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Federal Circuit Finds Infringement Under Akamai Of Two-Step Method Of Treatment

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In *Eli Lilly & Co. v. Teva Parenteral Medicines*, the ***Federal Circuit*** affirmed the district court decision finding infringement under *Akamai* of a two-step method of treatment when the prescribing information for the prescription drug component required coadministration of the other active agent. The appeal arose from ANDA litigation surrounding Eli Lilly's ALIMTA® product, which is to be taken with folic acid and vitamin B12 to reduce side effects. Although pharmaceutical companies may welcome this decision, they should be aware of the emphasis the court place on the specific guidance and instructions provided in the product labeling.

The Patent At Issue

The patent at issue was Eli Lilly's U.S. Patent No. 7,772,209. The court focused on independent claims 1 and 12:

> 1. A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium,
>
> wherein the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.
>
> 12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises
>
> a) administration of between about 350 mg and about 1000 mg of folic acid prior to the first administration of pemetrexed disodium;
>
> b) administration of about 500 mg to about 1500 mg of vitamin B12, prior to the first administration of pemetrexed disodium; and
>
> c) administration of pemetrexed disodium.

The ALIMTA® Labeling

As noted above, this case arose from ANDA litigation surrounding Eli Lilly's ALIMTA® product. As such, Teva's s proposed product labeling, which was based on Eli Lilly's label for ALIMTA®, was relied on as evidence of infringement. In this context, both the district court and the Federal Circuit considered the Physician Prescribing Information and the Patient Information.

The Federal Circuit noted these instructions in the Physician Prescribing Information:

> Instruct patients to initiate folic acid 400 [m]g to 1000 [m]g orally once daily beginning 7 days before the first dose of [pemetrexed]…
>
> Instruct patients on the need for folic acid and vitamin B12 supplementation to reduce treatment-related hematologic and gastrointestinal toxicity…

The Federal Circuit noted similar guidance in the Patient Information document:

> To lower your chances of side effects of [pemetrexed], you must also take folic acid and vitamin B12 prior to and during your treatment with [pemetrexed].

It is very important to take folic acid and vitamin B12 during your treatment with [pemetrexed]to lower your chances of harmful side effects. You must start taking 400-1000 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of [pemetrexed].

The District Court Decision

The U.S. District Court for the Southern District of Indiana applied what the Federal Circuit refers to as its "*Akami V*" decision, *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (*en banc*) (*per curiam*), and found Teva liable for induced infringement based on direct infringement by physicians. As summarized in the Federal Circuit decision:

> Regarding the first *Akamai V* prong, the court found, based on the product labeling, that "taking folic acid in the manner specified is a condition of the patient's participation in pemetrexed treatment." …. Regarding the second prong, the court found that physicians would "prescrib[e] an exact dose of folic acid and direct[] that it be ingested daily." …. The court therefore held that, under *Akamai V*, the performance of all steps of the asserted claims would be attributable to physicians.

The Federal Circuit Decision

The Federal Circuit opinion was authored by Chief Judge Prost and joined by Judge Newman and Judge Dyk.

As in many ANDA cases where the claims at issue are methods of treatment, Teva's liability was based on induced infringement. Under the Supreme Court decision in *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111 (2014), "liability for inducement cannot be found without direct infringement." Thus, the question on appeal was whether Teva's sale of a generic version of ALIMTA® would induce direct infringement of the '209 patent. The Federal Circuit agreed with the district court that it would.

Like the district court, the Federal Circuit applied the two-pronged test it had laid out in *Akamai V*:

> Does a single actor
>
> (1) condition participation in an activity or receipt of a benefit upon another's performance of one or more steps of a patented method and
>
> (2) establish the manner or timing of that performance?

Satisfying The First Prong of *Akamai V*

With regard to the first prong, the Federal Circuit agreed with the district court's finding that physicians "condition" pemetrexed treatment on the patient taking folic acid in the manner specified. In reaching this conclusion the Federal Circuit cited the Physician Prescribing Information which explains that the folic acid is a "[r]equirement for [p]remedication" in order to "reduce the treatment-related hematologic and gastrointestinal toxicity" of pemetrexed. The Federal Circuit also noted repeated instructions to instruct patients to take folic acid and information about the "dose ranges and schedules" for the folic acid.

The Federal Circuit read the following language in the Patient Information as "inform[ing] patients that physicians may withhold pemetrexed treatment" if they do not take folic acid as directed:

> You will have regular blood tests before and during your treatment with [pemetrexed]. Your doctor may adjust your dose of [pemetrexed] or delay treatment based on the results of your blood test and on your general condition."

The Federal Circuit also referred to expert testimony from both Eli Lilly's expert and Teva's expert regarding the "standard practice" for a patient to take folic acid prior to pemetrexed treatment to "avoid toxicities."

In reaching its decision on this prong, the Federal Circuit rejected Teva's arguments that the product label was a "mere guidance or instruction" insufficient to show "conditioning" under *Akamai V,* citing

the critical nature of folic acid pretreatment and the physician's ability to withhold pemetrexed treatment. The Federal Circuit also refused to require that physicians "verify compliance" with the instructions, and noted that the first prong does not require a "legal obligation" between the actors.

Satisfying The Second Prong of *Akamai V*

With respect to the second prong, the Federal Circuit agreed with the district court that the Physician Prescribing Information instructs physicians to tell patients to take folic acid at specific doses and at a specific schedule. The court also noted that the "dosage range and schedule overlaps with the asserted claims' dosage ranges and schedules." The court also referred to expert testimony that physicians decide how much folic acid the patient should take and when. Thus, the second prong was satisfied.

What Does The Label Say?

Although the Federal Circuit rejected Teva's arguments that prescribing physicians did not control the manner or timing of folic acid treatment in this case because patients ***could*** seek outside guidance, the Federal Circuit emphasized that it was ***not*** creating a rule that "patient action is attributable to a prescribing physician solely because they have a physician-patient relationship." Indeed, the court acknowledged (but distinguished) its decision in *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp*., 785 F.3d 625 (Fed. Cir. 2015), where the cited language in the label at issue was found to be too "vague" to support liability for induced infringement.

This decision highlights the importance of aligning claim language with FDA labeling. Since patents often are granted prior to FDA approval, it also provides another reason to maintain a pending application as a vehicle for claims that more closely parallel final product labeling.

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