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# Trial

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A large pile of orange and white pills is the central focus of the cover. The pills are scattered across a vibrant red background. The orange pills are the most numerous, while the white pills are fewer and more prominent. The overall composition is dense and visually striking.

# Drugs & Devices

How big pharma puts patients at risk



# BAD ACTOS

The safety of Actos, an oral diabetes drug that increases the body's sensitivity to insulin, has been increasingly called into question since 2010. That was when the FDA announced that it was "reviewing data from an ongoing, 10-year epidemiological study designed to evaluate whether Actos (pioglitazone) is associated with an increased risk of bladder cancer."<sup>1</sup> The results of the FDA study did not show an overall increased risk of bladder cancer with Actos use but did establish an increased risk among patients with the longest exposure to Actos and in those exposed to the highest cumulative dose of the drug.<sup>2</sup>

Last year, health officials in the United States and Europe issued warnings on the cancer risk that long-term use of Actos poses, and now patients are seeking redress for bladder cancer caused by the drug. New research supports the Actos-cancer link, but the plaintiff lawyer must also have a thorough understanding of the etiology of bladder cancer and a detailed knowledge of the client's medical history.

Research shows a link between the diabetes drug Actos and bladder cancer when patients use the medication for more than a year or in high cumulative doses. Here's what you need to know to argue your client's case.





By || **HOWARD L. NATIONS AND JOHN M. RESTAINO**



The FDA issued a warning in June 2011 that Actos use for more than one year may be associated with an increased risk of bladder cancer,<sup>3</sup> and the French Medicines Agency suspended the use of Actos in 2011<sup>4</sup> based on the results of a retrospective cohort study conducted in France by the National Health Insurance Agency.<sup>5</sup> Research published in *Diabetes Care* last year reaffirmed the drug's risks; researchers evaluated adverse events reported to the FDA from January 2004 to December 2009 and found that the reporting odds ratio (a measure applied to databases to estimate relative risk) of bladder cancer was increased in Actos patients by 330 percent.<sup>6</sup> The European Medicines Agency, prompted by an increased number of spontaneous reports of bladder cancer, concluded that the evidence provided a clinically relevant signal that required further evaluation.<sup>7</sup>

Takeda Pharmaceutical Co., the manufacturer of Actos, disputes the link between the drug and bladder cancer. The company relies on a flawed, industry-funded study conducted in 2005; researchers in that study found that bladder cancer in the Actos group versus the placebo group did not reach the statistical significance required to support causation.<sup>8</sup>

While the study's data and safety monitoring committee reviewed cases with "external experts," it excluded highly relevant data—such as tumors that occurred in patients within one year of entry into the study. This exclusion is not valid because the latency period between exposure to a carcinogen and the development of transitional cell carcinoma—the most common form of bladder cancer—varies between nine months and 23 years.<sup>9</sup> This exclusion makes the study suspect and vulnerable to scrutiny on cross-examination. Committee reviewers also excluded cases that had "known risk factors in their

history (smoking, exposure to potential carcinogens, family history, previous tumor, urinary tract infection)" in finding that bladder cancer was not likely to be a safety issue with Actos.<sup>10</sup>

Takeda researchers revisited the study data in 2009 and reported new findings supporting the company's view—that Actos does not cause bladder cancer and may actually help prevent cancer. "In fact," the researchers wrote, "in vitro studies suggest that pioglitazone may actually inhibit the growth of some neoplastic human urothelial cell lines."<sup>11</sup>

A significant weakness of the 2005 study is the exclusion of patients merely because they had one or more risk factors for bladder cancer. For plaintiffs seeking redress after contracting bladder cancer from taking Actos, there is solace in an unbiased review of the Takeda safety data. Independent researchers recalculated the Actos versus placebo data, adjusted it to take into account concomitant potential risk factors and treatment duration and, in a 2011 letter to the editor

published in the *Lancet*, reported "a significant relation between pioglitazone and bladder cancer, which has not been presented in the [industry-funded] study reports."<sup>12</sup> The independent researchers opined that bladder cancer in patients taking Actos contracted between 2005 and 2010 could have been prevented, but the industry-funded researchers failed to properly assess and report the results of the industry study in 2005:

This finding, associated with the pre-clinical and clinical findings reported on the FDA website in 2004, . . . could have led to an alert five years sooner. With this in mind, pioglitazone prescription could have been restricted, and monitoring of patients strengthened. Given the potential loss of opportunity for patients to have been treated otherwise or at least monitored carefully since 2005, vigilance and checking of all relevant safety data reported in clinical trials are crucial.<sup>13</sup>

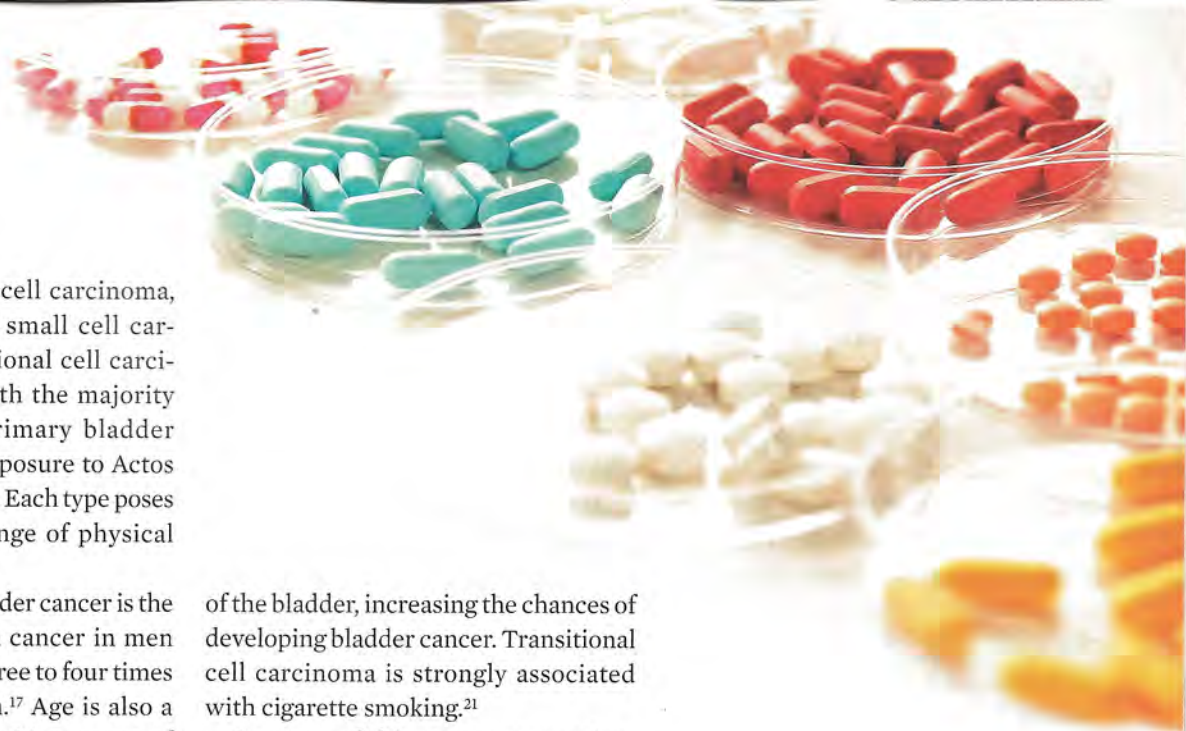
The plaintiffs in pending Actos cases allege that, when ingested for more than one year, Actos is a significant contributing factor in the development of bladder cancer. Plaintiff lawyers must carefully assess each plaintiff for Actos treatment duration, risk factors, and comorbidities for accurate case evaluation, preparation, and presentation. These factors may affect the development of bladder cancer, so Takeda will focus on them in its defense. Takeda is now the defendant in a federal MDL in Lafayette, La., as well as in state court actions in Illinois and California.<sup>14</sup>

### Bladder Cancer

Bladders are vulnerable to the adverse effects of drugs because urine carcinogens or inflammatory agents are stored for a prolonged period close to the cellular lining of the organ. The four types of bladder cancer are transitional cell

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carcinoma, squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. While transitional cell carcinoma is associated with the majority of tobacco-related primary bladder tumors,<sup>15</sup> prolonged exposure to Actos may cause all four types. Each type poses the same potential range of physical damage to the patient.

**Demographics.** Bladder cancer is the seventh most common cancer in men worldwide,<sup>16</sup> and it is three to four times more prevalent in men.<sup>17</sup> Age is also a factor; approximately 90 percent of new cases occur in people over age 55.<sup>18</sup> Caucasians are twice as likely to contract bladder cancer as African-Americans, while Asian-Americans, Hispanics, and Native Americans are even less likely to be diagnosed with bladder cancer.<sup>19</sup>

If you represent a 70-year-old white man with bladder cancer, be prepared to defend the demographic attack. Carefully analyze your case for comorbidities and causative risk factors that may combine with age to render the plaintiff at very high risk for bladder cancer, even without Actos ingestion. This combination of factors may not defeat liability, but it will come into play in assessing comparative causation of damages.

**Risk factors.** A risk factor is anything associated with the risk of developing a disease. Anticipate that the defense will examine the following risk factors and argue that they cause or contribute to causing your client's bladder cancer: smoking, industrial chemical exposure, chronic bladder irritations and infections, and chemotherapy or radiation therapy. Smoking is the most important risk factor for bladder cancer; it has been associated with 50 percent of bladder cancers in developed countries.<sup>20</sup> Carcinogens from inhaling smoke are absorbed through the lungs and into the blood, are filtered by the kidneys, and then are concentrated in urine. These carcinogens can damage the cells that line the inside

of the bladder, increasing the chances of developing bladder cancer. Transitional cell carcinoma is strongly associated with cigarette smoking.<sup>21</sup>

Because of this strong connection, some attorneys may not accept bladder cancer cases in which the client is a smoker. But a careful factual analysis of each case should precede the decision to reject a bladder cancer victim's case based solely on smoking. For example, if a 50-year-old Hispanic woman smoked for 10 years without cancer and developed bladder cancer after 18 months on Actos, you can make a strong argument that Actos was a causative factor in the cancer development, despite the smoking history.

The defense will also examine your client regarding exposure to certain industrial chemicals that have been linked to bladder cancer—primarily in the dye and printing industries and in manufacturing plants for rubber, leather, textiles, and paint. These workplace exposures, particularly when combined with cigarette smoking, may interact to increase the risk of bladder cancer. Long-term exposure to chemotherapy and radiation therapy also can irritate the bladder and increase risk.

**Comorbidities.** Certain comorbidities may increase the risk of bladder cancer. Be prepared to respond to the defense on these issues. Most Actos patients suffer from diabetes mellitus, and epidemiological studies suggest an increased risk of bladder cancer as a result of having diabetes. A 40 percent increased risk was found within seven

case-control studies (epidemiological studies to determine whether groups of individuals have experienced bladder cancer) and two cohort studies (where exposed and unexposed individuals are evaluated to determine who developed bladder cancer) in 2006.<sup>22</sup> Takeda was likely aware of these studies and failed to advise the industry and warn Actos users of this increased risk.

Other comorbidities that may bear on the increased risk of bladder cancer include a family history of bladder cancer; a personal history of urinary infections, kidney stones, bladder stones, bladder irritations from other causes; and a tumor in any part of the urinary tract.

### Causation Analysis

In 1964, the landmark U.S. Surgeon General's Report on Smoking and Health established the criteria to distinguish between causal and noncausal associations in environment and disease analysis.<sup>23</sup> The following year, Sir Bradford Hill, a British epidemiologist and statistician, listed nine criteria that are commonly followed worldwide in the epidemiological community in causation analysis: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy.<sup>24</sup> In



analyzing Actos as a causative factor of bladder cancer, each of these criteria can be met.

**Strength of association.** Hill noted, “We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so.”<sup>25</sup> After the European Medicines Agency reviewed recent data from epidemiological studies, it determined that the data indicates “a small increased risk” of bladder cancer for long-term Actos users.

**Consistency.** This refers to the repeated observation of an association in different populations under different circumstances. Evidence published to date on the association between Actos and bladder cancer is consistent, with

each study finding an increased risk.

**Specificity.** A cause must lead to a single effect rather than multiple effects. Actos is associated with an increased risk of bladder cancer and no other cancers, which meets the specificity criterion.

**Temporality.** The exposure must predate the disease. Actos exposure must have been for at least one year before the bladder cancer diagnosis.

**Biological gradient.** Several studies have shown consistently that the risk of bladder cancer increases substantially with cumulative doses of 28,000 milligrams of Actos.<sup>26</sup>

**Biological plausibility.** No other oral agent associated with increased bladder cancer risk and no increased risk of other cancers in Actos users support the biological plausibility of the causal connection.

**Coherence.** The cause-and-effect interpretation of relevant Actos and bladder cancer data does not conflict with the natural history and the generally known facts and biology of bladder disease.

**Experimental evidence.** Laboratory tests support the Actos-bladder cancer connection. Pre-clinical studies showed that male rats treated with pioglitazone developed more bladder tumors than male rats treated with placebo.<sup>27</sup>

**Analogy.** The literature is replete with observations of bladder cancer following drug and environmental exposures. Thus, both epidemiological studies and application of causative criteria support the causative relationship between Actos and bladder cancer.

### Case Evaluation

To analyze the nature and extent of damages associated with Actos-induced bladder cancer, begin by determining the stage and grade of the cancer; that is, the level of severity and how far it has metastasized. The most prevalent method of measuring the spread of bladder cancer

is the TNM staging system adopted by the American Joint Committee on Cancer.<sup>28</sup> Knowledge of these principles is helpful for plaintiff attorneys who are reviewing medical records to determine the nature and extent of a cancer patient’s damages.

Stage IV is the highest and most dangerous stage of bladder cancer. It indicates the presence of invasive metastatic disease through the bladder wall. The metastasis may involve all organs and tissue adjoining the bladder wall. In the worst-case scenario, bladder cancer can metastasize to the heart and brain and cause death. Stage III involves invasion of the bladder wall without lymph node involvement, and it may necessitate removing the bladder. Stage II indicates a flat tumor with changes, which may comprise layers of cancer cells lining the bladder. Stage I, the lowest level, involves cancer in situ, confined to the bladder. This cancer may be ablated or, in many cases, it may just be monitored to prevent metastasis.

Treatment options generally include surgery, radiation therapy, chemotherapy, or biologic therapy. The types of surgeries that may be employed vary with the extent of the cancer. Each has its own risks and postoperative sequelae.

You must thoroughly review your client’s personal health history and evaluate his or her medical records so that you can be aware of and prepared for the obvious defenses that premorbid and comorbid conditions will raise. In severe cases, it is advisable to use a life care planner, because future medical implications may be extensive.


Cases of bladder cancer in Actos users can vary widely, from cancer in situ—which may have no adverse impact on the plaintiff other than mental anguish—to cases involving death or loss of organs due to metastasis. But they all require close attention to case-specific details if each plaintiff is to recover the full

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range of damages to which he or she is entitled. 

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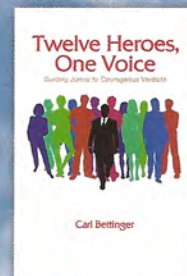
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