

THE RETURN TO THE USA OF THE DOXYLAMINE-PYRIDOXINE DELAYED RELEASE COMBINATION (DICLEGIS®) FOR MORNING SICKNESS - A NEW MORNING FOR AMERICAN WOMEN

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ABSTRACT

The US FDA approval in April 2013 of Diclegis®, the doxylamine-pyridoxine combination for morning sickness, is a major milestone, particularly since it is indicated for use in pregnancy and the FDA has labeled it a pregnancy category A drug the strongest evidence of fetal safety. After thirty years of being orphaned from an FDA- labeled drug for the most common medical condition in pregnancy, American women and their health care providers have a therapeutic solution that is likely to positively impact millions of women each year. This review highlights the milestones of this antiemetic agent over the last 40 years.

Key Words: *Nausea, vomiting, pregnancy, NVP, doxylamine, pyridoxine, diclegis, diclectin, bendedtin, Canada, USA*

Until the early 1980s, the combination of the antihistamine doxylamine succinate (10mg) and the Vitamin B6 analog pyridoxine hydrochloride (10mg), was marketed in the United States as Bendedtin®, for controlling the symptoms of nausea and vomiting of pregnancy. Bendedtin® was taken off the US market in 1982, not due to an FDA decision to remove the drug, but rather because of the lawsuits filed against the manufacturer alleging that the drug had caused birth defects. And despite periodic reaffirmations by the FDA that there was no evidence that it was teratogenic, women in the United States have been left without an FDA-approved drug for morning sickness for over 30 years.

Soon after Bendedtin® was taken off the market, a study found that the rates of hospitalizations for severe morning sickness in the United States increased by threefold.¹ Evidently, the removal of a drug taken by up to 40% of pregnant women in the United States during the late 1970s was not warranted and millions of women have suffered as a result. As Bendedtin®

was already off-patent, a Canadian company, Duchesnay Inc., (Blainville Quebec) began manufacturing the drug and marketed it as Diclectin® in Canada, where it remained available and has been widely used, with a solid safety profile and no evidence of an increased risk of congenital malformations/teratogenicity.

Overall, there has been no evidence of an increased malformation risk in women treated during pregnancy-far more than any other drug used in pregnancy.²⁻³ Specifically, studies have confirmed the fetal safety of the combination, including a meta-analysis of studies with over 250,000 women that found no increased risk of congenital malformations in general or specific malformations in particular, associated with prenatal exposure to Bendedtin®.² Additional 2 meta-analyses published in 1990s of 16 cohort and 11 case-control studies corroborated the 1989 analysis, finding no difference in the rates of birth defects among the babies exposed to Bendedtin® in the first trimester and those with no such exposure.³⁻⁴

The FDA approval of doxylamine-pyridoxine in April 2013 is a major milestone, particularly since it is indicated for use in pregnancy and the FDA has labeled it a pregnancy category A drug (the strongest evidence of fetal safety). For approval, the FDA required a new phase III placebo-controlled study conducted in the United States.⁵ The study, which enrolled 261 adult women seven to 14 weeks pregnant experiencing NVP, at medical centers in Galveston, Pittsburgh, and Washington, D.C., found that treatment with the doxylamine-pyridoxine combination was significantly superior in improving NVP symptoms over placebo, and improved quality-of-life, after two weeks of treatment. Women on the drug required fewer alternative treatments and more of them asked to continue treatment after the two week trial, than those on placebo. They also reported missing less time from work.⁵ Older antihistamines such as doxylamine tend to cause CNS depression, but in the US study, those who received the active drug did not report more sedation than those on placebo.

The cumulative experience in Canada has been similar. After 30 years of use in Canada,, quite a few Canadian physicians give more than the 4 tablets recommended in the label, which they feel is necessary to achieve the therapeutic effects in women who have severe symptoms, are overweight or obese. In a prospective observational study, we found no increased risk of malformations or developmental issues associated with prenatal exposure to the higher than the standard doses of 4 tablets a day.⁶ Motherisk has recently completed a study showing the benefits of pre-emptive treatment with Diclectin® on severe morning sickness in women who had experienced severe nausea and vomiting during a previous pregnancy. Those who randomized to commence treatment with Diclectin® before symptoms started had significantly fewer cases of moderate to severe NVP than those who started treatment once they started to experience symptoms.⁷

In summary, the introduction of Diclegis® in the USA is a major victory to American women and their health care providers, after being orphaned from FDA-approved medication for NVP for thirty years.

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