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Before Endocrinologic and Metabolic Drugs Advisory Committee
Meeting on Muraglitazar (Pargluva)
Silver Spring, MD
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In our comments today, we will first focus on the evidence for the efficacy of muraglitazar, then on its safety data and finally will draw the safety and efficacy data together. In sum, we do not believe the risks outweigh the benefits for this drug.

Efficacy

Although the sponsor has demonstrated that muraglitazar can reduce hemoglobin A_{1C} by a modest amount and can reduce triglycerides and raise HDL to a somewhat less-impressive degree, the following must be kept in mind:

• As noted by the statistical reviewer, the doses of pioglitazone used as comparators in various studies tend to put muraglitazar in a favorable light. Although pioglitazone is approved in 15mg, 30mg and 45mg dosage forms, only the 15mg (Study 006) and 30mg (Study 025) were used in the muraglitazar trials. This is one of the oldest tricks in the drug company playbook: comparing your drug to an underdosed competitor.

• The statistical reviewer notes that the 5mg dosage form has only "small incremental efficacy" compared to the 2.5mg form. Given the safety concerns, which seem to be clearly dose-related, the risk-benefit ratio for the 5mg form seems to be particularly adverse.

• The possibility of approving a 1.5mg dosage form has been raised, but none of the four Phase III trials actually tested the 1.5mg dosage form. Only the Phase II study did, and it did not contain a placebo group (the lowest-approved pioglitazone dose was used as a comparator). In our view, this does not provide a firm enough evidence base to conduct a risk-benefit assessment.

• Most fundamentally, the studies were not designed to look at hard diabetes outcomes such as micro- or macrosvascular disease. The randomized portions of the studies were of only 24 weeks' duration, so we know little about muraglitazar's impact, if any, on these outcomes. To the extent that hard outcomes such as deaths or cardiovascular-related deaths were evaluated, the data show the drug to be associated with an adverse impact.

Safety

Deaths

The most striking toxicity finding is the apparent increase in deaths – both total and cardiovascular – among patients taking muraglitazar in the clinical trials. The percentages suffering death from any cause in the muraglitazar, pioglitazone and placebo groups were 0.59%, 0.24% and 0.17%, respectively. For cardiovascular deaths, these percentages were 0.28%, 0% and 0.17%. According to the sponsor, the relative risks for 2.5mg and 5mg muraglitazar were 1.7 and 4.6 for all-cause mortality and 2.0 and 5.9 for cardiovascular mortality, respectively. While the sponsor is likely to try to dismiss these findings by claims of differences between the study groups (a claim that cannot be proved or disproved), we believe these findings are to be taken extremely seriously.

Congestive Heart Failure

Considering only the Phase III studies, the rates of congestive heart failure confirmed by the adjudication committee were 0.75% for muraglitazar (2.5mg and 5mg doses only), 0.17% for pioglitazone and 0% for placebo. This toxicity appears to be dose-related and is consistent with the toxicities of the approved PPAR-γ agonists (pioglitazone and rosiglitazone).

Of related concern are the increased rates of dose-related weight gain and edema in muraglitazar-treated patients, leading to many drug discontinuations. The 5mg muraglitazar dose was associated with weight gains of 2.9kg - 3.6kg in the various studies. As the safety reviewer notes, "Given the morbidity associated with obesity in the type 2 diabetic population, significant increases of body weight may limit the use of this drug."

Rhabdomyolysis and Hepatotoxicity

While the clinical trials show only scattered cases of muscle and liver toxicity, these are well-described adverse effects of PPAR-γ and PPAR-α agonists. As the toxicology review explains, the animal studies did not properly test for myotoxicity. If this drug is approved, a registry might help elucidate the magnitude of these risks.

Carcinogenicity

Muraglitazar causes tumors in both rats and mice, in both genders and at multiple sites, and is therefore properly classified as a "probable human carcinogen" using the criteria of the Environmental Protection Agency and the International Agency for Research on Cancer. Moreover, tumors occurred at precisely those sites where PPAR receptor concentration is high: bladder, adipose tissue, gallbladder and uterus. Of greatest concern are bladder carcinomas, which occurred in male rats at as little as eight times the human exposure, a very small multiple given the wide variation among humans in exposure

levels resulting from identical doses. The development of three dual PPAR agonists has been discontinued as a result of similar rodent carcinogenicity findings.

The sponsor will no doubt try to downplay the bladder carcinogenicity findings with a series of mechanistic arguments involving urine pH, crystal formation and citrate levels. However, many of these arguments apply only to male rodents and tumors were observed in both genders. Many of the (often negative) studies conducted in other species were either underpowered, of short duration or inadequately conducted (e.g., failure to use particular staining techniques) and so provide little reassurance.

Comparing benefits with risks

Muraglitazar is a drug with modest ability to reduce hemoglobin A_{1C}, but no proven ability to reduce the micro- and macrovascular complications that are the real concern in diabetes management. On the other hand, it appears to be associated with increased rates of total and cardiovascular deaths, congestive heart failure and weight gain/edema, and is a proven bladder carcinogen. While excitement about the novel action of this drug is understandable, the experience with troglitazone, which was also heralded for its therapeutic effects based on its mechanism of action, demonstrates that in the end the wisest course is to pay attention to the clinical data, not theoretical mechanistic arguments. On the basis of the data presented, muraglitazar does not merit FDA approval.