. The application also contains data from three other 12-week, Phase III legacy trials, completed in 1999, to support the generalizability of efficacy results to the US patient population.

In addition, data were submitted from a 24-week Phase IV trial (Study SPD555-401) that was conducted in Europe and completed in 2012.

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CV Safety A Class Concern

FDA notes there have been CV and psychiatric safety concerns with the class of 5-HT4 agonists developed to treat gastrointestinal motility disorders.

Two drugs in the class – *Johnson & Johnson*'s heartburn drug *Propulsid* (cisapride) and *Novartis AG*'s constipation drug *Zelnorm* (tegaserod) – have had a checkered postmarketing history in the US.

In 2000, J&J halted sales of cisapride due to postmarketing reports of serious cardiac arrhythmias and deaths. In 2007, Novartis suspended US marketing of tegaserod after a pooled analysis from 29 placebo-controlled clinical trials showed a higher rate of ischemic CV events in patients taking the drug.

Tegaserod remains available under a treatment IND, and its current sponsor is *US WorldMeds LLC*. (Also see "*US FDA Reviews IBS-C Candidates Both New (Tenapanor) And Old (Tegaserod)*" - Pink Sheet, 16 Sep, 2018.) On Oct. 15, the Gastrointestinal Drugs Advisory Committee will consider a supplemental NDA from Sloan Pharma, a US WorldMeds subsidiary, to return tegaserod to market for treatment of women with irritable bowel syndrome with constipation and low CV risk. (Also see "*US FDA Seems Ready For Return Of Zelnorm, But Seeks Advice On Best Subpopulation*" - Pink Sheet, 16 Oct, 2018.)

In November 2011, FDA convened its external experts to consider whether premarketing CV safety studies, similar to those conducted for type 2 diabetes drugs, should be required for 5-HT4 agonists.

A majority of advisory committee members voted against recommending dedicated CV safety trials but said that Phase III efficacy trials should include patients at high risk for CV events. (Also see "*FDA May Ease Up On CV Safety Requirements For GI Motility Drugs Compared To Diabetes, Obesity*" - Pink Sheet, 5 Dec, 2011.)

At a July 2012 Type C meeting with Shire, FDA said that given the drug class's history and the 2011 advisory committee, it has requested that the safety development program for 5-HT4 agonists include initiation of a premarketing trial with adequate CV safety evaluation as its primary objective. The size should be large enough to rule out a hazard ratio upper bound for major adverse cardiovascular events (MACE) of 2.0 to provide general assurance of CV safety, the agency said.

However, because prucalopride had been approved in Europe since 2009, the Division of Gastroenterology and Inborn Errors Products ultimately agreed that Shire "could submit results of a non-interventional pharmacoepidemiology study that used national claims data from four European countries (five data sources) in lieu of obtaining controlled clinical data on patients

treated for up to one year premarketing," FDA's briefing document states.

The NDA safety database includes data from short-term clinical trials as well as the non-interventional epidemiologic study (SPD555-802) conducted to estimate the adjusted incidence ratio and 95% confidence interval for MACE in prucalopride compared to polyethylene glycol (PEG). However, FDA's briefing document notes the lack of long-term (at least 12-month duration) controlled trials to inform the safety of prucalopride, a drug that would be used on a chronic basis.

Small Number Of MACE Events

FDA's briefing document makes clear that the numbers of MACE events in the clinical program were small.

For standard MACE (comprising CV death, non-fatal myocardial infarction and non-fatal stroke), there were two events each in the placebo group (0.1%, n=2,019) and in the double-blind, all-doses prucalopride group (0.1%, n=3,366).

"This small number may be explained by the lower baseline risk characteristics of the patient population included in the MACE analysis or other limitations of the available data or the duration of the trials (≤12 weeks)," FDA said.

Furthermore, there were low percentages of patients with standard MACE and extended MACE (defined as standard MACE plus unstable angina requiring hospitalization) in the overall safety database, which included open-label trials, "and the majority of these patients had baseline cardiovascular risk factors, thereby possibly confounding the causality determination," FDA said.

> ***Patients were identified using electronic medical records, administrative claims or national health-data registers, and the pooled analyses included 35,087 patients treated with prucalopride or polyethylene glycol.***

Study 802, the retrospective observational study, was designed to exclude a three-fold increased risk with prucalopride on a MACE endpoint comprising hospitalization for acute myocardial infarction, hospitalization for stroke, and in-hospital CV death. The primary analysis combined data from patients in the UK and Sweden.

Patients were identified using electronic medical records, administrative claims or national health-data registers, Shire's briefing *document* states. The pooled analyses included 35,087 patients treated with prucalopride (n=5,715) or PEG (n=29,372). The average total duration of use was 175 days for prucalopride and 82 days for PEG

In the primary analysis, the estimated MACE standardized incidence rate ratio (SIRR) for prucalopride compared to PEG was 0.64 (95% CI: 0.36-1.13). In a subgroup analysis in men ages 55 years and older, the SIRR for prucalopride was 2.57 (95% CI: 0.71 to 9.29).

FDA's assessment of Study 802 reached two main conclusions. Although the study satisfied a pre-NDA expectation for a European postmarketing observational study that reasonably excluded, with 95% statistical confidence, a three-fold MACE risk with prucalopride, it "does not definitively exclude" a possibly unacceptable level of MACE risk, the agency said.

"Primarily because of a concern about serious risk of bias due to confounding, FDA placed low confidence in the quantitative result, i.e., SIRR 0.64, from the SPD555-802 primary analysis," the briefing document states. "Interpreting this quantitative result as causally valid, a patient starting treatment might expect to suffer a 36% lower incidence of a subsequent major cardiovascular event, if started on prucalopride instead of PEG. However, the serious risk of bias due to confounding demanded more cautious interpretation."

Confounding factors included a generalized potential for channeling profoundly different patients to treatment with prucalopride or PEG, and patient-years in prucalopride and PEG distributed differently based on age and other baseline factors.

Shire asserts that prucalopride has demonstrated a well-tolerated safety profile.

"The clinical safety profile of prucalopride is also supported by over 282,000 years of patient exposure since its initial approval in the EU in 2009," the company's briefing document states. "Across eight years of real-world experience, the majority of reported post-marketing AEs have been non-serious, and no cardiovascular signal has been detected."

FDA's review of the clinical data also noted a "small number of events related to completed suicide and suicidal ideation which are also reviewed as a potential class issue." Nevertheless, "in general, the safety data submitted for patients treated with prucalopride at multiple doses (0.5 mg, 1 mg, 2 mg, and 4 mg) resulted in small numbers of patients with psychiatric adverse events."

Efficacy Appears Adequate

FDA appears more settled on prucalopride's efficacy than on the adequacy of its CV safety data.

All five of the Phase III trials in the NDA achieved statistical significance for the primary efficacy endpoint. "The treatment benefit of prucalopride compared to placebo for the five successful trials ranged from 10 to 23% of patients meeting the responder definition for the primary endpoint (defined by a mean of ⩾3 spontaneous complete bowel movements [SCBMs] per week over the 12-week treatment period)," the agency said.

However, Study 401, the 24-week Phase IV study, did not achieve statistical significance at week 12 or 24. Although the treatment effect in this study was lower than was seen in the Phase III trials, the prucalopride treatment group did have a numerically higher response rate at week 12 compared to the placebo group (25% versus 20%).

Efficacy analyses conducted using FDA's currently recommended endpoint for trials evaluating treatment of CIC (referred to in the briefing document as "Alternative Endpoint A") demonstrated a treatment benefit of prucalopride over placebo with a range of 6% to 16% of patients meeting the responder definition. "This treatment difference is generally consistent with what has been demonstrated for other approved products using similar efficacy endpoints (approximate range 8 to 17% treatment difference from placebo)," FDA said.