
Orexo owns two patents directed to Zubsolv, its US Food and Drug Administration approved product for treatment of opioid dependence. A common treatment for opioid addiction is a protocol called “substitution therapy,” in which the abused drug is substituted with a partial opioid agonist that is longer acting but less euphoric. The substitute drug reduces cravings and withdrawal symptoms while decreasing the patient’s dependency. A common “substitute” drug is buprenorphine, which can be administered as a sublingual tablet or as an oral film. Addicts have been known, however, to abuse buprenorphine by dissolving the tablets or film and injecting the solution intravenously to enhance the euphoric opioid effect.

To counteract this abuse, drug companies have combined buprenorphine with the opioid antagonist naloxone at a 4:1 ratio. Naloxone has poor transmucosal bioavailability, so if the mixture is taken in a sublingual tablet or as an oral film, the buprenorphine will act as intended to treat opioid dependency with little
interference with naloxone. If the tablet is dissolved and injected, however, the naloxone will antagonize the effects of buprenorphine, resulting in withdrawal symptoms and thus deterring abuse of the formulation. Naloxone’s functional blockade of buprenorphine’s action is partial and short lived.

Orexo’s patent describes a formulation that enhances the bioavailability of the buprenorphine, which permits a reduced amount of the buprenorphine in the tablet, thereby reducing the amount available on dissolving and injecting the product intravenously. The formulation works by adhering microparticles of buprenorphine to the surface of carrier particles of citric acid. The patent showed a 66 percent improvement in bioavailability in buprenorphine relative to the prior art formulations.

Actavis initiated a lawsuit by filing an abbreviated new drug application for a generic counterpart to Zubsolv. At trial, the district court found certain claims of one of the patents invalid as obvious. Specifically, the district court found that all the ingredients in the claims were generally known, and although the specific formulation was not shown or suggested in any reference, the new combination would have been obvious to a person of ordinary skill. The district court cited to Actavis’s expert testimony as showing that “citric acid is pharmaceutically acceptable, water soluble, and of the right size, so therefore it would act as a carrier particle, because it is in the Suboxone tablet.” Orexo appealed.

The Federal Circuit reversed the district court’s obviousness determination, finding that none of the prior art taught using citric acid as a carrier particle and that Actavis’s expert did not testify that a skilled artisan would obviously select citric acid as a carrier for buprenorphine—he simply stated that the artisan would expect it to work. The Court found that the expert’s analysis was incorrect, stating that the question was not whether the various references separately taught components of the patented formulation, but whether the prior art suggested the selection and combination achieved by the invention. The Court also stated that the district court improperly discounted the enhanced bioavailability of the patented formulation, and the real-world evidence that Zubsolv is less susceptible to abuse than Suboxone. Based on the entirety of the record, the Court found that Actavis did not establish obviousness by clear and convincing evidence.

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